Washington State Health Care Authority

Health Technology Clinical Committee Public Meeting

January 17, 2020

Copies of the audio recording for this meeting are available by request to: shtap@hca.wa.gov.

John Bramhall:	Good morning. I'm going to introduce myself. I'm an anesthesiologist at the University of Washington system at Harborview, a member of this committee.
Mika Sinanan:	Good morning. Mika Sinanan. I am a surgeon at the University of Washington and member of this committee.
Edith Cheng:	Good morning. I am Edith Cheng. I am maternal fetal medicine and medical genetics at the University of Washington.
Josh Morse:	I'm Josh Morse, Health Care Authority and program director for the Health Technology Assessment program.
Sheila Rege:	I am Sheila Rege, radiation oncologist from the Tri-Cities and the Chair of the HTCC.
Kevin Walsh:	I'm Kevin Walsh. I practice family medicine in Ellensburg at a community health center.
Austin McMillin:	Austin McMillin, chiropractor in private practice in Tacoma.
Tony Yen:	Tony Yen, I'm a hospitalist at Evergreen.
Janna Friedly:	I'm Janna Friedly, a physiatrist at the University of Washington, a member of the committee.
Laurie Mischley:	My name is Laurie Mischley. I am a naturopathic physician, and I do research at Bastyr University and the University of Washington.
Sheila Rege:	Would the agency medical directors like to introduce themselves?
Judy Zerzan:	Sure. Judy Zerzan, chief medical officer at HCA.
Shana Johnson:	Shana Johnson, medical director fee for service, Health Care Authority.
Sheila Rege:	Guests, you will introduce yourselves when you come up. Thank you for being here. We have amazing staff that helps put this together. Thank you, very

much. We'll have the evidence vendors also introduce at that point. If we could go to the program updates. Feel free to stop us at any time if we missed anything, or we need more time to discuss things. Josh, would you like to...

Josh Morse: Sure. Thank you. Good morning. Christine, this is not working at this point. Maybe you could just advance? Thank you. Okay. So, welcome. Today's agenda includes the cell-free DNA prenatal screening for chromosomal aneuploidies. That will begin after we finish the previous meeting business, which includes the minutes and the femoroacetabular impingement syndrome topic from the last meeting, and a review of work done, since the last meeting, on the whole exome sequencing covered with conditions. It's the list of conditions that was worked on. So, the committee will need to go through and vote on that.

So, a few meeting reminders. This is being recorded. A transcript of these meetings and of the proceedings here will be made available on our website. It does take some time for us to get the transcript back, normally a few months to a week. When participating in discussions, please state your name and use the microphone. That helps the transcriptionist hear what's going on and know who is speaking. To provide public comment during today's meeting, there is a signup table and a sheet outside that door if you wish to make comments during the public comment period.

So, on the next slide, again, this doesn't seem to be working. The Health Technology Assessment program is managed and administrated by the Washington State Health Care Authority. It was created in 2006, and it is designed to use evidence reports and a panel of clinicians to make coverage decisions for selected medical procedures and tests based on the evidence that's available for the safety, efficacy, and cost-effectiveness of those tests.

Multiple state agencies participate to identify topics for review through this process. Those agencies implement the policy decisions. These go through the Health Care Authority, which runs the Uniform Medical Plan and the state Medicaid program, the Department of Labor and Industries, and the Department of Corrections. Agencies implement the determinations from the Health Technology Assessment program within their existing statutory frameworks.

Is it working now? Now it's working. Thank you. So, the purpose of this program is to ensure that the medical treatments and devices and services that are paid for with state healthcare dollars are safe and proven to work. This program provides a resource for state agencies that purchase healthcare. We develop scientific evidence based reports on the devices, procedures, and tests that are selected for review, and we provide support to the clinical committee here who determine which medical devices, procedures, and tests should be covered, covered with conditions, or not covered in the state programs.

This is a very high level view of how this process works. Topics are nominated. They are put out for public input and prioritized. Ultimately, the director of the Health Care Authority selects technologies to go through this process. We then develop a research plan in the form of key questions and a work plan. These are released for public comment, as well. They are then finalized. We have contractors, technology assessment centers. They, then, get to work producing the reports that are the basis for decisions here. We then bring that information to a public meeting where the committee is able to review that information and make decisions.

So, the calendar for the rest of this year includes the next meeting on March 20th, which will be the topic for stem cell therapy for musculoskeletal conditions. Then, in May, two topics, tinnitus, which is a new topic and not a rereview, and a rereview of vagal nerve stimulation for epilepsy and depression. We will wrap up the work from the May meeting with a webinar phone conference on July 10th. The committee tends to meet in retreat in the 3rd Friday of September. Then, the next action meeting would be in November. We do not have a topic yet selected for that meeting.

So, to participate, the information for the Health Technology Assessment program is available on the Health Care Authority website. The web address is listed there. You can also sign up for our email delivery system from that website. Anyone may provide comments on proposed topics, final topics, key questions, draft and final reports, and draft decisions, and make public comment here at this meeting. Anyone may also nominate technologies for review or rereview. That concludes my updates. Thank you.

Sheila Rege: Thank you, very much. Now proceeding with previous meeting business. If we could pull up the November meeting minutes. Thank you everybody for making it safely today. I know the road conditions were a little tricky. So, we have to do safety on all these, I'm glad all of us are safe. It is online if Christine, okay. So, it's online. If you've had a chance to review the meeting minutes, I will take a motion to approve that. That will include the final coverage determination on the hip surgery, the FAI issue. It also has final draft coverage language for the whole exome sequencing. So, be aware, it is several pages long. So, I'll give you some time to pull it up. If you could, yeah. If you could put the final draft coverage language on the screen. I am going to do it piece by piece, but I just want everybody to kind of have time. So, I'm going to take it in three steps, one just the meeting minutes, that it was accurately represented. Two, the final coverage determination of the FAI. Then, the WES issue, unless anybody has objections. Each of those will take a motion and a second and a vote. So, Tony, did you make a motion? Seth seconded? Any discussion just on the minutes portion of it? John? All in favor, say aye.

Group: Aye.

Sheila Rege: Any opposed? Any abstain? Great. Now, we'll do the final coverage determination for the hip surgery. And that's also in the package starting on page 14 on my PDF. It is here. Correct?

Josh Morse: It is there. There is one comment in your binder on this decision.

Sheila Rege: Right. So, it's in your package. Let us read the comment. If you look at the comment that, um, came on December 30th, if you pull it up. There's no evidence... it's a personal email. So, I will have a discussion on that whether we want to discuss that or make a motion to accept our final draft, or our final coverage determination.

John Bramhall: I move approval of the final coverage determination.

Sheila Rege: And if we could just, for the transcriptionist, identify your name as you make that motion.

John Bramhall: John Bramhall.

Sheila Rege: Okay. Thank you.

Kevin Walsh: I second.

Sheila Rege: I should do that. Sheila Rege speaking. Any discussion or, everybody is ready to vote? Let's take a vote. Those in favor, say, raise your hand and say aye, just in case there's [inaudible].

Group: Aye.

Sheila Rege: Anybody abstain? Anybody oppose? No. So, that's unanimous in favor of that. Now, we move to... that's here under the next tab, if you are following along. Or if you're on the pdf. This again is now final coverage draft coverage language, and the final, final will be in March, depending on what we come up with, as a group. So, that I would like projected, Christine, if we can.

Christine Masters: The WES?

Sheila Rege: Correct. As background, remember we asked for more work to be done by the staff. This has been out on the website for us to review, as well. There it is.

Christine Masters: I'm not able to edit it on the screen.

Sheila Rege: So, to summarize, it does have what we had discussed, a board certified medical geneticist. Then, on point number two, either of the following. I know a lot of work has gone into this. Draw your attention to, also on the back, it's not medically necessary for. There. Any discussion, thoughts?

John Bramhall: Sheila, I have a question, and this is my ignorance. The rubric about the American Nurse's Credentialing Center, the ANCC, I'm ignorant about that body, and I'm wondering whether that credentialing qualification implies professional knowledge of genetic issues. This is purely my ignorance, and I'm sorry.

Sheila Rege: Do we have anybody in the room qualified to answer that? Dr. Johnson, would you... can we put you on the spot? I know this was done in collaboration with some of our experts from the meeting.

Shana Johnson: That's a good point. I think that wording came in concert with working with Seattle Children's. Can we go back up to the statement? The advanced practice nurse of genetics. I think that's a good question. Why don't I bring that back to Seattle Children's, that particular classification, ANCC?

Josh Morse: So, we are trying to get our phone line working, and Nedra Whitehead is our clinical expert. We can get her here to consult on this right now once we get the phone line working. Nedra should be able to answer any questions about this, um, policy.

John Bramhall: I don't want to hold anything up. It's purely my ignorance that it simply that the rubric in one is that somebody is making a decision here who is clearly qualified in medical genetics. That was our expectation, and I simply don't know whether the ANCC implies that similar level of education qualification. That's all.

Shana Johnson: It looks like we do have some background that that credentialing committee does do advance genetic nursing certification. So, I think we're okay to go forward.

Sheila Rege: And if we get our clinical... I mean, we can ask again, but we'll hold on that. So, it has these, is it eight things that have to be met. And I think it reflects what our kind of discussion was. Then, in number two, it goes into this pathway of either.

Mika Sinanan: I may not be recalling the discussion completely, but number five, point number one, WES is more efficient and economical than the separate single gene test. Who makes that determination that it's more efficient and economical?

Shana Johnson: I can help answer that. So when a genetics test is submitted for review, oftentimes if they ask for... a single gene test is often, like, $1500 to $2000, and they'll have the price listed with their genes. So, one or two genes, you're usually already at $3000 and a WES is typically, like, $4000. So, we have the cost information. So, I guess, basically, the payer looks at that, because we see the prices, and if it's the less costly alternative then per our 0165 rules, we can allow that procedure. So, that's what that sentence is meant to capture. If you order five gene tests, you're already at $6000, but if you order the WES, you're only at

$4000. So, in that case, the WES is the least costly alternative and is more efficient, so to speak.

John Bramhall: Thank you. So, I understand that. What if they're ordered sequentially? Not all at the same time. Somebody doesn't put an order for five genetic tests but orders one and says, okay. That one's negative. So, we need to look further. So, they order another one, and then another one, which seems to me a more common clinical scenario.

Shana Johnson: If they have... I find the genetics providers, as a whole, are actually very in tune to ordering the most efficient tests the first time. If they are highly suspicious of a single gene disorder, then they will do targeted testing first, but in general, I don't see them order five different single gene tests before they go to the WES. They kind of give it... And again, this is antidote, but in general, they tend to have a pretty good idea. And they do a single gene test, or they're pretty sure it's a genetic syndrome, but they can't place it in anywhere. Then, they go for the WES. I don't know if that helps answer it.

Mika Sinanan: So, your sense is that their knowledge and expertise and the payer reviews allow a two-level review of this so that it's not an issue. In fact, we are getting to an efficient and cost-effective sequence.

Shana Johnson: Yes.

Mika Sinanan: Thank you.

Sheila Rege: Mika, I want you to note that there is an agency director who says trust the treating provider.

Mika Sinanan: Let the record show.

Sheila Rege: Let the record show. You question.

Janna Friedly: May I ask a question? So, the number eight, I think it's just a minor grammatical thing. It's the only one that isn't actually a sentence. There's no verb in there. So, is it the pre- and post-test counseling is performed, is made available, is offered? What is actually required? Documentation that they actually went through with it? Or just that it's made available and offered to the patient?

Shana Johnson: Can you show number eight? Am I missing it? Very good catch. I'm impressed.

Janna Friedly: I'm an editor. It's in my blood.

Sheila Rege: That's a good performed. Is performed recommended? Performed? Okay. So, we will... any discussion on performed?

Shana Johnson: By the time they get to WES, they should be having formal genetic counseling. So, I would vote as performed.

Sheila Rege: Any discussion about that amendment is performed? If not, I will take a motion to, just on that point, to an addition of is performed in clause eight.

Janna Friedly: I so move.

Sheila Rege: Janna is making it.

Austin McMillin: Second.

Sheila Rege: Austin seconded, and Laurie. All in favor?

Group: Aye.

Sheila Rege: Okay. Now, looking at the revised document. John, are you comfortable with the American Nurse's Credentialing Center?

John Bramhall: Yes. It's my own, yeah.

Sheila Rege: Okay. You don't want... Okay. So, now, we're going to continue discussion on this now, as a whole.

Seth Schwartz: I just have one question, for number five, it talks about the differential diagnosis list. Is that just a generic statement? Or is there a differential diagnosis list that it's referring to?

Sheila Rege: Dr. Johnson, would you like to help us on that?

Shana Johnson: Could you show number five again? Sorry. It's been a little while since I've looked at the...

Sheila Rege: Good question.

Shana Johnson: ...so, this does actually refer to an actual differential diagnosis list. When a medical geneticist typically assesses the client, they will actually write the differential of syndromes that they are considering, and then consider how many gene tests that would be. Then use that to apply that WES is more efficient and economical. So, that is very specific. They, literally, need to write what disorders they're thinking about, what genes that would entail testing, and then that guides whether they should do single gene testing, panel testing, or WES. The medical geneticists routinely do that in their notes.

Sheila Rege: It looks like a documentation...

Shana Johnson: Yeah. It's a documentation...

Sheila Rege: ...recommendation...

Shana Johnson: ...requirement.

Sheila Rege: ...not a prescriptive, is that... Seth, you are good? Okay. No. This is good, because this... we need to make sure this is correct, because it's a complex draft. Any other discussion on this final draft coverage language? Let's go back up. Let's just take our time reading it on the screen, or on your... and one of my faults is, I'm impatient. So, I am going to actually give us two minutes, until 8:30, to just look at this. We're ahead of schedule. So, we're good. Since sitting is the new smoking, you are free to stand, because I am going to, as well. If we're good, I'm seeing people flip pages, if you'll go to the next page. So, people are reading this. Down, yeah. Yeah. Stop. Yeah. Then, we'll go to number eight. We can't amend it on the screen, but we're gonna add is performed on number eight. Also, look carefully at the not medically necessary list. Also, at the definitions that were included in point number two of the development delay or intellectual disability. If people are comfortable, and there is no more discussion, we could entertain a motion.

Kevin Walsh: My memory is that we thought this technology had effectiveness in a certain segment of people, or situations, and that we struggled to define those. I think that this reflects our intent. I think Dr. Johnson did a nice job of translating our intent into language. Thank you.

Seth Schwartz: I move to approve this as stated here with the amendment that we talked about for number eight.

Sheila Rege: Thank you.

Janna Friedly: I second.

Sheila Rege: Great. Thank you, Janna. Any other discussion? Or otherwise, we will make motion to adopt this.

Mika Sinanan: On number six, a diagnosis cannot be made by standard clinical workup. Does that mean a presumed clinical workup, or a clinical workup that has been done?

Sheila Rege: Back to point number six. It's displayed.

Shana Johnson: I think that means your traditional history, examination, and any other standard tests that would go with the findings have not led to a definitive answer.

Mika Sinanan: Okay. So, thank you. So, then I might suggest that we reword it and say that the standard clinical workup that has been done has not led to a diagnosis. Does that make sense?

Sheila Rege: I think that's...

Mika Sinanan: No. It just says that... the way it is stated, it could presume that you think that a standard clinical workup wouldn't lead to a diagnosis, as opposed to, a standard clinical workup has been done and didn't lead to a diagnosis.

Sheila Rege: I see. You just want to clarify that?

Mika Sinanan: Yes.

Sheila Rege: And you don't want an explanation of what a standard clinical workup is. You're okay with...

Mika Sinanan: I think that's, yeah. I think that could be accepted.

Sheila Rege: ...I'm going to reread Dr. ...and this is a motion, and we're gonna need a second, that again by addition, number six be changed to a diagnosis cannot be made by standard clinical...

Mika Sinanan: Standard clinical workup has been done, and a diagnosis was not made, or not...

Sheila Rege: So, if I substitute... deletion and substation.

Mika Sinanan: Correct.

Sheila Rege: Standard clinical workup has been done and did not lead to a diagnosis.

Mika Sinanan: Right.

Sheila Rege: So, that would be the amended number six.

Mika Sinanan: Thank you.

Sheila Rege: You still need a second.

Janna Friedly: Second.

Sheila Rege: Everybody okay with that being more clear? Anybody else want to help with that? Or are we good with that? Everybody in favor of that, raise your hand. Austin? Okay, and it looked like it was unanimous, so...

Austin McMillin: I do have one question. So, with respect to point six, as opposed to the reducing diagnostic uncertainty on the non-medically necessary list, if you're in a clinical workup with a differential diagnosis, and you can't arrive at a diagnosis, you're still at a point of uncertainty. So, where does that leave us with respect to the non-medically necessary list?

Sheila Rege: Are you saying we're going in circles on that one?

Austin McMillin: It sounds circular.

Shana Johnson: I think you could delete that sentence. I could see how it could be misinterpreted, and it's somewhat vague and...

Sheila Rege: So, Dr. Johnson is suggesting deletion of number six completely? No?

Austin McMillin: Reducing diagnostic uncertainty.

Sheila Rege: Oh, reducing diagnostic uncertainty. Where is that, Dr. Johnson? I'm lost now.

Shana Johnson: It's just under the non-medically necessary part. I mean, I think, in our minds it was...

Sheila Rege: Oh, I see.

Shana Johnson: ...you know? Some people can be diagnosed, like, 95% clinically, and you just want to run the tests anyway, but, as it's written, it's vague and I don't think it's obvious to the person reviewing the policy that that's the intent, which means it's not gonna be able to be applied consistently. It might just lead to problems into implementation. So, it may be best to just get rid of it.

Sheila Rege: Any comments or concerns about the recommendation to remove reducing diagnostic uncertainty under the not medically necessary?

Austin McMillin: So moved.

Seth Schwartz: Second.

Sheila Rege: Seth, do you want to say something on that.

Seth Schwartz: I was gonna second it.

Sheila Rege: Okay. So, then all if favor of that deletion, too? Dr. John? Okay. So, now, we have this, uh, with us with the three amendments, amended number six, a standard clinical workup has been done and did not lead to a diagnosis. Amended number eight, pre and post-test counseling is performed. That's the addition by the American Board of Medical Genetics or American Board of

Genetic Counseling Certified Genetic Counselor, and deletion of reducing diagnostic uncertainty and not medically necessary, four. Discussion on the amended final draft coverage language? We can take our time, because we're still way ahead on schedule. So, please keep looking at it. I'm going to... Christine is going to get tired of me asking to just scroll down, in case anybody wants. So, everybody is good with number one? Now, going back up, point number one. Let's just look back and read it, because that's what we would do normally. Number two. Hearing none, number three.

Mika Sinanan: Can I suggest that we change the "would not" to "do not"?

Sheila Rege: On number three?

Mika Sinanan: Right.

Sheila Rege: So, it is an amendment by substitution on number three, other circumstances, the brackets, would disappear and do not reasonably explain the constellation of symptoms. That's how you would like it to read? I think that clarifies things. I would [crosstalk].

Laurie Mischley: I would second.

Sheila Rege: I don't think it changes the intent. Dr. Johnson? So, all in favor?

Group: Aye.

Sheila Rege: Okay. Number four, [inaudible] clinical presentation. Then, we move to number five. We've already had a question and answer on who makes the decision on point number one. I think we're okay with that. Number six would be amended, as discussed. The standard clinical workup has been done and did not lead to a diagnosis. We've already voted on that. Number seven, results will impact clinical decision making for the individual being tested. Then, number eight was amended by addition. That was a good catch, good suggestion. Then, we'll go to the not medically necessary. That's reduced to four. If I would have you look at the definitions to make sure you are happy, because... and we're looking at significant delay defined as two standard deviations or more.

Mika Sinanan: Under the definitions, the very last line, there is... the wording is wrong. Dysfunction or impairment in more than two of areas. There's an extra of there.

Sheila Rege: I'm gonna read that again. Mika, will you read the whole sentence to me so you...

Mika Sinanan: The very last line of the point under the definitions, number two where it says more than two of areas of adaptive behavior or systems of support. There's an extra of.

Sheila Rege: So, you want to, yeah. That's an editor-, and, and right. That was, I think, a typo.

Mika Sinanan: Right.

Sheila Rege: That, I do not believe, needs a vote. Yeah. That's a script pickup. Now, in line with what we had agreed on as a committee before we take a vote on this, we were gonna give ourselves a ten-second break. You guys can just... don't think about it. Go back and look at it. We'll then vote on it. Is that okay?

Mika Sinanan: Motion to approve with the amendments, as stated.

Seth Schwartz: Second.

Sheila Rege: Any further discussion? All in favor, raise your hands please. So, we've got everybody is in favor that's present. Great. Thank you. Thank you, very much. Great job, to look at it and come up with a good [inaudible]. Thank you, Dr. Johnson. That was... we really appreciate it.

That is the end of old business. Again, this will be on the website. Then, we will be looking at this, as for a final at our March meeting. If we are good, oh, look. The fan stopped, too. It's like we're now in a new chapter. Everybody, please welcome first of all, our clinical expert, Dr. Cheng. Thank you, very much, for being here. You can... she has very kindly provided her CV, which is very, very impressive. So, we're going to rely on you for clinical expertise. We really appreciate your time.

Edith Cheng: Thank you. I'm happy to be here.

Sheila Rege: If there are no objections, we're going to put Dr. Johnson on the spot again for the utilization and outcomes presentation. We are a little ahead of schedule. Would anybody like a break? Or is everybody good to keep going? It's 8:45, and this was scheduled at 9:10. Josh, will that be a problem with the open public comment at 9:30?

Josh Morse: No. It shouldn't be a problem.

Sheila Rege: Okay. If Dr. Johnson is ready, I think the committee is ready. You know what? I'm going to make a recommendation that we actually take a two minute break. We're having some audio-visual issues we are going to solve during that time, because we are so ahead. So, we'll just take a couple of minutes. Sorry about that. Which means, I don't expect any bathroom breaks or anything during the presentation.

Thank you. Thank you, very much. If we can reconvene. Dr. Johnson, if you wouldn't mind introducing yourself again. Thank you for doing this.

Shana Johnson: Sure. Welcome everybody. I am Shana Johnson. I am the medical director for fee for service at the Health Care Authority. I wanted to thank all the stakeholders for coming today and being a part of the meeting. We look forward to hearing your input on the topic, and also thank you to our expert. Alright. So, today, we're going to talk about cell-free DNA prenatal screening in those not known to be at high risk for carrying a fetus with aneuploidies.

So, my talk today is going to be three main parts. I'm going to go through the policy question at hand, 'cuz it's a little bit nuanced. Current state policy utilization, our approach to screening programs from a public health perspective, and go through the evidence summary, as it led to our rationale and final recommendations.

So, cell-free DNA is widely accepted, as a good first tier test for screening for aneuploidies in those known to be at high risk for aneuploidies. Our policy question today is whether it should be covered for the general obstetric population, those at low risk for chromosomal abnormalities, or limited to the population at an increased risk of aneuploidies. Those with a higher prevalence of the condition.

When we look at our current state agency policy, you'll see that there is a split. Our PEBB/UMP program covers cell-free DNA for the general obstetric population, while the Medicaid programs cover it for those at high risk of aneuploidies.

Similarly, when we look at other insurer's coverage policies, we see this split, as well with Aetna covering for those at high risk. Regence and CIGNA are covering it for the general obstetric population. Of note, CMS does not have a formal stance on this.

So, on this slide, it shows the utilization for Medicaid and PEBB over the last couple of years. I'm going to focus on 2018, because the numbers are fairly similar from year to year. In the Medicaid program, we have upwards of 39 to 40,000 births per year. PEBB is a smaller program, more like 2000 births per year. We see that for those women under 35, prenatal screening is 28% in UMP and 23% in Medicaid for the conventional screening. When we go down to cell-free DNA, we see 20% in the less than 35 and 4.5% in the less than 35, which likely reflects the fact that they have two different policies. So, PEBB is general obstetric, and Medicaid is cell-free DNA only. When we add these numbers together, in Medicaid, the total number of women less than 35 receiving prenatal screening is about 28%, whereas in UMP it's higher at about 48%. It's also of note that the amniocentesis rate overall is quite low, and it is slightly higher in those over 35, as we would expect.

The next part of the talk, I just wanted to take a look at our approach to screening tests from a public health perspective. So, the screening test, as most in this room know, test a population with no signs or symptoms of the disorder, to detect the disorder at a stage when the treatment is more effective. It's used to identify people who required further investigation is not primarily a diagnostic test. The potential benefit of this screening program should not cause harm to a population that is otherwise well, and should have strong evidence. Additionally, there is economic considerations in a screening program. Its implementation is influenced by the distribution of limited resources across the population, as a whole for maximum benefit.

A little bit more detail on what makes a good screening test. Obviously, we want the screening test to be sensitive and not miss cases. We want it to be specific, so it doesn't lead to false-positives and unnecessary testing, lead to improved health outcomes, and again, it has to be cost-effective. It's often being done on a high volume of people.

Taking the test performance metrics one step further, I'm also going to talk a lot about positive predictive value and negative predictive value, as it relates to screening test, as a predictive value takes into account the prevalence of the condition. With a low prevalence condition, the predictive value of the test inherently will be lower. The positive predictive value of many screening tests is low due to the low prevalence of the disorders, typically. Or if the test has low specificity. The downside to this fact is that it could result in positive screenings but no condition. So, false-positives and unnecessary procedures. This issue is balanced by concentrating screening efforts on people with a higher prevalence of the condition.

The third part of this talk, I want to just go over the points and the evidence summary that led to our rationale and our recommendation. So, there are four major points that I'd like to discuss. One is that both tests have a good negative predictive value. They are both good at ruling out the disorder when it's not done and that had moderate quality evidence. Two, cell-free DNA had a higher positive predictive value, although the evidence there was graded very low quality, due to wide confidence intervals and differences among studies. Cell-free DNA did have less unnecessary procedures, graded with moderate quality evidence. The third point I'll be talking about is that the positive predictive value in low risk is lower, due to its lower prevalence. Lastly, I'll be talking about the cost-effectiveness studies, which varied from less costly to more costly and were sensitive to multiple inputs and the perspective taken on that incremental cost-effectiveness ratio.

So, just to show these four points with the slides, so this is table 8 from the evidence vendor report. The negative predictive value on cell-free DNA was good, 99.5 to 100%. Likewise, the negative predictive value on standard screening was also good. So, you get the test done. It's negative. You're done.

The second point was about cell-free DNA having a higher positive predictive value. The median positive predictive value for cell-free DNA was 79%. Compared to the positive predictive value of conventional screening of 28%. The differential here is that the evidence graded for the positive predictive value for cell-free DNA was graded as very low quality. Cell-free DNA did have less unnecessary procedures.

Looking at 1000 pregnancies, cell-free DNA up to 6 of 1000 unaffected pregnancies would undergo unnecessary invasive testing where conventional screening up to 44 in 1000 undergo unnecessary invasive testing.

The next point I had talked about was when the condition is lower prevalence, you naturally have a lower predictive value. This slide pulled from the Norton paper demonstrates this. Again, just inherently, when there is a lower prevalence, there is a lower positive predictive value we see in the low risk, the positive predictive value, the chance of you actually having the condition if you test positive is 50 in the low risk, and 80 when looked at the group.

The last point in this part that I wanted to make was about the cost-effectiveness. Really, the point of this slide is to demonstrate the variation that cell-free DNA screening ranged from less costly to more costly, based on the study, the input, the assumptions, and the perspective. The cost-effectiveness study by Walker was a low risk study done on cost-effectiveness that I thought brought some interesting perspectives. It found that the cost-effectiveness point for cell-free DNA was $549. However, there was large uncertainty based on the model inputs and assumptions, and the ICER was sensitive to each input.

Similarly, this same study talked about how the ICER was very dependent on the perspective taken. For example, from a societal perspective, it was cost-effective. However, as you narrowed your perspective to the payer, the cost-effectiveness number lowered to around $200 per test.

So, we've kind of talked about cost-effectiveness from these big studies. Let me narrow this down and just give you a little bit more sense of the rates in Washington. So, in Medicaid fee for service, conventional screening, this comes from our fee schedule. Our triple screen is about $70. Our quad screen is about $80. The Medicaid rate for cell-free DNA task varies from about $500 to $700 based on whether it's in the managed care plans or fee for service. So, it can be up to 10x the cost in a large population.

So, bringing everything together about the points we've talked about, we've talked about our approach to public health screening program. We want an accurate test. It has to economically make sense. We want to balance our screening efforts with the condition prevalence. Our evidence summary has shown us that both tests have a good negative predictive value. Cell-free DNA

has a higher positive predictive value and less unnecessary procedures. The cost-effectiveness studies vary from less costly to more costly, and they are very sensitive to the inputs and the perspective taken.

From a health system perspective, both tests have negative predictive value for ruling out aneuploidies. You do the test, and you're done. There is a lower predictive value in those at low risk, due to the low prevalence of the population. There is the important factor, that there is a distribution of limited resources, and the cost of cell-free DNA is up to 10x the cost of current standard screening. Taking all of these points into consideration, the EMDG recommendation is that cell-free DNA prenatal screening is not covered for those not known to be at high risk for chromosomal abnormalities. However, cell-free DNA is covered following a positive test on standard screening, and continues to be covered for anyone who has any other features suggestive of high risk of aneuploidies. We're ready for questions.

Sheila Rege: Thank you.

Kevin Walsh: Dr. Johnson, did you do any modeling to look at how many in Washington, how many abnormal triple screens or quad screens there were and what the... I'm trying to get a handle on how many cell-free DNA tests we would be doing if we did it for abnormal initial screening.

Shana Johnson: That's a good question. We didn't do any of that modeling. We do, I'm trying to think the best way to answer that. Most of the tests are negative. So, and that's our current policy. If they have a positive standard screen, we approve the cell-free DNA. So, that's currently in practice. So, its current state, but I don't have the modeling numbers for that.

Janna Friedly: Does that suggest then from your utilization data that in 2018, for example, if in the Medicaid population you have 7900, or almost 8000 people who got conventional screening under 35, and then there were 1500 cell-free DNA tests that those by definition had to have been ones that were positive conventional screen... or conventional screening that had a positive finding and then went on to cell-free DNA under the current coverage?

Shana Johnson: So, that's a good question. My data analyst told me all these numbers were unique people. And can you just repeat the numbers that you were looking at again?

Janna Friedly: I was looking at, just as an example, the 2018 Medicaid conventional screening under 35 is 7970, and then, the cell-free DNA was 1544. So, if those who got cell-free DNA had to have a positive conventional screening prior, are those the subset of 7970 that went on to cell-free DNA.

Shana Johnson: I'm making an assumption here that my data analyst said it was one case count per person per test.

Edith Cheng: So, can I interject for a little bit?

Shana Johnson: Yes. Please.

Edith Cheng: So, your serum screening testing is set. The positive... screening positive for serum screening is set for a 5% screen positive rate. So, just empirically. So, you know, how did we decide that we were gonna use like 1 in 350 or 1 in 360 in your screening tests to say that this person screens positive. So, we've modeled that a million times, and it's always constantly how many pregnancies do you want to subject the traumatic counseling in an amniocentesis in those days before we had cell-free DNA paired with what your pickup... what you desire to be your pickup rate. So, we modeled it so that collectively, we all agree that we would accept a 5% screen positive rate among the women who underwent screening. So, you can just kind of empirically figure out what those numbers are. If our birth rate in the state of Washington is 80-something, and 40,000-45,000 were under this plan, then you could do just the math, and assuming if you had 100% pickup rate, which is not true, I think that our screening rate is probably closer to 60% or so. Then, you can do an empirical mathematical calculation. So, I would say that if you make an assumption that the cell-free DNA of 4.5% in 2018, perhaps reflects the fact that these were women who this was, then, you know, you're pretty close.

Shana Johnson: That is an interesting... yeah. This is really close. Yeah. There's four or five other instances where you could be less than 35 and you qualify for cell-free DNA just based on high risk features. That would be the other place the number comes in.

Janna Friedly: May I ask a follow-up question to this data? Maybe it's just me, but I'm really struck by the low percentages of total pregnancies that undergo screening. Is that... am I wrong to think that this is a problem?

Edith Cheng: I'm interested... I'm surprised to hear that you used the world problem. I'm just gonna say that that is truly an observation for somebody who is in the trenches across the board, not in the ivory tower. I think that I'm out in the Tri-Cities, in Yakima, you know, Arlington, Olympia, and the pickup rate for antenatal screening is low. I don't know why. I think some of it has to do... I don't know why. I mean, some of it has to do with maybe we don't have time to adequately counsel, but I think that even in our clinics, in which I have a full time genetics counselor, and they actually do the counseling, they still come out with no thank you.

Janna Friedly: But this is, just help me understand, this having gone through several pregnancies myself, I just assumed that this was something that is standard of care, recommended for everyone. Is that not the case?

Kevin Walsh: Well, it's recommended and offered, but I think you're... I think you're wading into cultural territory. I think it's a different. I would pause it as someone who practiced OB for 30 years that it's different cultures have different values, and I think it's value-based.

Janna Friedly: Okay. I just wanted... it just struck me as a low percentage.

Sheila Rege: And that's an important observation. That was Kevin speaking, but it's good to get a perspective, but let's go back to kind of questions on... while poor Dr. Johnson is standing at the mic there. Any more questions for Dr. Johnson?

Mika Sinanan: Has the cost of the cell-free DNA changed over time? I assume it has. What's the rate of that change?

Shana Johnson: So, that is a really good questions. I have to admit, in the fee for service world, we follow CMS rates. So, for us, it's pretty straightforward. CMS sets a rate, and then we follow that rate. I think it gets more complicated with managed care contracts. 'Cuz, they can contract the rate. Right? So, that's the piece that I don't know how much that changes. I don't know if there's anyone else here who knows about how the cost changes over time.

Male: [inaudible]

Sheila Rege: Thank you.

Chris Hearne: Am I correct in understanding that if under your recommendations if traditional screening is positive, and then a subsequent cell-free DNA is negative, then there's no more testing. Is that correct?

Shana Johnson: Well, that would be up to the patient. I mean, theoretically, they could still want to pursue an amnio.

Edith Cheng: That is true. I mean, that generally is the practical thing that we are facing, because patients really don't want to undergo an invasive procedure. From an academic point of view, you're really doing two screening tests. So, you have a screen positive test. Although historically, all the screen positive tests have been directed to Down syndrome, and we now, you know, of course [inaudible] defects and Trisomy 18, etc. As a practitioner, I see it really just as a test of a red flag that something is going on. The most likely reason is X, if you were, let's say, 35 or over. So, when we counsel such patients, they will want to avoid an invasive procedure and accept a limited yet more if you will specific, I'm gonna use these words loosely. 'Cuz, clearly you have a 36-year-old who goes through

screening and it's screen positive. Her a priori risk grade is going to be... if you screen positive for Down syndrome, her a priori risk is greatest for Down syndrome. So, if she wants to avoid an amniocentesis, then the counseling becomes, okay. You can choose this, cell-free DNA, and it will only limit you to this information about these three chromosomes, but you theoretically are at risk for other things other cytogenetic aneuploidies if you will, but you will only get that information if you have an amniocentesis. So, these are the nuances in the level of counseling. You know, the thing is, it's unusual, but every once in a while, we will get a patient who goes through cell-free DNA and says, I changed my mind and now I want an amnio. It's rare, but this is what we face in clinic.

Sheila Rege: Thank you. So, let's direct questions for Dr. Johnson, and then we'll have time to discuss among ourselves also.

Mika Sinanan: So, your recommendation would apply to PEBB, SEB, and Medicaid, which would change the current policy.

Shana Johnson: Yeah.

Mika Sinanan: It would remove the now general obstetric population from PEBB.

Shana Johnson: That's correct.

Mika Sinanan: So, that's potential blowback.

Shana Johnson: Yes, and I'm glad it's your decision.

Sheila Rege: That's why, Mika, we have to look at what our evidence expert presents, because that's our charge is to come up with recommendations. This is the agency's initial recommendation. We will go through the process. Any other questions for Dr. Johnson.

Janna Friedly: On slide 16 under the test performance where the data that you present shows up to 6 out of 1000 unaffected undergo unnecessary invasive testing for cell-free DNA versus 44 in 1000. Can you... or do you know A) what the cost of that difference is, you know, in terms of unnecessary invasive testing, at least monetary cost.

Shana Johnson: I think amniocentesis, when you take into account the facility fee and the test, it's about $1000. So, $38,000 less of amniocentesis.

Janna Friedly: Okay, and then presuming that that data is people who get conventional screening and then go directly to unnecessary, potentially unnecessary invasive testing not taking into consideration the pathway of conventional screening to cell-free DNA. Does that make sense?

Sheila Rege: Do you want to repeat that second question. I'm sorry.

Shana Johnson: Yeah. The second question part.

Janna Friedly: So, if this is 44 in 1000 who undergo conventional screening, undergo unnecessary invasive testing, was that data using a pathway of conventional screening directly to amnio...

Shana Johnson: Yes.

Janna Friedly: ...or conventional screening to cell-free DNA and then to amnio, and it still, by going through that pathway, you still...

Shana Johnson: No.

Janna Friedly: ...end up with additional unnecessary...

Shana Johnson: This is not contingent. This data does not come from contingency testing, which is kind of what our recommendation is.

Janna Friedly: Mm-hmm.

Shana Johnson: No. This is... and actually, the evidence vendor will actually go into this detail a lot more.

Janna Friedly: Okay.

Shana Johnson: But yeah. This is straight conventional screening, no cell-free DNA is part of the picture.

Janna Friedly: Thank you.

John Bramhall: Can I ask you two questions. Again, it's my ignorance again. What is conventional screening? Does it involve blood work?

Shana Johnson: So, conventional screening, I'll have our expert make sure I get this right is typically the triple screen and the first trimester ultrasound, or the quad screen.

Edith Cheng: Technically, the triple screen really doesn't exist anymore. We went away from the triple screen many decades ago. So, conventional screening has different options. So, the blue plate special, if you will, is that you come in, in the first trimester, between 11 and 13 weeks and get a first trimester ultrasound with a nuchal translucency. You have your blood drawn. Then, you wait at 16 weeks, and you get your blood drawn again, which is "your quad screen." Then, you combine all of your observations, likelihood ratios between the two testings. So, it's called an integrated screen. So, that is the blue plate special. Then if that

comes out positive, then you would then be counseled and offered genetic amniocentesis. That would be what we would do. In the old days, before cell-free DNA, a second part of conventional screening is something called a first trimester only. So, you would come in, get your ultrasound, get an NT, get your blood drawn, and it would then calculate an odds ratio. If it was elevated, then you would be counseled and offered invasive testing. At that timeframe, it generally is a chorionic villa sampling. So, then there are different nuances above, but that's really the principal of genetic screening.

John Bramhall: And the blood work is looking for aneuploidies, one of the observations is whether or not aneuploidies is present in that conventional screening bloodwork. Is that right?

Edith Cheng: Yes.

John Bramhall: Okay.

Edith Cheng: The blood work is to measure certain proteins and given their levels, we do a calculation and develop a likelihood ratio.

John Bramhall: Right. And at this time, I'm baffled by your slide on the cost-effectiveness. We've dealt with this before, I know. You have it slide, I don't know what number it is. ICER dependent on the perspective...

Sheila Rege: What number is it on yours?

John Bramhall: ...yeah. So, I'm... can you just flash that up a little. It looks to me like there's a societal cost of negative, and then there's this payer cost-effectiveness of a positive number, and I am not certain why one wouldn't simply look at the societal cost. Why is the payer cost-effectiveness relevant?

Shana Johnson: Well, I think this is an interesting slide that showed the cost-effectiveness data based on perspective. Let's say, you know, most private payers, well I shouldn't assume, but...

Sheila Rege: It comes from a paper, John. It's from a paper.

John Bramhall: Yeah. I know. I get that, but so... I just don't understand it. So, the...

Shana Johnson: Well, I think...

John Bramhall: ...payer, the payer cost-effectiveness would be then whether... some influence on the total cost of the payer of whether or not this test was done or not. Is that where we're going? So, you don't do a test, and as a result no cost to the payer. Or you do a test, and there's a cost reduction for the payer.

Shana Johnson: ...this is a good question.

John Bramhall: And I'm sorry to get in the weeds here, but it's just, I'm just struck by that, the societal benefit seems to be there, and the payer benefit seems not to be there. That's all.

Sheila Rege: That's a good question. Maybe we could have that question answered during our evidence review. We could hold on, and you'll remember that question?

John Bramhall: I will remember it.

Austin McMillin: To get into the weeds with you, I think that looking at cost-effectiveness data is not really representative if we're not also factoring in people moving on, or pregnancies moving onto unnecessary procedures. So, that looks like a factor of eight comparatively. I don't know if that, if this data factors that in.

Sheila Rege: I think we'll get in the weeds after we hear the public comments and the evidence report, if that's acceptable to everybody. Dr. Johnson is not responsible for the evidence. So, let's not shoot her out there. She's just putting up slides for us.

Austin McMillin: I just didn't want you to feel alone in the weeds, John.

Sheila Rege: Any other questions for Dr. Johnson before we move onto open public comment? You got away with it. Thank you, very much, Dr. Johnson. We actually are good. We are 9:25. If it's okay, we can open it up to scheduled and open public comment.

Josh Morse: So, we have one speaker signed up in advance. Daniel Grosu and he will go first. And then, we will check for who is signed up here, and then we'll check the phone.

Sheila Rege: Dr. Grosu, if you would, uh, come up and we really appreciate your making the time. We would appreciate your keeping your remarks to three minutes, and if you could begin by... is that good or?

Josh Morse: We actually had a discussion a little earlier, and we'll go with four minutes if that's okay.

Sheila Rege: Four minutes, if there's no objection from the rest of the committee. And if you could start with your name, conflicts, and disclose if anybody has paid for your travel or time here.

Daniel Grosu: My name is Dr. Daniel Grosu. I used to be a chief medical officer of Illumina and a chief medical officer of Sequenom. I am currently medical director on a very part-time basis for the Coalition for Access to Prenatal Screening, which is a

coalition of six different laboratories and somebody there paid for my travel, or will pay when I submit the report.

Sheila Rege: Thank you, very much, and do you have slides you want projected?

Daniel Grosu: I do. I hope they will come up on the board.

Sheila Rege: Dr. Grosu, where did you come in from, if I can ask? Hopefully, you didn't have travel problems like I personally had some snow issues and stuff.

Daniel Grosu: I flew in from San Diego.

Sheila Rege: Okay. So, you're okay.

Daniel Grosu: I will not comment further, because I don't want to antagonize everybody before I even begin speaking. It was tough, but I made it to be here with you.

Sheila Rege: Thank you.

Daniel Grosu: Thank you, all. So, I will go quick. These are my conflicts and my background. The key takeaways from our point of view are that cell-free DNA is increasingly utilized across all pregnancy risk groups. Cell-free DNA has been extensively studied in the general population, over 15 studies over 80,000 patients, and has a very high PPV compared to traditional screening or standard screening. It provides better detection of the core trisomies and I would say also more recently for many other trisomies and sex chromosome aneuploidies leading to far fewer invasive procedures and procedure related losses. All the major professional societies either endorse or recognize cell-free DNA as medically and clinically appropriate. There is the clear disparity in access to NIPS coverage for many women enrolled in Washington State Medicaid.

So, when you choose the right screening test, as we learned earlier, it's important to look at false positives and false negatives. The impact of false negative is obviously missed diagnosis. You may be unprepared for the birth of a baby with special needs, missed opportunity for specialized care, and there may be also some medical legal risk for a provider. So, in that context, I would point out that the detection rates for NIPS are far higher than the detection rates for standard screening.

But that's not really the reason that cell-free DNA and NIPS were developed. It was developed because many women had unnecessary invasive procedures. This was not to [inaudible] those few positives. Fortunately, most pregnancies are normal. It was to help those women who are concerned that they may have an affected fetus who are screened with very perfect screening methods, and then had a false positive and had to go through the anxiety and the risk of an amniocentesis or CDS. So, that's really where the false positives really come in.

There is anxiety. You have to wait to see a specialist, unnecessary invasive procedures. You have to come back for that. There is a huge societal cost, as was pointed out earlier. When we compare the false positive rates between NIPS and standard screening, there is a factor of 100. So, that is not [inaudible], by the way. Standard screening has 100x the rate of false positives compared to NIPS. The slides 13, 14, and 15 on the previous presentation, we would like an opportunity to discuss in more detail and go back to the source documentation. I found them to be a gross misrepresentation of the data out there, and I do realize these comments are on record. I would welcome the opportunity to again go back to the source data.

Yes, NIPS has better detection compared to standard screening, but again, that's not really the crux of the story. The crux of the story is that there are far fewer false positives leading to fewer invasive procedures, much fewer invasive tests, and these invasive tests have a 1 in 200 to 1 in 1000 risk of pregnancy loss, therefore, the procedure related losses, and most of these are normal pregnancies by the way, are much, much lower with NIPS.

Sheila Rege: We did not count the time we took. So, you'll have to [inaudible].

Daniel Grosu: Ye. I'm, I'm done. So, multiple states have...

Sheila Rege: Thank you.

Daniel Grosu: ...now covered NIPS regardless of risk and our simple ask is to streamline the criteria to read that NIPS, based on cell-free DNA, is medically necessary in all women with singleton pregnancies. This is the current coverage that you know well. We'll just point out that there is a clear disparity in access to prenatal screening for women enrolled.

Sheila Rege: And we have that in our binders. So, thank you for submitting your slides ahead of time.

Daniel Grosu: Thank you.

Sheila Rege: We appreciate it. Any other stakeholders wishing to comment who are present in the room? I think unless you have made special arrangements, we usually allow three minutes. I am going to ask, since Josh has stepped out, can some other committee member do... oh, Josh is here.

Josh Morse: Just grabbing the list.

Sheila Rege: And again, if you would indulge the committee by stating your name, your conflicts and disclose if anybody has paid for your travel or time here, we'd appreciate it. Thank you.

Ashley Svinson: Good morning. My name is Ashley Svinson. I am a fulltime employee of Myriad Genetics. So, I'm here in that capacity today. I practice as a prenatal genetic counselor for over 10 years, and I have been in the field of clinical genetics for almost 20. What I would like to highlight today, we will go over the evidence showing that NIPS is effective in the average population. What I would like to highlight is the provider and patient preference for NIPS. When polled, providers usually say that their number one priority when selecting a testing modality is accuracy. There was a survey done in 2016 of OB/GYN providers to elucidate their opinions about NIPS, and in that 103 respondents who submitted their answers, of those, 92% agreed strongly, or agreed that NIPS was superior to standard screening; 81.5% agreed or strongly agreed that they would offer NIPS to all risk patients if it was reimbursed by insurance. Of the respondents, the majority already had implemented NIPS to some extent in their practice, and of those, almost 90% agreed that the quality of care had improved with introduction of NIPS for the reasons that Dr. Grosu explained, fewer false positives, better detection, fewer invasive procedures, and fewer referrals. The last thing I'll say about providers is that I want to be very clear that, again, ACOG does have a statement that acknowledges that NIPS is appropriate as a firstline test for all risk patients. They also acknowledge that doing NIPS as a second tier test will delay diagnosis. For patients, when polled, their number one priority is usually safety, although timing and accuracy is also important. So, there was a similar survey done on patients, it came out last year. It was done in Canada where they are also looking at this question. Of 882 pregnant women of all risk categories, four out of five women said they would agree that the current paradigm should be replaced by NIPS, as a firstline test. Again, having been a prenatal counselor, this was probably the most common indication I saw patients was abnormal serum screening. I don't want to discount what a burden this anxiety places on a very vulnerable patient. So, going back to the survey of why women chose NIPS as a firstline test. They preferred to have this accurate test that could be done in the first trimester than delaying this process. So, in conclusion, I believe that the evidence is there to support NIPS in the general population. Based on what we discussed earlier, and we'll discuss later, it may or not be more cost-effective. So, I think that it's very important...

Sheila Rege: Thank you. I think that we can start...

Ashley Svinson: ...that we consider patient...

Sheila Rege: ...cutting, I've been...

Ashley Svinson: ...and provider preference.

Sheila Rege: ...I've been a little, yeah. Thank you, very much. We were over time now, and I'm a little concerned, not to indulge the committee as my first time as chair. So, I really appreciate you coming here. I'm sorry we had to cut you off at that

point. I will, for the next one, I will sit back for 30 seconds. So, you have some warning. Any other stakeholder who would like to...

Josh Morse: So, we have... so we need to check the phone.

Sheila Rege: Right, but any other stakeholders here that are present? Okay. So, then we will go to the phone lines. Good morning. Thank you for being here. Anybody on the phone who wishes to speak?

Female: Yes. Hello...

Sheila Rege: And again, if you would start by your name, conflicts and, if anybody is paying for your time, or has asked you to speak. Thank you.

Female: Are you able to hear me now?

Sheila Rege: Yes. We are.

Female: Great. Hi, I am Claire Clark. I am a prenatal genetic counselor with Integrated Genetics, which is a LabCorp specialty group. I live up in Bellingham, Washington, and we're still getting more snow than we can handle up here. So, I'm sorry I couldn't be there today, but I have been seeing patients by telegenetics in Washington and other states for three years now. Before that was a prenatal genetic counselor on site at Eastside Maternal Fetal Medicine in Bellevue. I want to thank you first for considering expanding coverage. I'm proud that our State sees the need for this review, um, I worry that when multiple marker screening, or what we call conventional screening, is presented as a firstline test, some women, especially those in our Medicaid population, who have more difficulty with transportation and childcare barriers can't make it for the multiple appointments that we need in certain timeframes for that screening and don't complete their testing. Others decline it because they fear the undue anxiety from a false positive result, and I have found false positive information is widely spread by word of mouth. So, people are skeptical of screenings. Without that screening, often their first assessment for aneuploidies is at a 20 week ultrasound, and if that then identifies any self-markers or even true anomalies, many then opt for further testing, but because of the later gestational age, it leads to really difficult decision making. Like others have mentioned, invasive testing is done that could have been avoided, if the patient had the option of NIPS or cell-free DNA earlier in pregnancy. For the other women who do have [inaudible] screening and are in the 5% or more with a screen positive result, I usually encounter them a few days after they've been informed of their results. Sometimes, that is at late as 20 weeks' gestation if the second trimester screen was performed. They are distressed, it's obvious, since they've received a call that their pregnancy was an increased risk for Down syndrome or Trisomy 18. They've spent hours imagining the implications of this news and fretted over what decisions they would make. Many then often

pursue NIPT. More often than not, they receive a normal result, and those agonizing weeks were unnecessary. The other sphere is only to take action if a diagnosis is confirmed and don't want to add the extra time for another screening test and again, have invasive testing at an additional cost and risk that was unnecessary. For the rare few that the diagnosis is confirmed, after completing the series of testing, the timeline is extremely tight for them to gather information about the conditions and to consider those pregnancy options. By contract, the patients that have cell-free DNA usually performed at 10 weeks' gestation have this information as much as two months earlier, and because of this, many healthcare providers, including myself, feel we're doing low risk patients a disservice by not widely offering NIPT to get them earlier and more simple and more certain information with ample time for informed decision making.

Sheila Rege: Thank you, very much, and thank you for keeping your comments within three minutes. We will go to others. Hang on just a minute. I'm seeing somebody comment here.

Kevin Walsh: Can we... I would appreciate if Dr. Cheng could offer her perspective on what was just said?

Sheila Rege: But can we hold off until we...

Kevin Walsh: Please.

Sheila Rege: ...in case there are other public comments, and then after that, if that's Okay. Any other public comments? In case somebody stepped away from a patient or something and is...

Ken Schneider: Yes. This is Dr. Ken Schneider. I'm with Tri-Cities Community Health in Richland, Pasco, Kennewick, Washington.

Sheila Rege: Welcome. Thank you for stating your name, any conflicts, and if anybody is paying for your time here, and if you could limit your...

Ken Schneider: Yeah. Nobody is paying for my time.

Sheila Rege: ...to three minutes.

Ken Schneider: Yes, I am away from patients at this time, but I just wanted to throw in my comments in that I am definitely in favor of early testing. I think it saves us scheduling conflicts. The earlier that we can schedule our patients with maternal fetal medicine and genetic counselors, the better, especially with the population that I serve. It is underserved and mostly underrepresented in the genetic database. Back in the early '90s, I did research on the human genome project. Mostly back then, it was the Caucasian database. Now, with widespread

screening, we are increasing the database significantly with underrepresented populations. I think it just adds to our wealth of knowledge of genetic screening and the services that we can offer our patients.

Sheila Rege: Thank you. Thank you, very much. Thank you for taking the time. I know it's difficult to schedule time when you're seeing patients. If we could see if there's anybody else who wishes to publicly comment. Then, we will...

Kimberly Martin: Hello?

Sheila Rege: Yes.

Kimberly Martin: Hello. My name is Dr. Kimberly Martin. I'm actually a board certified OB/GYN and clinical geneticist. I was a fellow in Vancouver, British Columbia and a contemporary of Dr. Cheng. I left practicing maternal fetal medicine in the United States for over 20 years and retired after four years in industry, I do remain employed as a consultant at Natera, but I don't plan on billing for the time I'm spending during my retirement, because I feel so passionate about this issue about Adrift. If you had told me four years ago I would have be having to still advocate for all women to have the option for first trimester NIPT, I would have told you, you were crazy. I echo the recent providers' comments. There are many, many, many women who work and live in communities where they do not have access. What Dr. Cheng omitted was that not only is the conventional test screen include a first trimester nuchal translucency, that nuchal translucency is to be performed by a certified provider. I routinely saw women during my 15 years on faculty in St. Louis who had driven over two hours each way from Rowland, Missouri, because they did not have a certified NIPT provider in their region. They wanted the best possible screening. That best possible screening is now available. It's a single blood test that can be given at the time of a routine OB/GYN visit. I'm happy to provide you with a PDF of a study from midwifery in the UK. Minschitty [sounds like] is one of the authors. It addressed direct costs to women associated with various screening and diagnostic paradigm. Not surprisingly, the most expensive to women and their partners was invasive prenatal diagnosis. The next most expensive was a combination of serum screening with a reflexed NT. The next most expensive was serum screening. The least expensive in time and cost is NIPT. I strongly encourage a review of the data that was presented by the public slide set, which I appreciate having an opportunity to review. The data specifically related to the next study, which was funded by the NIH, a lead journal article in the New England Journal of Medicine is grossly misrepresented and listed as poor quality evidence. I thank the committee very much for the time that you've allowed me to speak. Thank you.

Sheila Rege: Thank you for making the time. We appreciate it. We'll still stay with public comments. And we will have review of the evidence coming up. Any more public comments, either from people on site or on the phones? Okay. Then we can close... is there somebody else there? No? Okay. We can close public

comments. I don't know if we can close it. It's a little early. So, I want to... maybe you can keep it open while Dr. Cheng has a chance to answer a question that came up from Kevin. Would you like to...

Edith Cheng: I think, at the end of the day, it's a shift in paradigm having started prenatal diagnosis in 1977 here at University of Washington as a genetics counselor. It's a shift in algorithm and paradigms in prenatal screening for women for aneuploidies. I think from my personal experience is that the hiccups really are patient education and physician education, and setting appropriate expectations so that a patient understands that this is still a screening test for a limited number of chromosome abnormalities, which is 13, 18, 21 right now, and your sex chromosome aneuploidies. That it is not that my baby is normal. So that when you get your 18-week anatomy scan and there are anomalies, that there is a, oh, my gosh, but you just, you did this test on me at 10 weeks, and you told me that my baby was genetically normal. So, I think that it all has to do with appropriate pre-test counseling at the level of the physician who provides that test and the patient that accepts that test. That is overwhelmingly... so that's the first thing. I think that what I'm seeing in the community is that we sometimes forget that other screening tests that we're supposed to have, which you can argue is maybe still archaic, now archaic because of ultrasound, but I do run into situations where the MSAFP is not done, and I'm out in the community. I am all over the state of Washington. So, I cover every socioeconomic community in the state of Washington. So, we miss that MSAFP. I mean, I just recently had a patient in whom this was a 20-week ultrasound, because the MSAFP wasn't done, because there was a cell-free DNA that was done. The baby was normal, and we had a whopping neural tube defect, at 21 weeks. So, at the end of the day, whatever decision we make, it has to be coupled with appropriate physician and patient education and expectations about what this test provides and what this test does not provide, because when we talk about, you know, cost-effectiveness, if the understanding is not up front, appropriate, and follow-up still prenatal care, you're still gonna lose the money that you potentially gained as a State in offering cell-free DNA to everyone, because we have to backtrack and order additional tests to kind of clarify what happened with the cell-free DNA, because of incomplete counseling and incomplete expectations.

Sheila Rege: Thank you, Dr. Cheng. Any other public comments on the phone? Or otherwise, we're gonna close the phone. Yes?

Kimberly Martin: Yes. This is Dr. Kim Martin. Could I have 30 seconds to respond to Dr. Cheng?

Sheila Rege: I am going to look around the committee. That is a little unusual. So, I am seeing no, but what I would like is, if you could email any comments for the committee to consider, as part of our process, we would definitely be looking at that. So, thank you. At this point, we're going to...

Kimberly Martin: What is the email?

Sheila Rege: It is on the website. If you could go to the website. The Health Technology Clinical Committee website, it is on there. Now, I'm going to have us go break while we transition to the evidence report. So, again, I encourage all of us to stretch.

Austin McMillin: I have one, I think, brief question for Dr. Cheng. Given the fact that you were recommending tying education to the procedure, are you a proponent of just having that left up to the individual provider or counselor? Or a proponent of having specific talking points to go with the testing.

Sheila Rege: Maybe we should... you're looking for, I think, going back in the weeds. Let's wait until we have the evidence, and then this will part of the committee discussion if that's... I just don't wanna keep going. Okay.

Edith Cheng: One more thing is. I just want to be clear. I don't know that it was said. I am just a content expert here. I am not a voting member in this decision making. So, I'm here really to answer questions from many different perspectives.

Sheila Rege: We really... it's an interesting and important perspective based on your clinical experience that we don't have. So, we appreciate that, but let's go ahead and transition. I would encourage everybody, including the stakeholders and the agency, to do some standing or stretching while we change slide sets.

If we could start with the evidence report. I know Dr. King, we don't need an introduction, but if you would indulge us by introducing yourself. Thank you, again, for doing this.

Valerie King: Hello. I am Dr. Valerie King. I am a family physician preventive medicine physician professor at Oregon Health and Science University and director of research at the Center for Evidence Based Policy, who are your evidence vendors. In addition, I am a women health's specialist, and I provide antenatal care and take care of moms and babies in the hospital. So, I'm personally interested in this field.

So, on this particular evidence report, we're going to start with a bit of background, a tiny bit of methods, and then we're going to go into a summary of the findings. This is quite brief compared to the entire report. I've only got about 35 slides, but what we've done is segmented these slides so that we can drill down if you have more specific questions at any point. A lot of the information about test performance really is same song, second verse, looking at the various aneuploidies. So, because it's so similar, we're just going to do a high level summary. We'll take your questions and then do those detailed results.

So, I think as you already know, prenatal screening is really part of what's offered, as standard prenatal care. It can include a range of tests and procedures, like, ultrasound, first trimester screening. Dr. Cheng went over already. It typically is that integrated screen that combines some serum testing with ultrasound results. Then, it can be combined or even started in the second trimester with ultrasound and different types of serum screening.

I think the important thing to know here is that all of the tests that we're talking about today really are screening tests. They are not diagnostic. No one suggests moving, making an irreversible decision about the pregnancy based on a screening test alone.

So, what does that positive screening test mean? It really indicates that the fetus is at a higher than average, or higher than expected risk of having a disorder compared to the population, but it, again, does not definitively diagnose that disorder. A negative screening test, conversely just says that the fetus is at a less than expected risk of having that disorder.

Screening for this common aneuploidies that we're talking about today really involves the risk of a fetus having an extra or missing copy of a chromosome. When that chromosome is the 21st one, it's called Down syndrome. Edward Syndrome is Trisomy 18. Patau Syndrome is Trisomy 13. There are also missing or extra copies of sex chromosome, either the X or Y chromosome, and there are many, many, many of those. The most common that you will have heard of are Klinefelter syndrome, which is 47XXY, and Turner syndrome, which is 45X, or monosomy X. Down syndrome is the most common of these, effecting about 1 in 800 live births. Edward syndrome, very uncommon, 1 in 5000. Patau syndrome is even less common at about 1 in 16,000 live births. The prevalence does vary, but so does the impact. So, for example, infants who are affected with Down syndrome have an average lifespan that's been estimated in the upper 40s and has been increasing and may be high as 60 now with good care. For Edward syndrome, or Trisomy 18, those children seldom live past their first year of life. With Patau syndrome, although those children can live for about a year, they typically do die within the first couple of weeks after birth, if they survive to that point.

Cell-free DNA testing is a type of NIPT or noninvasive prenatal testing or screening, NIPS. It does help to determine risk about whether the fetus has certain cytogenetic abnormalities that we're talking about today. It's noninvasive compared to traditional testing methods that include amniocentesis or chorionic villa sampling. It does analyze fragments of DNA that are in the maternal blood. It's a little bit of a misnomer to call it fetal, because it fetal, because it really comes from the placenta. In embryonic development, those are usually the same cell lines, but sometimes there can be differences. The placenta can be made up of a variety of other cells, as can the fetus. So, this is

part of why it's not a perfect test. It's not always exactly what the fetus has. So, it's not 100%.

As you've heard already today, cell-free DNA is covered by most commercial and public insurance plans for women who are at higher than average risk. Some insurance companies, including those in Washington, do cover it for general populations. Clinical practice guidelines vary across the world. Questions still remain. So, this topic was selected.

Just in terms of methods and things that I want you to know are that the population that we looked for studies for was the general obstetric population. We accepted studies that had mixed risk populations, but only if they presented the risks separately for high and low risk women. We were looking for screening using cell-free DNA for those trisomies. We essentially accepted any comparator that was out there. We looked for outcomes that had to do with pregnancy outcomes, what happened in terms of how people used the results of the test, the uptake of the test, quality of life outcomes, safety related to direct harms of the test, and indirect outcomes are really mostly what was reported. Those are measures of test screening performance. We also looked for economic outcomes with cost-effectiveness types of studies. We had four key questions that dealt with the efficacy or effectiveness of the test, the direct harms of the test, anything that we could find on subgroups related to the test, such as maternal characteristics by age, by whether it was a singleton or multifetal pregnancy and when the screening was done. Then, we finally looked for cost-effectiveness and other economic outcomes.

In terms of the studies that we looked for, for each of these key questions, for key questions, all of them, we accepted randomized controlled trials, systematic reviews of those trials, and nonrandomized but comparative studies. For the harms questions, we looked at nonrandomized studies that did not have a comparator, as long as they had ten or more participants in the study. Then, for key question four, we additionally looked for cost-effectiveness modeling and other studies.

We looked across a range of evidence sources, and we searched from 2007 on. That was the date of the first research paper on cell-free DNA, up through July of 2019. A lot of the evidence really came out of the Ovid Medline search, but we looked for all kinds of other things, as well. What you'll see here, in very small print, is that we looked at 2104 unduplicated records and ultimately came down to 18 studies that were... 18 individual studies that were reported across 20 papers. There was 1 randomized control trial, 9 test accuracy studies, and 8 economic studies. We also identified 13 relevant clinical practice guidelines.

We did grade rating of the outcomes. Just to remind you, a high certainty of evidence means that we're quite confident that that estimate is probably true

for the outcome. At very low, we're not very confident that the study estimate represents the true outcome.

Dr. Johnson went over this some, but what you'll see highlighted in the yellow, going from the sensitivity, specificity, false positive and negative rates, and positive and negative predictive value. We've just highlighted the three in yellow that we think are the ones probably to pay most attention to. The false positive rate is important. It's the percentage of screening tests that are incorrectly positive within the population. The reason that's important is that those people then will go on to be referred for a diagnostic test. The false negative rate is important, because you don't want to get this wrong. If somebody is signing up for screening, you would like to get them the best advice that you can. Then, positive predictive value is just a really helpful statistic that says, if you had a positive test, what's the actual probability that that can condition is present, but we'll variously talking about all of these measures.

So, I'm going to start the actual results of our evidence review starting with effectiveness and harms, then looking at measures of test performance, and then finally cost-effectiveness.

So, for effectiveness and harms based on primarily the one randomized control trial, we looked at the reported outcome of the false positive rate for Trisomy 21. Cell-free DNA screening did have a lower false positive screening rate than conventional first trimester screening. Our certainty of evidence on this was low, downgraded for risk of bias and imprecision meaning wide confidence intervals. On test failures, based on this one randomized control trial, 8 cohort studies and an additional case control study. We have very low certainty of evidence that cell-free DNA test failure rates might be somewhere between 0.9 and 8.5%. We do think that they're in that range, but exactly where they are in that range, we're not so sure about. Looking at the outcome that I think you're all very concerned about, invasive testing, based on the randomized control trial, about 1.7% of women in the first trimester screen group, the comparator group, and about 0.3% of women in the cell-free DNA group, and that was a group that also had ultrasound, opted for invasive testing. So, there were more that were referred or could possibly have had invasive testing, but that was the actual uptake of invasive testing. We have low certainty of evidence there. Looking at two cohort studies that also reported invasive testing, about 3000 women, cell-free DNA in those studies was associated with lower rates of invasive testing.

You've seen a version of this slide presented by Dr. Johnson, and we have detailed slides for each of the trisomies, again, but what I'm going to do in this summary is just give you the overall for these three trisomies. You're not going to pick up one or the other when you order the test. You're going to get a report that gives you all of them together clinically. So, I think this is probably the most relevant piece of information for you. The median prevalence of these three

trisomies across these studies added together was about 6 per 1000 individuals. Most women with a positive cell-free DNA or conventional screening test really don't have an affected fetus, but do have an affected fetus, but some do not. In determining whether or not the fetus is affected requires the diagnostic test, either amniocentesis or chorionic villa sampling. So, cell-free DNA would be expected to miss no cases, and up to 6 of 1000 unaffected pregnant women would be referred to have an ultimately unnecessary invasive test. Conventional screening would be expected to miss 1 case of 1000, and 44 in 1000 women with unaffected pregnancies would be referred to ultimately undergo an invasive test. The median positive predictive value for the cell-free DNA test was just about 80%, although it ranged quite broadly from 40% to 100%. That is compared with a number that is just under 30% for conventional screening.

In tabular form, what I want you to see here is, we're presenting the sensitivity, or true positives, false negatives, specificity, or true negatives and false positives by prevalence. The column in the middle, the one that starts 5 to 6, 0 to 1, is the median. The column to the left of that is the lowest prevalence study. The column to the right is the highest prevalence study. The next column over gives you the number of participants and the number of studies. Then, our certainty of evidence grade rating, and the rationale for that rating. So, what we've talked about, and what you should see is that as the prevalence increases, the true positive rate goes up. It should, and you'll see that the true negative rate goes down very slightly. [inaudible] false rates, the false negative and false positive rates really don't shift very much. This will come, again, as we talk about positive predictive value, because it's really related to this concept of prevalence.

This is a similar table looking at conventional screening. On the left, you'll see we've got the low prevalence, or the median prevalence studies, and then the high prevalence studies. So, you'll see that the true positives go from 6 to 17. The true negatives go from slightly down from 950 to 939. The false positive and false negative rates really don't shift very much. They stay at 0 or 44 respectively. The information here comes from a particular study that just under 3000 women in it. We had moderate certainty of evidence about these findings.

Then, if we look further at the screening test performance, looking and comparing the positive predictive value and the negative predictive value, on the top looking at cell-free DNA screening, at the bottom looking at conventional screening, this is where we get the positive predictive value for cell-free DNA being about 80%, and for conventional screening being just under 30%. The positive predictive value for cell-free DNA, we have low certainty... very low certainty of evidence for, this is a little bit an artifact of the grade system, but we downgraded one level for each... for risk of bias, and there was inconsistency with different, quite wide confidence intervals, different results across studies, and imprecision with those wide confidence intervals, but most of the inconsistency was with one particular study that was on one particular brand of

test. It was the only study on that test. So, I this is a little bit of an artifact having to do with that particular study. What you'll see is that we're quite confident about the sensitivity and specificity. It's just, when you then take those figures on to compute a positive predictive value, that may shift a little bit. On conventional screening, we had moderate certainty of evidence, and we're just downgrading one level for risk of bias.

Mika Sinanan: I just want to make sure I understood that last point on positive predictive value. Your comment is that you think that it's been assigned a very low accuracy because of the effect of that one study that you quoted. Is that right?

Valerie King: It's three factors. So, I think that one study really contributes to it, because it's the one study that had 40% positive predictive value. There were other studies that had quite a bit higher positive predictive value. So, the average is really dragged down by that one particular study. Okay?

Mika Sinanan: Thank you.

Valerie King: But there were other issues. There really were wide confidence intervals. There was some risk of bias. So, it may just not be quite as bad as very low. Okay?

When we looked at subgroups, we first were able to find evidence to do with multifetal or twin pregnancies. No higher order gestations beyond twins. Those pregnancies do carry higher risk for aneuploidy, and we would expect about 52 out of 1000 pregnancies would be effected. Cell-free DNA would be expected to miss 5 cases. That ranged from none to 23 with low quality evidence. No effected pregnant women, and that ranged from 0 to 19, would ultimately undergo unnecessary invasive testing. The positive predictive value of cell-free DNA was 100%, moderate quality of evidence, but again, this is all based on one study.

This is that information in tabular form. So, you'll see the positive predictive value around 100% based on that one study, and a negative predictive value also very high at 99.5%.

Moving on to sex chromosome aneuploidies, among these studies, we found that about 4 out of 1000 pregnancies would be expected to be effected. Cell-free DNA testing would be expected to miss no cases. That ranged from 0 to 3. No unaffected pregnant women, ranging from 0 to 8, would ultimately undergo unnecessary invasive testing. There is very low quality of evidence. This is all based on one particular study, but the positive predictive value in that one study was 100%.

So, for sex chromosome aneuploidies, what you see in tabular form is very low certainty of evidence around the basic test parameters for cell-free DNA, but

then at the bottom quite high positive and negative predictive value at 100% each. This is one study of just over 400 people.

Tony Yen: Do you have any comparison what the twin studies and the sex chromosome aneuploidies with conventional screening at all?

Valerie King: Yes. None of them were comparative in that way.

Tony Yen: Okay.

Valerie King: Moving onto cost-effectiveness screening, there were two types of studies. So, the predominant, and seven of these economic studies were modeling studies. They typically would do things like have a theoretical cohort of a million women and make predictions based on that cohort of normal risk women. There was one actual study that came out of an urban center that reported economic outcomes of just under 600 women. So, based simply on the modeling studies, they showed that cell-free DNA was more effective than conventional screening in the first trimester, but could be more costly. We have low certainly certainty of evidence on that. The one individual study also found that cell-free DNA was more effective than conventional screening, but it could be more costly, depending on the cost of the test itself, but we had very low certainty of evidence.

You've seen a portion of this slide in Dr. Johnson's material. If you look at the top of the slide on this quadrant graph, you will see everything toward the top says that screening is more costly. Everything toward the bottom says that it is less costly than conventional. If you go to the left, it says that cell-free DNA is less effective. If you go to the right, it's more effective than conventional screening. Then, there's some color coding here. So, if the study name is marked in green, that says that it was a good methodological quality modeling study. If it's orange, it's somewhere in the middle. If it's red, it was a poor methodological quality study.

What you'll see is that there, the study on the upper left hand quadrant, come on, is represented in both that and the quadrant just to the right of it. That's because they subsegmented their results. The one to the left is for women ages 20 to 38. Then, to the right, it was women who were over age 38. So, two different groups that were reported. In the upper left hand quadrant for women 20 to 38, Kamal found that the test was both most costly and less effective. Then, to the right, you'll see that there were four studies that judged the test to be more effective, but more costly than conventional screening. Then, five studies in the lower right hand quadrant that found that the test is more effective and less costly, but again, I want to reiterate what Dr. Johnson said, that these estimates are really dependent upon things like the cost of the test, the uptake of the test, what people do with the test results, what other procedures might be required, and also had to do with the perspective. Is it just

the payer? Or is it all society, and the timeframe. Are we talking about this pregnancy, the next nine months? Or are we talking about the lifespan of an affected child?

So, we did find 13 clinical practice guidelines. These were really from all over the world. Two of the 13 were of good methodologic quality. The first was from New Zealand. Both their genetic society and their OB/GYN society, they recommend the use of the test. The NHS guideline, on the other hand, deferred universal use until the impact of the method's adoption could be explored, and this largely had to do with infrastructure and systems issues around whether or not the test represented good value for money, and whether there was able to be the provision of adequate genetic counseling provided with the test. One of the 13 was a fair methodologic quality. This was a Canadian guideline. It did recommend the use of primary cell-free DNA screening where it was available, but that guideline recognized that the test might not be able to be funded in all provinces across Canada. The other of the 13, the 10, were of poor methodologic quality. None of the 13 guidelines, however, regardless of quality, recommended the use of cell-free DNA screening for sex chromosome aneuploidies, although some of them permissive and say that women could be made aware of the option.

In terms of payer policies, you've already heard this from Dr. Johnson. There is no relevant Medicare, either national or local coverage decision, perhaps not surprisingly, but for the other private payers that are relevant in Washington, Aetna was restricting the test use to women known to be at high risk. CIGNA covered for all. Both Aetna and CIGNA considered the use of cell-free DNA to be experimental and investigational for multifetal pregnancies. I think Dr. Johnson was able to get better information from Regence than we were, despite many phone calls to their provider line. So, I would trust her information that it is universally covered. Then, none of these payers considered cell-free DNA to be appropriate for sex chromosome aneuploidies.

Looking at clinical trials databases about ongoing studies, we were shocked to find that there really is only one randomized trial out there. It's the Pegasus 2 study. It's due to be completed about a year from now, or two years from now. They are trying to enroll 10,000 women with singleton pregnancies only. They are comparing using cell-free DNA as a first tier test, universal screening versus a second tier approach, which is really what your medical directors have recommended. So, that would be the use of the test after a positive conventional screen. So, I wish we had this particular study right now, but we don't, but it is coming.

Mika Sinanan: Do the guidelines for high risk pregnancy, or the definition, is that a standard definition that everybody accepts? Or does it vary by study?

Valerie King: It could vary a bit by study, but not very much. So, it had to do usually with things like advanced maternal age, but where that cut off was sometimes varied a little bit. So, it was usually 35 to 38 years of age. Certainly, women who had a prior effected pregnancy were known to be translocation, balance translocation carriers, had family histories that were concerning, or had other testing, so an abnormal ultrasound or an ab serum screen. So, that was fairly consistent across studies. They might have just varied a little bit on maternal age, was basically where it changed.

Mika Sinanan: Thank you.

Valerie King: So, what we found is that universal screening with cell-free DNA is more accurate than conventional screening in terms of picking up cases and positive predictive value. It's likely to be more expensive than conventional screening, but it does depend on not only the cost of the test, but all sorts of other inputs into the system that policymakers like you get to decide whether or not it represents value for money. I don't envy you there. Economic modeling studies really do suggest that it can be cost-effective, but probably when you're considering a societal perspective, and probably when inputs are on the lower end.

The references based on the slides are really key to the reference numbers in the report, itself. I'm happy to drill down anywhere along the line with additional more detailed questions.

Seth Schwartz: I'm trying to understand the information related to the twin pregnancies, or multiple pregnancies and where this test fits in that setting. Certainly, it's not quite as precise or as sensitive as it is under single pregnancies, but I'm trying to understand, relative to what is conventional testing for these patients, how is this test viewed. I would welcome any comments about that, just some context for that.

Valerie King: Dr. Cheng may want to comment on this, as well. So, we know that multifetal pregnancies are at higher risk than singleton pregnancies for all of the trisomies. Additionally, we know that different fetuses in a multifetal pregnancy may be affected or not affected. So, you could have twins where one was affected and one wasn't. That feature kind of screws up the test, because, you'll get a reading that might be relative to one fetus and not accurate for the other. So, you still end up needing to do invasive testing.

Edith Cheng: Yes, because you're just blasting the maternal, because what you're doing... remember that this is placental DNA. Placental DNA is a surrogate for fetal DNA. So, if you've got a twin gestation, you just have DNA blasting into the maternal system.

Seth Schwartz: I think I understand that. I guess my question is more, what are we currently doing? How is this test viewed in that circumstance?

Edith Cheng: I think that it has been program MFM program dependent. I know at the University of Washington, we do counsel our patients and inform them that there are labs and there are other centers that are offering them, but there are caveats involved, because of that. They can choose to go down that pathway. There are other MFM programs who feel comfortable, but I think that everybody is getting counseled appropriately about the nuance of twin gestation cell-free DNA testing and accepting or not accepting. The same is kind of true for serum screening, too, for twin gestation. It's good, but it's not as good as a singleton.

Sheila Rege: Would that qualify as low risk or high risk?

Valerie King: We're talking low risk today.

Sheila Rege: So, is that even in our scope, as I ask the evidence expert or?

Valerie King: We're really talking about average or low risk singleton pregnancies.

Sheila Rege: So, we're not, I don't think we're discussing... we don't have to discuss that unless you want to go that route.

Tony Yen: I have a question for you about how you calculated the positive predictive value. I think it's on slide 22. It's the top of the table. I think there was a prior question about this from another committee member. Is that the Bianchi study that you're referring to that's pulled down the positive predictive value?

Valerie King: No. It's the Ashoor study.

Tony Yen: Ashoor study? Hmm.

Sheila Rege: Would you like us to delve into that study?

Tony Yen: I was trying to reference the literature over here on the full evidence report. I'm just trying to understand why the positive predictive value has very low accuracy. That's all. It seems to be attributed... I think your comments before were that it was attributed to one of the studies was actually substantially lower than the other studies.

Valerie King: So, there ends up being this, I'm sorry. There, it was the Bianchi study.

Tony Yen: Yeah.

Valerie King: It's a different test is one feature that I think you'll see. So, most of these studies, the vast majority used the Roche test called Harmony. Bianchi used a

test produced by Illumina called Verify. So, that... I can't see whether or not that one test is better or worse. I can only tell you that it did have somewhat different test characteristics that we pulled out. I think it does influence the width of the confidence interval that you see when you pool those.

Tony Yen: Thank you. That's help, because when I look at the larger table, the positive predictive values are... they seem to be quite a bit higher. Maybe the range would be 75 to 86%.

Valerie King: Yeah. That's why I think it's a bit of an artifact of the grade system getting there. Because I think the sensitivity and specificity that you see across these studies is actually quite consistent.

Tony Yen: Thank you.

Janna Friedly: Is that particular test used in clinical practice? Or is that...

Valerie King: It's different methodology. It's just a different platform. The other thing I'll say is that these tests can shift every few... the actual specific black box of the test, companies are always trying to improve its performance. So, any one published study is a slice in time. It may not represent the current test.

Edith Cheng: I think that's a really important point for the committee to understand. Probably on a six-month basis, everybody is fine tuning the platforms. So, remember, this is a 2014 paper. In the world of cell-free DNA, 2014 is the dinosaur age. So, that platform is kind of nonexistent anymore. Right?

Valerie King: It's the limitation of an evidence review.

Edith Cheng: This committee is being asked to make some decisions based on technology that is moving forward, as we speak.

Janna Friedly: Presumably, all of these are going to be getting better and better.

Edith Cheng: They're going to get better and better. Yes.

Janna Friedly: Over time. So, this is the minimum.

Edith Cheng: Correct.

John Bramhall: Can I ask you a question about slide 19. That's just for your memory. It's the test performance. That's a slide that you state the conventional screening will give you a false positive. You've got a number on the slide of 44 per 1000. Do you recall the slide?

Valerie King: Yeah.

John Bramhall: So, the essence is that you are stating that the data shows that there is a false positive rate, which is pretty high, with conventional screening and reasonably low with the cell-free test. My question is, with conventional screening, does the result come out with specificity, for example, about Trisomy 21. Would the conventional screen say, you have Trisomy 21, which is a false positive result? Or does it say there is something wrong?

Valerie King: It tends to say there's something wrong.

John Bramhall: There's something wrong. So, really, my secondary question was then, it looked like with a false positive on conventional testing, you would then go for invasive testing, as opposed to going to the cell-free test, as a second line test, because you don't know whether it's an aneuploidy that's at fault here.

Valerie King: Yeah. So, with contingent testing, which is not something we explored in this particular review, you would go from a high risk result on conventional to a cell-free DNA test to specify, hopefully, that risk a little bit better, and with a negative cell-free DNA test with its very high specificity, you could probably say with good certainty, this fetus is not effected at that point. That's different than going straight from a conventional at risk to an invasive test.

John Bramhall: Let's just speculate you have a conventional test, which gives you a false positive result, something is wrong. You go to a cell-free test. That cell free test says, well, there's something wrong maybe, but it's not 21, 18, or 13.

Valerie King: Correct.

John Bramhall: Is that what happens?

Valerie King: Yes.

John Bramhall: Alright. And so, you still have an uncertainty at the end of the day in that setting?

Valerie King: Correct.

John Bramhall: Okay.

Valerie King: Although that lab report will spit out what the risk is for each of those three trisomies.

Edith Cheng: Well, no. So, the second trimester quad screen will spit out a report for the risk for Down syndrome. So, you know, if I was 27, well let's just do numbers. My A priori risk was 1000 and I took the quad screen, the lab report will spit out an independent risk for neural tube defect and independent risk for Down

syndrome, and it could say, hey, your risk is now 1 in, you now 10. You know, that of a 45 year old or 46 year old. It doesn't mean that you have it, but it's higher than expected for you. It will also spit out a risk for Trisomy 18. It does not spit out a risk for Trisomy 13. We don't have the numbers, historically, to basically model what we would use for that. It's from those numbers then that we would then provide the counseling. So, clearly, if the risk elevation is related to Down syndrome, then one could go to just a cell-free DNA and say, this is... you'll do your cell-free DNA, noninvasive, and you will get this information, but this doesn't totally exclude the possibility it could be something else.

Mika Sinanan: Could you pull up slide 18, please?

Valerie King: Sure.

Mika Sinanan: I had two questions on the test failure and the invasive testing. So, the middle and the third categories. The comment is, the highest rates of failures occurred with twin pregnancies or mixed risk populations, both of which are not included in our assessment. We are trying to talk about singleton average risk, not high risk pregnancies. Right? So, if we were to, if you have any comment, if we were to take out the higher risk and the twin pregnancies, that would presumably raise the certainty of evidence in outcome test failures. It would improve your result.

Valerie King: Yeah.

Mika Sinanan: Okay. So, that's an artifact of having that complex population.

Valerie King: Mm-hmm.

Mika Sinanan: And then under the invasive testing, the first slide, the one RCT, the comment is, in cell-free DNA plus ultrasound in group opted for invasive testing, but it doesn't say whether the cell-free DNA was abnormal or normal. It just says they had it or they didn't have it. Is that right? Or was it abnormal?

Valerie King: Yeah. That was on the basis of a positive cell-free DNA.

Mika Sinanan: So, abnormal?

Valerie King: Yeah.

Mika Sinanan: Okay.

Sheila Rege: If I could ask a question. I see on the list of studies, there was by an author Norton a 2015, as part of my research, I also read up, and there's a 2016 article where Norton compared sequential versus just a CF. Would that be something you would be discussing? Or was it...

Valerie King: That was the sequential uses specifically excluded from this scope of the review. So, we were really looking at universal use versus high risk use.

Sheila Rege: Thank you.

Valerie King: But that is one of the major studies for that contingent testing.

Sheila Rege: You have to still have to go over the key questions. Correct?

Valerie King: Pardon?

Sheila Rege: Are you going to be going over the key questions, as finishing your slides or?

Valerie King: We really... that was in the conclusion, but if you want me to say it by key question I can do it.

Sheila Rege: Would the committee like that? Or are we good with... because it is in your handout. So, we can keep on with questions then. I just wanted to make sure that... any more discussion, questions for Dr. King? Otherwise, thank you, Dr. King.

Valerie King: You're welcome.

Sheila Rege: We are scheduled for a break. When we return, we did this when I first came on the committee. We went around the room just a one-liner from each of us about our gestalt, I call it, on the strength of evidence, you know? Kind of what our take is about... do you remember? So, I'd like to do that. So, just be prepared to just speak about it, what you would like to see, and that'll help shape the discussion. Or not straw vote, nothing like that, just strength of evidence. That helped me, hearing everybody else's thoughts. Thank you.

Mika Sinanan: Before we break, could I ask a question of Edith Chang?

Edith Cheng : Yes.

Mika Sinanan: Thank you. So...

Valerie King: Do you want Dr. King to stand guard there or?

Mika Sinanan: ...I think it's not so much a question to you.

Valerie King: Okay. Thank you.

Mika Sinanan: It's more someone who is actually doing it right now. If cell-free DNA is not available for an average risk singleton pregnancy person, is that it? Do they stop if they're interested? Or do they... I mean, what happens?

Edith Cheng: So, we do this every day in our counseling. If it's not available, then they go through the traditional screening. If we have an opportunity to see the patient for counseling early in their pregnancy, then we would offer first trimester ultrasound between 11 and 13 weeks, do a nuchal translucency, and then offer maternal serum screening as part of the conventional screening. So, that's what we're doing now, too. So, there is an option. I think the committee has... one of the questions that the committee is charged with, obviously, is to say is that a reasonable choice for our low risk women versus just allowing everybody to have cell-free DNA. I think that the committee should consider the hardship, I think as Dr. Martin pointed out, of women and providers in trying to get patients into clinic to see us in a timely manner, to offer them the ideal situation, because the ideal state is the best performance is for the patient to show up, to get her ultrasound, to get all, and get her labs done and everything, to give you these pure numbers. That really doesn't happen in real life. So, that's really what you're comparing.

Mika Sinanan: So, I don't hear from what you're saying that this changes the indication for an ultrasound. That's independent of cell-free DNA testing.

Edith Cheng: Well, my bias will be that it doesn't change the indication for ultrasound, only because you're eight to nine week ultrasound is great for dating, and necessary if you have a woman whose dating is unclear, but your sort of 10, 11 week to 13 week ultrasound, which is within that window, let's say of offering conventional screening, it's actually quite valuable. In terms of still having accurate dating. In terms of ruling out some major significant anomalies, like anencephaly, there are components of that first trimester ultrasound that we actually mark off. Like, we should see four arms and legs. Sometimes, we've picked up hypoplastic left heart at that time. We can pick up gastrosis, perhaps an omphalocele, but we can pick up some pretty major anomalies at that time. So, that is an important ultrasound for dating and for ruling out these big anomalies. So, you can argue that we should do that, and if all of that looks good, then you go and say, okay. We move forward with your cell-free DNA.

Mika Sinanan: So, they are independent?

Edith Cheng: They are independent. You need both.

Mika Sinanan: And then, my last question for right now is, the timing of both the traditional and cell-free DNA, how critical is the timing relative to their stage of pregnancy for accuracy? 'Cuz, that's not really addressed in our discussion.

Edith Cheng: So, my bias is... it's not a bias. I am very respectful of the cost. I am very respectful of my time. I am very respectful of patients needing to take off work, and I'm very respectful of the money. So, for me, I think that it's very cost-effective, and also efficient clinically to bring your patient in between 10 and 13 weeks, get your scan done. You've got your data. You've ruled out major anomalies, get your cell-free DNA. The other piece of the technology is that we do know that the "accuracy" of your cell-free DNA is dependent on your fetal fraction. So, we do know that super early. So, theoretically, less than nine weeks you have a slightly higher risk of low fetal fraction in which you cannot give... so you would have a noninformative result.

Mika Sinanan: Inaccurate, so a negative, false negative.

Edith Cheng: Well, we don't say that it's a false negative. We just say that we don't have enough fetal DNA fraction to provide you with...

Mika Sinanan: Okay.

Edith Cheng: ...a result.

Mika Sinanan: So, again, does that mean you wouldn't offer it? Or you would tell the person to come back in a week?

Edith Cheng: Right. So, you run a little bit of a risk if you draw it at 9 weeks and if it comes back as inadequate fetal fraction, then the patient has to come back, and we have to redraw. So, just from a practical aspect of care, I just kind of educate my patients. I know that you're impatient, but, this is what I recommend.

Mika Sinanan: Is the first one the same process as the second one?

Edith Cheng: You mean of repeating?

Mika Sinanan: You get inadequate fetal fraction, do they charge you the full rate?

Edith Cheng: Technically, they shouldn't.

Mika Sinanan: I don't know. You guys don't. We don't. We shouldn't. If you don't have... if the test does not provide you with...

Sheila Rege: Maybe we could have the agency look into that during our break, because right now, I think, that's an interesting clinical perspective. We need to kind of focus on the literature. So, we will take a break. If the agency wants to work on that during our 10-minute break and come back at 11:00 a.m. Is that good? And be prepared to go around the room and your gestalt on the evidence. This is a hard one.

So, going around the room, since you started, we'll start there. Just one sentence going around the room whether, you know, comments on the current evidence, use of the test. Just comment, just a comment.

Chris Hearne: It seems that there's some good evidence that this has at least the same negative predictive value as standard screening and better positive predictive value. So, it all seems to be pointing in the same direction.

Laurie Mischley: So, can I expand on that a little bit? So, I certainly agree with that interpretation of the science. I think the science, from the quality, there's no question that this test provides. I really am stuck on the societal cost part of it. I heard, whoever first spoke up, about the underserved communities, delaying this by a month or two, I was personally one of the 44 people screened as being at risk, and I question whether the time I took off work and the implications on my personal is coming into play in these economic evaluations. So, I don't want to be dismissive of just because it doesn't save us money in the next year, it doesn't save a tremendous amount of money over time. I know that these conversations about how many people get abortions and things like that are beyond the scope of what we're here to talk about today, but it factors into the economics of this. I don't have a clear impression from the analysis that's been done whether, or to what extent, those variables have been factored into these analyses.

Janna Friedly: I would just like... I think for me, the evidence seems fairly clear about this test. It's hard for me to look at that in isolation from the issues related to access and choice. This, for at least a very small number of people, can provide earlier options for people in terms of making decisions about the pregnancy that they wouldn't have otherwise. So, I would agree with those issues. Having been through this myself, as I mentioned, those barriers in terms of multiple repeated appointments and scheduling and all of those things really, it does create an extra layer of burden for people who are at the margins. I can see that a lot of things would fall through the cracks. I can't take the science in isolation of those issues.

Seth Schwartz: I think often... part of our job here is to be good stewards of our State's resources, but I think more importantly, our job is to offer effective care that adds value to the patient population in the state of Washington. I the ink what we're looking at here is a good test, a test that's substantially better than what is currently available in many circumstances, and the data is pretty good, about as good as we ever get for that. You couple that with some of these other issues that we've heard about, access to care and timing of diagnosis, or timing, at least of identifying increased risk, which I think can be really valuable for a lot of people. Then, finally, we have a circumstance where always the cost-effectiveness is uncertain, but we have real equipoise on that and potentially cost savings, particular with a test that's likely to become less expensive over

time. So, to me, I think this is... we're looking at a good technology that has real value for our patients and the women of our State.

Tony Yen: I think the evidence actually shows us the floor of the technology more than anything else. That's kind of the bottom line. I think this is an effective test.

Austin McMillin: I would mirror all of that. I think that the science looks very favorable. I pulled out clouds related to moving onto other procedures and costs not being factored in there with traditional serum testing, but also, I think the timing issue here. This is something that can't be pushed down in the track for long, and then the mental anguish issues that tie into all of that really can't be discounted. The only caveat that I would have would be to voice a concern for consideration of when the testing is done so that the fraction rate is appropriate to get a good result.

Kevin Walsh: I agree if we just look at positive predictive value. If we look at, um, the potential for saving unnecessary invasive testing that the technology looks good. The reality, however, is much different. I guess I have a question for Dr. Cheng. I'm interested in knowing, what are the potential harms or dangers of offering cell-free DNA without some kind of genetic counseling?

Sheila Rege: Maybe we will hold that question and just go around the room to... if that's okay. So, Mika, do you want to go. So, I would agree. I think the charge to us is to use the evidence, safe, effective, and does it provide value and separating that from the emotional aspect of making it sequential and offering both, conventional and this, it's going to be tough, but I think there is evidence. I must commend our evidence reviewers for the work they've done. Dr. Cheng, do you have any comments? You're a committee member?

Mika Sinanan: Nonvoting though.

Edith Cheng: Were we going to finish that, and then I can comment?

Mika Sinanan: Sure. So, I think that absent the cost, if the cost were zero from a safety, efficacy, and value standpoint, social value, value to the knowledge of the patient, the family, the mom, this would be a test that would and is widely adopted. So, it comes down to the cost issue. I am surprised at the paucity of evidence that actually supports the value for this, the small number of studies for something which seems to be ubiquitous or about to be ubiquitous in the population of women who are having babies. So, that is a surprise to me, and I think an opportunity for future studies. Having said that, I think that it would be... we would have a very hard time, I would have a very hard time not making something like this available, I think. I suspect that if it were unavailable for the population for whom it is now a covered thing, it would become a source of a lot of anguish and a lot of backfill. People would have to pay for it, or they would have to figure out how to do the same testing and achieve the same goals. It would replace, as I think Edith has said, a fairly accurate test or a high accurate

test, a safe test with tests which have a lower rate of accuracy to look for indications to do the higher value, more accurate tests. So, it would add the significant cost, which I don't think was captured in the costs evaluation.

John Bramhall: I confessed early on I'm confused and ignorant about the cost, financial cost issue. I don't understand it at all at any level. This is a test that seems scientifically supported. It's clearly widely used by people who know their subject. I was impressed by Dr. Cheng's comments about catching the sweet spot. You don't do the test too early. You can't do it too late. There's no benefit. There's a sweet spot, and with the underserved population, which is overrepresented in the Medicaid population, which we are concerned with, I think it seems like you are provided with limited opportunities sometimes to have a woman come, subject herself to the basic screening, and then... if you don't get everything that you need at that point, you risk not getting everything that you need later on. That was one thing. The second thing, Janna, when you commented on the fact... it seems like the majority of Medicaid women who are pregnant are not getting any screening. That's outside the scope of this particular discussion, but it's a societal issue. I mean, they're not getting the screening, according to the data that we were presented with.

Kevin Walsh: It's not for lack of access. It's a choice.

John Bramhall: Well, then. Okay. So, it's not within the scope of this decision, but then you... it's a societal problem at some level, whether it's because of education, access, economic, I don't know. I was just surprised to see that there many, many, many pregnant women who are under the Medicaid envelope who get zip. My own personal sort of problem with cost, financial cost, is then just from personally you have 44 women per 1000 who get a conventional test who then are very high risk for deciding or being advised to have something like amniocentesis, which is expensive and invasive, and has problems. That's one cost issue. The second cost issue is if you have women who slide through the system and don't get testing or get testing that's inaccurate, what is the consequence of that if they turn out to have a trisomy child? I don't... I just don't understand how you can put a dollar value on that. Therefore, I tend to discount that. I think it's appalling if that happens, and if we have an opportunity to provide a modest financial cost, a test that reduces that incidence, well we'll vote later on, but you can see I'm positive.

Sheila Rege: One thing that Dr. Cheng said that resonated with me is the importance of a medical provider to help guide, because this test only does Down, which a person may live with. I mean, those other two syndromes, they die. So, it's... and then, the other tests have other things they may cover, and I don't know how many other things whether incidence of Down's compared with all the others. So, if Dr. Cheng wants to comment on Dr. Walsh's comment.

John Bramhall: That was something wrong sort of nonscientific state, but there's something wrong, but it's not Down's. Well, you're asking what's the frequency and how often is that something real?

Sheila Rege: It only covers certain things, and the other tests cover more. It's more... this is a very specific test, not broad.

Edith Cheng: So, you're not going to find resolution in those two conflicts. I think that we are going to have to live with one or the other. While the... as an MFM, I do find that the quad screen provides me with other information, as an MFM, but the frequency with which that quad screen provides me with other information besides the three critical issues is relatively low, and it's in my prevue. So, I would suggest to the committee not worry about sort of missing that other stuff with losing the quad screen. I think that I can answer many things from many perspectives. So, the science is there. I know the science. It's good stuff. It's only going to get better. So, there's no doubt about the science. Okay? My personal bias is again finding that sweet spot for a lot of reasons, for the patient's work schedule and hardship, for timing early on enough in her pregnancy so that we get an early enough diagnosis so that we have time. I'm going to diverge a little bit. That's super important when you guys think about cost and what the ramifications of a late diagnosis is, because I see that a lot. Late diagnosis, tears, hardship, all of that from a medical standpoint if an abortion is a choice, it is more riskier to do a second trimester abortion than it is to make a diagnosis at 13 or 14 weeks. So, just from a personal safety issue, from an emotional safety issue, and from a cost issue, there is reason to move forward to explore earlier and earlier diagnosis. I mean, that's why CVS was brought on board. So, now we have a noninvasive earlier diagnosis. So, that's really important. I do think that there is an equity in cost. There's tremendous cost disparity across the many provider companies, if you will. I think that needs to be resolved in some way. So that, in and of itself, is inequitable, because currently right now, we can counsel a patient who is under 35, and she makes the choice of conventional screening, because she can't afford. Okay? So, that's inequity number one. I think that inequity number two, it has to do with access. Access also has to do with education. Please do not forget that this is not a routine CBC that you can order on anyone without informed consent. It requires education. We talked about the down side. Most of the time, the down side is not very much, but again, as the committee talks about the emotional turmoil of getting a late diagnosis, or a positive screen at 18 weeks, think about the emotional turmoil if you did not consent to this, and this result comes out, and it's funky. So, the A priori, the pretest counseling, pretest education of both the physician and the patient is really crucial to having this test be what you want it to be. If that's the case, it is a very efficient test, and it's a good test. The last piece will be, and that actually helps with our access, because again, our communities, outside of King County, do not have access to providers who can do a nuchal translucency ultrasound. Again, that in and of itself pushes a lot of people out of access right now. Then, if you think about, okay. If the patient

does want to do that, she has to drive to Yakima. She has to drive here. She has to drive to Tri-Cities, whatever. Then, we can't get the NT the very first time. So, then we have to bring her back. So, there's a lot of stuff that this move... doing the cell-free DNA will actually take away and will be more cost-effective if you will, the return ultrasounds, but I also will have to echo that we have to remind the providers that this is only one test. They still cannot forget the MSAP. They still cannot forget getting an ultrasound, because other things do come up.

Laurie Mischley: I really appreciate and keep hearing you talk about the importance of education and appropriate counseling. In terms of our implementing policy, what would that look like? I mean, can we just assume any OB/GYN and midwife is appropriately trained? Is there some sort of additional training and certification one gets for this?

Edith Cheng: Across the State, there is already inaccurate understanding and training of even offering the quad screen. We've had the quad screen for 40 years. I saw one provider who, anyway, forget it. So, I think that I would encourage the committee to tag at least some language that says there needs... we strongly recommend appropriate education, pretest counseling. I would then say that the committee really should consider providing or assigning a subgroup that would come up with an educational tool that we could automatically give to, or say this is the tool that... this is the slide deck. These are the elements of the counseling. I think that we have prenatal counselors in the audience, and I am sure that they have these slide decks and teaching tools, just as we have teaching tools. Our prenatal patients, immediately when they come in for their first prenatal visit actually sit at a booth. We actually run a 13, 15 deck slide deck on all the options of prenatal counseling. You can argue... we need support to make that slide deck. We need support to translate it into multiple different languages. To that extent, if the committee does do that, then you have, in some ways, fulfilled your mission for access, because it's available. You can't just say, I'm gonna authorize the cell-free DNA and not educate the physician. So, those are my thoughts. Those would be my recommendations if you are going to move forward with this.

Sheila Rege: It's very helpful to have your perspective based on your expertise and experience, but any other questions on kind of our discussion on the evidence, as we start getting to thinking about the next steps.

Mika Sinanan: I have a question about the Pegasus-2 study. What exactly are you expecting to get out of that? I mean, it was referenced in the...

Sheila Rege: And it's going to be a year or more.

Mika Sinanan: ...right. I mean, I'm just looking at the website. It looks like a Canadian study, but the question they're asking is the one we're asking as well, whether it should be a firstline test earlier in pregnancy for women for the set of syndromes, as I

understand, just from reading this, but is it something that MFM's are looking forward to results from?

Edith Cheng: We are. I think the questions that we have will be really performance, patient uptake...

Mika Sinanan: Uptake meaning the number who are offered it to accept it or have it, right?

Edith Cheng: ...mm-hmm. I think coming out of it there would also probably be some patient experience. I think that we're probably gonna be seeing maybe a more bias free look and comparison of conventional versus cell-free.

Mika Sinanan: Interestingly, they also comment that one of the goals is to reduce cost by 50% for the test.

Edith Cheng: There was an interesting study. I can't remember it. I was reading about it. It came out of our genetic counseling journal. It was a very small study, but it was basically an interview of women who had gone through cell-free DNA, some of whom had ambiguous results, some of whom just kind of... so, it's across the board. It was very interesting in that about a third of the women actually said that they didn't feel that they were adequately counseled. There were some women who said that they regret it, taking the cell-free DNA. Although the overarching was because of ambiguous results, but then the overall arching was that... they did say that if they were offered this again that they would still do this, but they did highlight that there was inadequate counseling, and especially for the women who had ambiguous results. They just didn't understand. So, when we talk about harm, that's really going to be the issue is adequate counseling. Again, because on the streets, the friends talk to each other. They say, oh, I got my blood test at 9 weeks, and my baby is fine.

Sheila Rege: How long does it take to get this test?

Edith Cheng: I think the turnaround is about five working days. It's very quick.

John Bramhall: Is it automated? Or is it microscopic?

Edith Cheng: It's automated.

John Bramhall: It's automated. So, a sample goes in, and the machine reads and says, yes-no to trisomy. Is that right?

Edith Cheng; Yes.

Sheila Rege: But each lab can do it their own way. Right? Or is there a standardized?

Edith Cheng: Not really. This is part of the technology that everyone is fine tuning, fine tuning, fine tuning. Every lab is fine tuning the assay. There's a general platform, but there are nuances to the platform.

Tony Yen: Can I ask you a question about, why is it that this test does not perform as well in women who are overweight or obese or have larger BMI? I don't understand that at all?

Edith Cheng: So, there are a couple of biological situations where this test has been shown not to perform well. We think the first kind of possible obviously explanation is just maternal weight. So, your volume is greater. So, you have cell-free DNA that's kind of floating around in greater volume. So, it's diluted. I think that there's going to be more pathology than that. The other situation where the test doesn't perform well, or there is inadequate cell-free DNA is... in Mary Norton's paper there is a subset of... she looked at the subset of women in whom there was inadequate cell-free DNA. She, unexpectedly, identified or found that there was... within this subgroup, there were other chromosomal abnormalities that were rare, unusual, and complex that fell into this subgroup that had low fetal fraction. So, again, these women came in, routine screening, for 13, 18, and 21. They fell into what... we ran this twice, and we still got inadequate fetal fraction. Then, when we actually looked at this subset, there was a relatively high percentage of women in who they actually had other chromosomal abnormalities that this cell-free DNA would not have picked up. Now, it's becoming... so, I just finished reviewing a paper in which there is an association between low fetal fraction in women who are on heparin or anticoagulated. So, I think there's more biology going on in this placenta through the cell-free DNA. We're at the super top level of something very simple, but it's actually other stuff going on. So, this is the reason for all of these nuances about low fetal fraction, but again, at the end of the day, when we're looking at the population of Washington, and we're looking at access and equity of access, it's a good test. What we're really doing is replacing serum screening. I remember having this same conversation in this committee 20, so 30, 20, 10 years ago, as we moved from MSAFP to what about the triple screen? What about the quad screen? So, this is just the evolution of that. We're just replacing with serum screening.

Sheila Rege: Any discussion? Should we have the analytical tools kind of help guide our discussions, as we go through, maybe go to page 5 in safety outcomes based on the review, testimony, and safety. We've got listed here test failures, false positives, false negatives, and then it may lead to invasive testing. Any discussion on that?

Kevin Walsh: Well, I think there's another safety issue that's been kind of pulled out of this discussion, and that is that without proper context, just doing a cell-free DNA test and giving that result to a woman can result in decision to terminate the pregnancy. I think that it would be... I'm challenged to understand how we can, in any way, legislate adequate counseling. The reality is, I work in a really

resource poor county in a resource poor clinic. I am struggling to imagine how we would be able to adequately counsel every woman. So, that leads me to wonder, well, then is it better to not offer the test? Or is it better to offer the test. So, I'm just trying to say that an additional safety outcome is inadequately preparing a person for the result.

Janna Friedly: But they already have access to these other screening tools. I guess the question is, how is that different than this?

Sheila Rege: From their own OB.

Janna Friedly: So, currently, all of the other... the conventional screening tools are available and covered without stipulation that there has to be counseling. Right? Or there isn't anything sort of legislated about that, right or wrong, but that's already built in. So, what we are tasked with doing is now looking at this tool sort of in comparison to that. Why would you need to incorporate that into this decision, if it's already available? Or how does that change things? I guess that's what I'm struggling with, how that would change? I'm not disagreeing that the education is critical. It's important. I'm not disagreeing about that.

Sheila Rege: Not looking at it as a barrier, but we're just talking right now about if inadequate education or counseling may be a safety issue. I think that's... we're not looking at crafting language. I think that's what Kevin is saying.

Seth Schwartz: I agree with Janna. I think, absolutely we want these people to have appropriate genetic counseling in making this decision, but they're already getting the same information. There is no stipulation on how that counseling takes place. Now, that may be problematic, but to some degree, that seems outside of our charge to change that requirement. This is just the tool that they're using to do the screening. I completely agree that these people should be appropriately counseled, but to what extend do we need to limit access to this technology to add a stipulation that doesn't currently exist for similar information.

Edith Cheng: I wear so many different hats, and I have conflicts in all the different, depending on which hat I wear. So, I agree in the sense that we've been doing serum screening for a very long time with inadequate counseling. I think that people come in and say I never knew what this quad screen was all about. The stories of my previous pregnancy, they scared me to death because they told me that my baby had Down syndrome with this blood test and this and that and that. So, we already have had 20 to 30 years of serum screening with absolutely inadequate counseling. So, you're right. Within the charge of this committee, so offering cell-free DNA for everyone, we're still going to be in the same boat. It's definitely the same boat. So, as I wear my purist hat in informed consent, particularly in genetics, that is the harm. We've had the harm with serum screening with inadequate counseling, and we will face the same thing with our cell-free DNA.

Janna Friedly: I guess my point was that whatever decision we make today is not going to reduce the harm, because the harm is already there. So, our decision, if we take into consideration harm, if we make the decision not to cover this because of the harm, then we're not mitigating harm, because there's still...

Edith Cheng: Right. I just want the committee to understand that this is not just getting your CBC. There are significant ramifications, and you're dealing with a pregnancy.

Chris Hearne: Do you see any potential differential harm between inadequate counseling with the quad screen and cell-free DNA? Or the harm is the same?

Edith Cheng: The harm is the same.

John Bramhall: Is the harm less because this test is 'more accurate?'

Edith Cheng: No.

John Bramhall: So, conventional testing would lead to inaccurate results in a proportion of patients. That may lead to unnecessary interventions in that number of patients. This test is 'more accurate.' There must be less harm.

Edith Cheng: Well, there is less harm in terms of the number of invasive procedures that you would subject...

John Bramhall: And possible terminations, as well, perhaps?

Edith Cheng: No. So, the caveat is going to be that one would never consider termination of pregnancy based on a positive quad screen. It's stipulated in every single committee that you should never make a decision about termination of pregnancy based on your cell-free DNA, absolutely not. So, the harm there is... once you... so yes. You potentially have less false positive cell-free DNA's, but once you have a positive cell-free DNA, then you still have to go through the same processes of counseling and invasive procedure.

Seth Schwartz: Just talking about harms, I was struck. We're talking about these high risk tests. I didn't really realize what that meant, but I think someone stated that with amniocentesis, there is 1 in 200 amniocentesis that result in the death of the fetus. Is that accurate?

Edith Cheng: It depends on who you talk to. I would say that for providers... so, for sure, back in the '90s and 2000's when we were performing, for example, the State, at the University of Washington, 1500 amniocentesis a year among three providers, no. I think our loss rate was probably less than 1 in 800. Again, the loss rate is related to the experience of the provider. So, what's happened is that with increasingly better noninvasive testing for fetal aneuploidy, the experience of

providers doing amniocentesis is now less. Therefore, we went from super, super low risk to now we're creeping back up, too. So...

Seth Schwartz: Okay. Well...

Edith Cheng: ...we're, like 1 in 200 to 1 in 500.

Seth Schwartz: ...Okay. Anyway, just loosely looking at this. So, we're talking about essentially 40 people per 1000 births are currently being referred for amniocentesis. Then, in a population of what is it, 39,000. So, say 40,000 pregnancies a year. We're talking about 1600 people are getting amniocentesis. Of those, so we're talking about, what is that 8, you know, somewhere in the range of 5 to 8 fetal deaths as a result of referral. We can cut that down to what would be more like 50 referrals. So, less than 1 death per year based on amniocentesis. I mean, that's not a trivial difference. When, we're talking about the risks of confusing counseling, which is certainly a real risk, but we're talking about actually death to the baby is a pretty real risk, as well. So, I don't know how you weigh those differences, but those are not trivial numbers is my point.

Sheila Rege: Are we pretty comfortable that this document has all the safety outcomes that we would be factoring into our decision later? How about effectiveness or efficacy? Is it effective? I think it's effective for what it's testing, but there's a lot it's not testing, and that's the education part of it. Any consideration of... we should go to the providing value. Value has cost in it. I think that's our big thing. Before we go there, let's go to special populations. Are there some special populations we should... this is low risk is what we're talking about today. Is there a special population looking at diversity groups and stuff that we have to really be concerned about? No? I didn't hear anything in the data on that.

Tony Yen: I think there are clinical populations, like the women with larger BMIs more than a singleton pregnancy. I think those are the special populations, but I really don't know how traditional testing or conventional testing really compares head to head against cell-free DNA testing. I have no idea.

Sheila Rege: Alright.

Edith Cheng: I don't think that... with conventional testing, the patient's BMI is a correction factor when we calculate out the risk, but the overall performance is still not... I mean, it's six of one, half dozen of the other. I mean, you just have to recognize that women with higher BMI's, you are at a slightly increased risk for equivocal result in the second draw.

Sheila Rege: Now, here's where I'm looking to the committee members for input. We usually go is it safe? When we look at equivalent to existing technology. I really don't know how to frame the question here. So, I'm looking for help on framing that question. What are we comparing it to? Are we comparing it... it doesn't sound

like it's instead of conventional. So, help me out with just a discussion on that. In all of that, safety, effectiveness, and cost-effectiveness.

Seth Schwartz: I think this is always challenging, because there is the direct comparison. Is it safer to draw blood? Or is it safer to do the quad screen? That's probably kind of an inane question. The safety issues tend to come based on the results of the test and what happens next. So, I think it depends how we, as a group, want to look at that. Do we want to look at it in isolation? Or do we want to look at the broader picture. I don't know what the right answer is to that one. I think you can make arguments either way.

Tony Yen: I prefer to look at this in the context of the results that we get.

Sheila Rege: Based on?

Tony Yen: Based on our discussion and based on the literature and the evidence that we have in hand, rather than... because a blood draw is a blood draw. That's equivalent, as far as I can see it. Whether you draw blood for serum markers versus cell-free DNA testing. That's equivalent.

Sheila Rege: Any discussion just on safety? Should we do a straw poll? And I think in my mind, I'm looking at it as compared to... I'm not looking at it as compared to the invasive testing, the amniocentesis and all that. I'm looking at it just in comparison to the other blood draw, the quad screen is what you're calling it or an ultrasound.

Seth Schwartz: It's providing information. So, it's how you act on the information, which is where the risk comes in. Again, it's hard to know how to look at it. I think we're looking at a test that gives information that is going to cause fewer people to have testing that has more significant risk. So, by that calculus, it's safer, but then, there's all these subtler issues about decisions to terminate pregnancies and things like that. I mean, I think in general, you're going to see fewer people in this situation where they're going to have to make complicated decisions about more invasive and dangerous testing and things that are dangerous to the fetus. So, even in a broader context, it seems safer to me, but if you're looking at just the test itself, it's equivalent.

Mika Sinanan: Yes. I would agree. I think that the test appears to improve the information and the accuracy of the information that is provided to the patient.

Edith Cheng: I would also add that the time is also... you're getting this information earlier.

Sheila Rege: With a five day turnaround. Just on safety, if we're comfortable what we're voting on, and I will to a member to... what's the question? Is it... do we have sufficient evidence that the technology is safe? In my mind, when I say safe, I'm comparing it to other conventional screening. Okay.

Tony Yen: The testing itself or the... I'm still... I apologize. I'm still trying to get clear on the actual...

Sheila Rege: It's the testing, the actual test.

Laurie Mischley: It's how you interpret it.

Sheila Rege: The CFDNA test. Everything.

Josh Morse: Okay. I'm going to count more in all's first. So, there's one, two, three, four. I count more in all, one, two, three, four more in all. Four more in all. Then, more in some, one, two, three, four, five, and one equivalent. Thank you.

Sheila Rege: You know, the reason I said... and I'm going to ask everybody who is the single person why, in case we're missing something that we want to discuss. The only reason I said that is, I can see a woman stressed for time, money, time away from work, if the accuracy is so high just saying, oh my gosh. I probably have Down's. Why would I go through any amniocentesis and stuff? Let me just terminate, you know? That's my... so that was kind of why I said equivalent, not to change anything. Let's talk about, do we feel we have evidence about the effectiveness of this test? Will it have meaningful impact on patients and patient care? Here, also I struggle, because we've seen the agency medical directors' recommendation. We've seen other discussion. I'm having a hard time with the question I'm asking. Help me out. When we say equivalent, is it equivalent to conventional? Is it more in some, more in all? That's how I am interpreting it, but if anybody else wants to suggest an alternative? Compared... so effectiveness compared to conventional.

Josh Morse: Counting more in all, one, two, three, four, five, six, seven, eight more in all, two more in some.

Sheila Rege: John, since we were the minority, would you like to go on why you said more in some?

John Bramhall: Well, I'm sort of... my logic may be flawed, of course, but there's only some people for whom the test is... there is a subset of people, subset of women for whom this test is a different result from the other test they would get. The majority of women are going to have a negative test. The specificity of the test was not that different from the conventional test. That's my thinking. It seems like there is a group of women who are at risk. There's a group of women that get a test, this test, how do I want to say it? Well, I've said what I want to say.

Sheila Rege: On the cost, and I know we had an outstanding question about whether if the cost came back equivocal and the recommendation was to repeat it later whether the cost for the second time or the first time when it was equivocal was

the same. I don't know if the agency has had any, I suspect it's the same. I mean, why wouldn't it be?

Female: [inaudible]

Sheila Rege: You would?

Female: [inaudible]

Sheila Rege: You would not? No. Okay.

Shana Johnson: The way the system is currently set up, we would not catch it. It would get double billed, but that's not to say there couldn't be a system edit put in to prevent that.

Sheila Rege: The question was whether it would be the same cost. I'm suspecting it is, because any genetic test seems to be the same cause. Based on that assumption, cost-effective to conventional, less equivalent, more in some, more in all. So, more in some means it's cost-effective? Or it's more costly? More cost-effectiveness.

Josh Morse: Count unprovens, I see one, two unproven, one, two, three, four, five, six, seven, eight more in some. Thank you.

Sheila Rege: So, we didn't get any, well, we've got to have the unprovens talk about why you thought the cost-effectiveness was unproven if you want.

Kevin Walsh: There were different assumptions used as a basis for each of them. I think we all pointed out flaws in those. And that's why I think it's more complicated than they were able to capture.

John Bramhall: More in some, but I still struggle with that slide that I referenced earlier on that makes a distinction between societal cost-effectiveness and agency cost-effectiveness. I just wasn't sure about what that meant.

Shana Johnson: I did get clarification on that. Society doesn't have to pay for the test. So, they're just getting the benefit.

John Bramhall: That seems a bit narrow, but I accept your comment, but...

Shana Johnson: Dr. King, would you like to expand on that at all?

John Bramhall: ...Okay. So, there may be... so the mathematical calculation made by an agency, not ours necessarily, but an agency that says if we provide to all comers, there's a bill here, which is so many dollars. If we don't provide the test, there's a different bill. The bill is not simply the cost of the test, it's the cost of the

ramifications of the test. Fine. So, that's narrow and it's structured, and it has to do with budgets. The societal issues are very nebulous and have to do then with values, probably, as much financial as philosophical, but from a financial standpoint, the society bears the cost of a Down's patient who goes through life, or the society bears the cost of a mother who terminates her pregnancy. Society bears those types of costs, but the agency doesn't. So, I get that. Then, I struggle with, is my fiducial duty now, here, to the agency? Or is it to the society? That's for the retreat.

Seth Schwartz: The other thing I would say about, when we assess studies, in general, I think we downgrade a lot of studies based on bias. One of the things we don't talk a lot about is which direction is the bias effecting us in. So, oftentimes, it's biasing towards a result when there may not really be in effect. Whereas, I think, when I'm thinking about cost-effectiveness in this situation, I think the bias may be the opposite direction, which I think there is a lot of cost of missing these things or of doing these additional testings and a lot of the stuff that follows from poor tests that is not captured here. So, I think, probably the cost saving of a better test in this situation is actually higher than what we're capturing, not even to mention the equity issues and some of the other things that are at play here.

Edith Cheng: I've actually tried to answer this question, just for our own, because the frontlines, just the gut feeling is, all the return ultrasounds, because we didn't get we needed, so that's one level of the cost of the agency bearing for those return ultrasound visits to get what we need. Then, if you think about the cost for the patient, work, taking her day off of work and all. So, my gut feeling is because a lot of times, we can't get what we need. The patient has to come back. The purest algorithm would be, really, ultrasound dating, get your cell-free DNA. You're good to go. I'll see you back at 16 weeks. Come back at 20 weeks. We're going to do your anatomy ultrasound. So, if we can really kind of think of it that way, just my own experience would be, that cuts a lot of money right there. We've provided really a very efficient and good screening tool for your patient.

Chris Hearne: I think you also have to factor in that we've cost is actually dropping over time, as technology is improving. So, that's an unknown, but something to consider, as well.

Kevin Walsh: You mean, like, the cost of insulin?

Sheila Rege: I think at this point, what I am just curious about, and help me out in how to shape our discussion. Just a straw vote. I want to see if anybody would say not cover this at all, cover unconditionally, or cover under conditions. Again, just a straw vote. This is not the final. Then, we start a discussion about how we go about that. If you say not cover, we go home, and you'll have tomatoes thrown at you, probably, by people, but, or not cover is what I meant there. I'm gonna struggle on this one.

Seth Schwartz: Listening to everyone around the table, I think it's pretty clear, it would be rare for one of us to vote not cover. So, I think we're talking about cover or cover with conditions. I think it's fair to say, among those two, you could say, who would agree to just cover and then do a straw poll. Then, the same for cover with conditions.

Sheila Rege: Let's, so Seth, you want to say that? Who would vote for cover? Then, how would we vote. Let's go with who would cover with conditions? Or who would cover. We're gonna count first. I didn't want to be in the minority. We've got to speak now.

Josh Morse: There's three cover with conditions, and seven cover.

Sheila Rege: Austin McMillin would you like to say kind of where you were on cover with conditions?

Austin McMillin: I think it should be covered with the conditions that you're in the right window... timeframe window.

Sheila Rege: So, don't do it in the third trimester?

Austin McMillin: Right. Or the eighth week.

Edith Cheng: So, that's a good point about that. So, you know, the... so, be careful when we... I'm sorry, I actually didn't even think about this until now. So, thank you for bringing it up. I think that we actually could do... so, this is for screening. Yes. You can say that, but remember that cell-free DNA can... but you know what? That's for low-risk. If you found something abnormal, let's say at 28 weeks, you can offer that person cell-free DNA, but that's not part of the screening. So, I don't think that we...

Sheila Rege: That's high risk birth.

Edith Cheng: ...yeah. So, we don't have to worry about third trimester.

Sheila Rege: And we're low risk.

Janna Friedly: So, what is the timing? If we were to put a window, what [inaudible]?

Edith Cheng: This is my own personal bias. I think from my efficiency and sort of what I understand in terms of ideally optimizing the biology. Certainly, you have a thin woman. If she wants hers at nine or ten weeks or something like that, I guess, we can do it, but I think that to optimize and be efficient, I personally would, and I do that now is, I personally encourage when I counsel my patients that we will... you'll come in between 10 and 13 weeks. We're gonna get you ultrasound,

confirm that your baby is alive, confirm that the rudimentary anatomy that we should be seeing we see, and it's good to go. More often than not, you will have adequate fetal fraction. So, I would say that for me, the window is between 10 and 13, 10 and 13 weeks.

Tony Yen: Is that evidence based?

Laurie Mischley: Can I ask the evidence vendors if that was the methodology that was employed in these studies, is a certain window of time?

Valerie King: The majority of the studies definitely looked at that window as the study protocol. I don't believe that any study used the test before eight weeks, there is kind of a biologic minimum, but then there were studies that used it through the second and into the third trimester, as a screening test. Ideally, you would be screening earlier in pregnancy.

Edith Cheng: This is a test that you can use at any time in pregnancy. Right? 'Cuz, if you find an AV canal at 27 weeks, and she's 41 years old, A priori, this baby has Down syndrome. You don't want to do an amniocentesis on that baby, but if she wanted to know, we now can offer cell-free DNA, which we couldn't do ten years ago. We have that diagnosis confirmed. So, you can do your cell-free DNA any time in pregnancy. The question is, for the committee, if you're voting on if it's a screening test, what is the best time to do it, well, the earlier the better, but what are the biological constraints. Biologically, we know that we have a higher risk of having inadequate fraction for sure at eight weeks, probably nine weeks. That's why all of these studies kind of confine the cell-free DNA draw around 10 to 13 weeks.

Seth Schwartz: This is a little bit of a struggle, I think, if we had specific data on this, you know, then that's one thing. I think the test is clearly better in that timeframe, but is it totally useless earlier? Is it really screening if you're doing it later? What do you do if you have a woman who comes in from, like, some distant corner of Eastern Washington at 8.5 weeks and you're not going to see her again until she's 20 weeks. Should you not do it? I think there's a lot of complex questions. We can pick out exceptions to the rule, but I think when we're talking about across the State on a broader perspective, I don't know that we need to be too limiting other than... 'cuz, the test has parameters under which you're supposed to order it anyway. So, I don't know that we need to be proscriptive about it. That's just my perspective on it. When we don't have more solid data.

Mika Sinanan: I would second that, as well. Also, the uncertainty of knowing how they are measuring the dates. Is it by ultrasound?

Edith Cheng: I think as I wear the hate of let's say a committee member, and I'm just making this decision, it's really not our role to kind of... you hope that the physicians understand all of these nuances, but in some ways, it's not... well, I'm not going

to say responsibility, but we should not... our decision is this a good... your decision, not my decision. Is this a good test? Does it meet your criteria for all of this? In some sense, I have brought up a little bit of a nuance for you guys. I hope you guys don't get too stuck on it. It's just basically for you to understand that as you vote on this, there are some biological nuances. We're going to have to take that risk, just as currently you have providers in the community who order the quad screen at the wrong time.

Sheila Rege: You could say preferably around 10 weeks or more, or something, when we get to that stage.

Edith Cheng: If you wanted to put all these... I think that's a good point is to say...

Sheila Rege: It would be educational.

Edith Cheng: ...yeah. The ideal for early screening in the first trimester is this time, but theoretically, you're absolutely right, Seth. If somebody shows up at 18 weeks for her first prenatal visit, she still could have this as her screening test. It's still a good screening test.

Sheila Rege: Would you do it at seven weeks? You probably wouldn't do, I would think.

Edith Cheng: I would not do it at seven.

Sheila Rege: And not at eight is what it's sounding like.

Chris Hearne: I think it was looking at the lower limit like that. When is it appropriate to start running these tests?

Sheila Rege: I hear the comment about somebody coming in from a rural area, but we can look into the nuances, but that was interesting. That was an important point. You voted with conditions, too.

Kevin Walsh: I find the agency case compelling. I respect the fact that we want to avoid the risk of unnecessary amniocentesis, and certainly the positive predictive value of the cell-free DNA is better than our current technology, but when we're looking at the general population, because the prevalence is so low, then I think that's where a case is made for looking at the cost, the overall cost of universal testing, as opposed to a staged format where people who have positive serum tests then have the ability to get the cell-free DNA test. That's the condition that I would support.

Mika Sinanan: Could I just ask a question in that regard? If we were to make access universally available, what proportion of average risk women do you think would accept it?

Edith Cheng; It's very different. So, within. So, within the Puget Sound area, centrally local, the uptake is pretty high. I think once we...

Mika Sinanan: [crosstalk] percent?

Edith Cheng: Not quite that high, but it's high, but once you get out into rural areas, it's pretty low.

Mika Sinanan: I'd say my gestalt is an average of about 50% or less.

Sheila Rege: I struggle between cover and cover with conditions. I was looking back on what you had said about the quad screen is done at 16 weeks typically. So, if we are projecting the agency medical directors' recommendation, if we did that following a positive test on standard screening, that would be at 16 weeks. So, that increases the likelihood that you're gonna get less equivocals, even with a bigger BMI and all. I don't know the data. There was no data on that. You are now limiting it on people who have not had miscarriages. That was my struggle, just personally, but no data on that. So, I am the first to admit that was... so I am curious, how many would lean towards what the agency medical director, just a show of hands versus how many would want to just cover? So, how many would be leaning towards something similar to that, we could... not exactly that. Go ahead, John.

John Bramhall: The agency knows the proportion of take-up in the PEBB population, presumably, because the current... is that right?

Sheila Rege: Let me ask the agency representative who is here.

John Bramhall: The current coverage is what, universal for PEBB? So, there's data collected there to say how many... what proportion of that risk pool takes a... and now the question, well, one question that we were originally sort of faced with is whether to expand that policy to Medicaid patients, which is a different population. I gather.

Sheila Rege: Right, and that would be expanding, versus this is actually shrinking, which is very [crosstalk].

John Bramhall: Yeah. I see that. Yeah.

Shana Johnson: Does this data answer your question. Our best proxy for low risk in this data was just less than 35. The uptake in UMP for prenatal screening of either type was 48%. The uptake for less than 35 of either prenatal screening was 28% in Medicaid.

John Bramhall: Thank you. That's helpful.

Sheila Rege: A show of hands... so this would be contracting it. A show of hands on how many would be supportive of something like this. Actually, I am probably like you, Kevin. I would probably go for that, because of that reduced equivocal at that point, and...

Chris Hearne: My hesitation with this is, that it's basically outlying a contingent testing strategy, but I don't think we saw any evidence in the studies that looked at how that works and whether that works. So, if we made that decision, we'd be pretty much outside the scope of what we were presented.

Valerie King: Do you want me to respond to that at all?

Sheila Rege: Yeah.

Valerie King: So, we weren't really asked to look at contingent testing that was out of scope. I will say that there was a whole contextual question that I didn't talk about, which was what's the effectiveness of the test in high risk populations. So, there was a Cochran review that addressed that. It has about 40 studies in it. There were a good number of studies included that did look at a contingent strategy. It appears that the test works about as well in that way, because it's a high risk population. So, if you have a prior serum screen or ultrasound that says there is increased risk, now you are high risk. So, the test seems to work about the same no matter who you are applying it to.

Kevin Walsh: The Kagan paper, I think, talks about that staged testing. So we do have some evidence. We make conditions all the time based on the evidence that we're given when we have concerns. So, I think it's reasonable to potentially put conditions on it.

Valerie King: There was one of the economic analyses, one of the Walker ones. Dr. Johnson, that was the one that she was showing data from and graphics. And they really looked at comparing no screening conventional screening, universal cell-free DNA screening, and contingent cell-free DNA screening. Then, they analyzed that about perspective. So, payer, governmental, societal perspective. So, all of that was in Walker. We thought that their assumptions relative to what rates of XY and Z were in Washington were reasonable. It was a good quality study. So, I think that's something that if you want to delve a little more into, we're happy to detail it.

Tony Yen: What I appreciated was the evidence that the vendor presented. I think it was on slide, if I'm referring to it correctly, 20 and 21 shows the prevalence, the performance of the test prevalence percentages, and slide 20 actually shows how the test performs in terms of cell-free DNA with lower prevalence populations. That, to me, was I think convincing, that it actually works well within a lower prevalence population. Perhaps, that already embeds in the age

cutoffs. I do appreciate where the agency is coming from, but the evidence seems to be somewhere different.

Sheila Rege: So, you are advocating for cover.

John Bramhall: Dr. Cheng, this is a bit subjective, I know, but in your practice, do you sit down with a women who is, let's say, 12 weeks along, do you say I think you should have a cell-free test? Or do you just say here's the test we're going to do. I mean, everyone gets... it's automatic.

Edith Cheng: Never automatic. I generally sit down with somebody and basically kinda say it is... every woman who is pregnant is offered screening for certain chromosomal abnormalities. Down syndrome is the most common and that you're most familiar with. These are the options available. That's kind of... I go through what they are. I actually explain what cell-free DNA is. So, if I see them... if they come in at 9 or 10 weeks, I explain all of this to them, and it's their option. Then, they say, okay. This is what I want to do. We then schedule her appropriately for all of her necessary visits to accommodate that.

John Bramhall: So, is it then, not to put you on the, but is it her decision? Or...

Edith Cheng: Yes.

John Bramhall; ...it's her decision to make a scientific evaluation of whether the test is appropriate for her, not your decision.

Edith Cheng: It's not my decision. It's my decision to inform her.

Female: It's always the patient's decision.

Edith Cheng: Just as it is the patient's decision...

Sheila Rege: Are you saying, is it the husband's decision? Where are you going with this?

Edith Cheng: Just as it is a decision for that example of the 27 week pregnancy where I am highly suspicious that this baby has Down syndrome, she has the right not to do any kind of testing, even in a, what I consider is a blood draw. We would get the result, but she has that right to not take that test.

John Bramhall: So, I get that... you sit down, so the point is, should it be conditional? It looks like in your practice, it is conditional.

Edith Cheng: It is conditional in my practice, but I will also say that as Kevin knows, I am in Tri-Cities. I am in Arlington. I am in Yakima. Half of the patients that I see in the MFM clinic don't speak English. So, the ideal state, of course, is that. So, I think... I will say that I... approving this with condition, I think, has some issues. I

know that we're all concerned about it, but approving it does have some conditions, because I think that the point raised earlier is that we are already offering quad screens and have been doing that for 20 to 30 years really without condition. I will just also tell you that patients are not counseled about their quad screen. Many of them don't know what they're getting with their quad screen. So, it's going to be the same situation with the cell-free DNA.

Sheila Rege: Have they changed anybody's mind? Since it's only two saying cover with conditions and majority, even after, saying... has anybody changed their minds or want to speak on... anybody interested in a period of coverage, not for eight weeks, just, okay. Any other discussion or do you want to kind of take a final vote?

Mika Sinanan: We've heard one condition. Are there any other conditions? Kevin, did you have any other conditions you were thinking of?

Kevin Walsh: My condition was that we do the sequential screening.

Mika Sinanan: Beforehand. Okay. The quad screening.

Kevin Walsh: No. Not the quad screen, because the quad screen doesn't happen until later.

Mika Sinanan: 16 weeks.

Kevin Walsh: You do the initial screening at 12 to 13 weeks. If that's positive, then you do cell-free DNA.

Mika Sinanan: So, what's the first screening?

Edith Cheng: Okay. So, the first trimester screening requires that we do an ultrasound between sort of, like, 10 to 13 weeks, requires that we get a nuchal translucency, or a nuchal thickness, which is the measurement of the back of the fetal neck. So, when we talk about access and equity of access, it has to be trained sonographers. It has to be trained MFM or somebody who is certified. We actually have to have a number that certifies us in order to do these NT's. So, that alone restricts your access. So, that's your first trimester. So, you need that ultrasound. Then, you can draw blood for two maternal markers, pap A and ACG. So, these three are independent variables for which we create likelihood ratios. Then, the three independent variables gives you a likelihood ratio. So, it is a little bit of quad. It's a first trimester screen to give you some answers that, again, it is an earlier version of a quad screen, but it requires a very specialized ultrasound that you will not have equity in terms of access.

Kevin Walsh: But it only changes the results by 5%. Right? Doesn't the nuchal translucency only shift things by 5%?

Edith Cheng: Yes, but you can't really create... right, but you can't really create a first trimester screen without the NT. Then, you might as well just go for the cell-free DNA, because your predictive value and your sensitivity just using the maternal serum without the ultrasound is lost.

Mika Sinanan: Just to be clear, the ultrasound is going to happen regardless of anything that we agree on today. Would those two other tests happen regardless of cell-free DNA? Or are they replaced by cell-free DNA?

Edith Cheng: So, you can do one or the other. They are two different types of first trimester screening for aneuploidy, for Down syndrome.

Mika Sinanan: So, it's one or the other, but not both, in general.

Edith Cheng: Correct.

Mika Sinanan: Okay.

Edith Cheng: And I think what Kevin is proposing is that we... for first trimester, let's just focus on first trimester, that we just do the first trimester screen, which is your NT and your two serum analytes, generate a risk. If that risk is negative, then you're done. You've theoretically done your first trimester screening. If your risk is positive, then, before cell-free DNA, we would move to counseling for an invasive procedure. That generally would be a CVS. Now, what we have is cell-free DNA. What Kevin is proposing is that we would offer cell-free DNA in that. So, that's the contingency.

Mika Sinanan: And if we were to do that contingency process, just the accuracy, the ultimate accuracy before birth, of course, any different? Are we going to identify any more at-risk pregnancies, truly at risk pregnancies by doing cell-free DNA? Or not?

Edith Cheng: I'm going to answer it this way. I want you to conceptualize that this is no different than if you are comparing a quad screen with your cell-free DNA. It gives you two different piece... so again...

Sheila Rege: It's different information.

Edith Cheng: ...it's different information. All the first trimester screening with the NT is a red flag. It just says something is wrong. Which is what your quad screen is telling you.

Mika Sinanan: But is it the same things are wrong?

Edith Cheng: Not necessarily.

John Bramhall: Kevin, the conventional test, this is conventional testing, as we looked at it before that generates that number of 44 in 1000. Is it your thinking that you would identify those 44 and then do cell-free DNA on them. So, you're reducing... instead of testing 1000, you're testing 44 people. Now, you're accurate. You've got information that you can act on.

Kevin Walsh: The accuracy is no better. It's just that you've saved those other...

John Bramhall: You've got something, which will allow you to make a very specific set of decisions on those 44. That's what...

Kevin Walsh: ...I don't think that approach changes the quality of the care that we're offering everyone. Maybe Edith disagrees with that, but I can't see that it does. That's why I'm saying, if the quality is the same, if the benefit is the same, then it becomes appropriate to look at cost, as well.

John Bramhall: You're thinking now, in terms of equity...

Edith Cheng: Well, I would caution that this contingency proposal is you're replacing one screening test with another. So, once you have a positive screening test, whether it is cell-free DNA or a quad screen, or the first trimester, it, again, it just says something is wrong. Really, the definitive test is an invasive procedure to get to a broader diagnosis. What we've introduced now is a noninvasive but limited test to look at the red flag and say, well, let's get rid of these three noninvasively, but it doesn't take away from the possibility that you have other things going on. So, that... does that make sense?

Sheila Rege: Like cancer. It's a generic cancer test versus something that just does Down's and those other two that people don't know. So, that's... but it doesn't sound like we're changing anybody's mind. So...

Mika Sinanan: Well, but the last set of comments confused me. Imagine that this cell-free DNA testing required a critical re-agent that is no longer available. It was in Puerto Rico and the factory was crushed by the earthquake. So, it's not available for a year. Is your comment to your patients, it's okay. We have other testing and other ways to get to the same information and figure out the risk. Don't worry about it. Or is it, that's really too bad, because we've lost something that we previously could do better or faster, or easier or cheaper. So, that's the question is, I don't understand that, because that's the value measurement.

Edith Cheng: We can always fall back on ultrasound and maternal serum screening. It will give you information, as opposed to no information at all. The value is going to be that the maternal serum information is... has less positive predictive value. It has a broader false positive. Right. The cell-free just kind of narrows it down a little bit better for you, but you will always still have serum screening, always, as a fall back.

Laurie Mischley: And the reminder that it will delay the diagnosis and require additional visits. Right?

Edith Cheng: Correct. Well, yes. So, I know you guys are confused in some ways, because I think that what Kevin has brought up, and because he's well versed in the screening is that, we actually have many different ways of screening. So, we have a first trimester of serum screening that requires a specific ultrasound. We have a second trimester serum screening only, which is your quad screen. So, there are places in which they just do the first trimester screening, because it's good enough. It basically deals with the question of delayed information. So, what's happening is that the cell-free DNA is just a more sophisticated first trimester screening if you will.

Kevin Walsh: Kevin suggested... so I was listening to him very carefully, that this proposal, what the agency recommends, doesn't change the quality of our care. It doesn't change the quality of our care. Would you agree with that?

Seth Schwartz: I think we're getting a little bit lost in the weeds. I mean, I think, the data that we looked at showed us that we have a test that has a higher positive predictive value, a higher at least equivalent negative predictive value. It's a good test. I think we're... the cost question is out there, but I think if you took cost and you said, okay. The cost of the current screening and the cost of cell-free DNA are the same, is there any reason not to offer cell-free DNA? And I haven't heard anything that would make me feel otherwise. I think the cost is an open question. We're talking about utilization. We're talking about weird scenarios where we might do one thing or another. I think, again, we are just getting a little bit lost in the weeds of how these things could be used, but ultimately, do we want to restrict access to what, to me, looks like a better test is the way I'm starting to interpret this conversation.

Sheila Rege: And a test for Down and those other two.

Seth Schwartz: For these aneuploidies. It's not just Down's. It's the three, which are, and we haven't talked about this. So, we're talking about some other thing. So, what is the likelihood of these other things? Are you talking about, like, 1 in 40,000 pregnancies? Are you talk... I mean, these are really rare things. Yeah. There may be some other things we're going to capture, but they're really, really rare. Does it matter? I guess, we don't know that. We haven't seen any data on that.

Kevin Walsh: Am I misunderstanding? I thought that it was not offered in Medicaid, except for high risk pregnancies.

Seth Schwartz: It's not offered on Medicaid. It's currently offered in PEBB. It's currently offered in other things. I think one of the... by restrict, I don't mean beyond what we

have currently, but in general, we're still restricting access to a good test for the entire Medicaid population. If we say you have to have this other thing first...

Kevin Walsh: I respect your opinion. That's your opinion.

Seth Schwartz: ...I agree with that. I'm not saying I'm right. I'm saying that's... and I may not, but...

Sheila Rege: That's why this is difficult because somebody mentioned here it's surprising that there is not more data on that. There is another trial. Any other discussion? Anybody not want to vote right now? Raise your hand now. Okay.

John Bramhall: I just have... it's my last question. I asked you earlier about... and I got beaten up for... the conventional screening is offered to all women that come to see you and recommended by you to those women 100% of the time. Or do women come to you, and you say, I don't think you need any screening. They get the screening.

Edith Cheng: ACOG, SNFM, every pregnant woman is... it's mandatory that we discuss and offer. They don't have to do anything, but it's a requirement that they are offered.

John Bramhall: Right. And you offer it and it's your professional opinion that they should undertake these screening tests?

Edith Cheng: It is my professional opinion that they should be offered. They should be educated and offered. Then, the decision is their choice.

John Bramhall: That's a little semantic, but okay. Alright. I go to my car repair shop, and they say you need a new alternator. I get a new alternator. Right? I mean, they don't say, but it's up to you.

Kevin Walsh: It's called patient informed care, John.

John Bramhall: I mean, anesthesia, right?

Sheila Rege: Any other follow up on John's... any requests for conditions?

John Bramhall: Not to talk. No. Not to talk.

Sheila Rege: So, we can go ahead and take a final vote. On coverage of this, unconditionally or with conditions, using your pink little cards.

Josh Morse: Eight votes to cover, and two to cover with conditions.

Sheila Rege: And I think we've had time to opine our thing. So, going on to doing our homework. Page 7, now we have to go to page 8. We talked about Medicare local coverage determinations. If a Medicare patient, I guess, it could be a kidney failure patient, a younger patient, but where there is none there. We've already been informed. Clinical practice guidelines. I don't think our coverage is different than some of them. I let our clinical expert if she wants to opine, opine, but otherwise.

Josh Morse: And we need to check that we're consistent with any Medicare national coverage decision.

Sheila Rege: We're not out of line. Then, we are done with that topic. Last chapter, Health Technology Assessment reviews in progress. It's on the website. I don't know if Josh wants to comment. Again, we will be bringing back the whole exome for final, final in March. So, that'll be in addition.

Kevin Walsh: Can I… I'm sorry to interrupt. I just want to say I really appreciated the presentation by the vendor. When I talked to Dr. King, she deferred to Josh and said that this high level overview with the ability to drive into more detail, if we requested it, was something that you had recommended. I appreciate that. I would advocate that we make this kind of the approach moving forward for all of our reviews.

Sheila Rege: Any discussion on that, or any objections? I will say, there is a lot of work, I know, that happens behind the scenes. Christine and Josh, and I'm sure other people to put this together for us. So, thank you, very much, for all your work and support. We appreciate it. Anybody who has any comments on how we can make this process better? Committee members, since this was our first time, the dual, please email us and let us know if we can make the process better. There are lunches, and we will see you in March. Thank you.