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Emily Transue: ...did surveillance about 24% in patients who have testing versus not. Again, no data on impact on long-term recurrence, and these are based on four studies with a high risk of bias.

Prolaris similar population, again, high clinical validity, again a substantial impact on treatment recommendations, 37 to 48% seeing a change, back to about a 3:1 ratio of reduced increased intensity. Again, no known data on long-term recurrence, smaller number of studies here. Decipher is a different population. So, this is using men who have had a radical prostatectomy who are deciding about adjuvant therapy, typically radiotherapy. High clinical validity, again a substantial impact on treatment recommendations, 18 to 42%, this time, an actually roughly equal ratio of decreased intensity to increased intensity. Also, substantial decrease in decisional conflict for both providers and patients here, a small number of studies.

Cost impact on prostate GEP, you'll see more data later around this, but again, kind of all over the place, including positive and negative net impact and a generally low quality of evidence.

Guidelines: American Urologic Association and American Society for Radiation Oncology saying these have not shown a clear role in decisions about active surveillance for localized prostate cancer. NCCN, though, recommending Decipher after prostatectomy if specific criteria are met on Prolaris and Oncotype Dx for low-risk patients who would be a candidate for either active surveillance or more definitive therapy.

Payer policies around prostate: No national coverage decision from Medicare. We do have local coverage decisions, which are covering with conditions sort of basically what we discussed about, but a little bit more detailed. So, Decipher after radical prostatectomy that has to have been pretty recent, within five years. The PSA has to have nadired after surgery.

They can't have already had the neoadjuvant therapy, and they have to have an adverse surgical pathology. Prolaris and Oncotype Dx for localized small tumors are either low or very low risk or favorable intermediate risk just for Prolaris, and again, the requirement that they be used to determine treatment. AETNA, Cigna, and Regence either don't have coverage or don't include them specifically on a list of covered medications.

Colon cancer: These are used in patients with stage 2 disease, so into the muscle but not through it. Unestablished clinical validity, per the NCCN guidelines. Impact of treatment recommendation, again pretty high. Increased intensity for 11%, decrease for 33%, and essentially the same numbers coming out for the patient choices for patient recommendation. Again, no data on long-term recurrence.

Cost impact: Really, only one study here showing a slightly lower lifetime risk with testing than without.

Colon policies: There are no clinical practice guidelines that have recommendations around these. The NCCN guidelines, which was felt to be of fair quality, said there is no evidence of predictive value for these.

Policies: No Medicare, national or local coverage decision, and no coverage from AETNA, Cigna, or Regence.

And the last one, I promise, multiple myeloma: Here, really not much data. So, unclear how much these tests add predictive information beyond the clinical prediction. We don't have any studies available on clinical utility, and the guidelines kind of saying it could be helpful. More research needed, and either not covered or not mentioned by Medicare, as well as AETNA, Cigna, and Regence.

So, back to our kind of questions, as we thought through each of these stages of potential impact. First off, do these test results add significant information about prognosis and recurrence risk? And here, it, it varies by test. The strongest information we have is really around the breast tests, especially Oncotype Dx, but the others, as well. There are a number of studies in prostate, but not quite as substantial as for breast and not really well supported for colon or multiple myeloma at this point. Second question, do these tests impact treatment recommendations, and here, we have really strong evidence for a very high impact on treatment for both breast and prostate. We only have one study to look at in colon, but it only showed a large effect. We don't have evidence around multiple myeloma. Do those results actually impact the selection of patients? We

have kind of limited data, but what we have suggests that patients pretty closely follow what the recommendations are. Finally, of course, the big one, does this impact patient experience and outcomes, both in the short-term and in the long-term?

Here, I would say we have extensive evidence here that many patients will choose to forgo chemotherapy or hormone therapy based on the results of these tests, and a smaller number will choose more aggressive treatment. So, this is having a very significant impact on what patients go through in terms of treatment and the associated risks and side effects. Long-term, we don't have much evidence. We really have one trial showing that patients with a high clinical risk and a low Mammaprint score can safely forgo chemotherapy, but we don't have a lot of that long-term data.

So, kind of thinking back to this model, what are these tests doing? Again, people start out with a certain clinical risk. Many of them will be rearranged by this testing. Most of them toward a lower risk and less need for treatment. Some in the other direction. So, we know that they're shifting our assessment of risk, and that's impacting decisions. What we'd love to have is ten years later, how do all these people do, and we don't have that.

So, variable on the first question, yes on the next couple, yes on short-term impact and really unknown at this point on long-term impact and very variable estimates on costs. What do we do with all that?

So, I think we've really seen here that the value that patients and providers place on these tests is very high. We're seeing a huge impact on treatment recommendations, essentially in every study. We know that adjuvant therapy carries significant short-term and long-term potential impacts on symptoms and associated quality of life. We are not likely to get in the short-term that really long-term data on kind of the final impacts of all of this, between the timeframes and barriers to stud. We would argue that given the value that patients and providers are putting on using these tests to make these very significant preference sensitive decisions, that deferring coverage, that isn't reasonable.

Gregory Brown: No. I actually had a question for Dr. Davidson. I don't think you're ever going to have a well-designed study to do this long-term, but do you have registries that track this so that you can get a data-mining effort out of the registries to see if it looks like it's effecting long-term outcomes also?

Nancy Davidson: There are a number of registries, but actually, we taxpayers have paid for two trials in the United States on one of these tests, on Oncotype Dx, through the National Cancer Institute. We have one randomized trial that looked at using the Oncotype Dx to do the recurrence scores on those women with no negative breast cancer. We have another one for positive low burden node positive breast cancer, and the design in each case was that women who have the low recurrence score would receive only hormone therapy. The women who have the high recurrence score would receive hormone therapy plus chemotherapy, and the women in the middle, those intermediate people where there was [inaudible], there is actually randomization between chemotherapy or not in addition to hormone therapy. We have seen the very first results of one of those trials in the New England Journal of Medicine a couple years ago. We saw the results of giving hormone therapy alone to node negative receptor positive breast cancer patients if they had a very low current score on Oncotype, and they do great. They do really, really well. We're waiting for the results of the randomized portion of those trials. So, it is gonna come, but if I'm allowed to interject an opinion, I would agree with your assessment here, which is, it's not going to be tomorrow or next year. I think your conclusion number three, or your recommendation number three is a very good one.

Gregory Brown: But it's at least in the pipeline is what you're saying.

Nancy Davidson: Oh, yeah. Yeah.

Gregory Brown: Awesome, great.

Nancy Davidson: And the Mammaprint information that we have, I think we already have also in the New England Journal of Medicine.

Emily Transue: So, our assessment is based on all of that, but the tests should be covered when there is high evidence of clinical validity and also of impact on decision making, that that would be the rubric for making these decisions.

So, how does that play out? For breast GEPs, we would recommend that Oncotype Dx, Endopredict, Prosigna, and Mammaprint be covered with conditions and those be early stage cancer, stage 1 or 2, as we discussed, estrogen receptor positive, HER-2 negative, and either lymph node negative or 1-3 positive, and the requirement for all of these is that test results would impact treatment decisions. Mammostrat and BCI, more of the data is around decisions around hormone therapy. So, it would only cover those for women in that situation who are deciding about hormone therapy and not about chemotherapy. Other tests may come down the road, and those could be covered at agency discretion, if developers can

show prognostic equivalence or superiority to the tests that we're covering.

For prostate, recommended coverage...

Sheila Rege: Can I ask a question of the clinical expert on the breast? Do you envision a point where somebody would do an Oncotype Dx and then order... because now if it does get approval, then order a Mammprint because that's, you know, kind of just your opinion on that.

Nancy Davidson: I would have to tell you that people do that. I get emails from folks who are trying to figure out what to do about that. Sometimes, what happens is, with the Oncotype, if you order that first, you get this intermediate score. And then, you and the patient are, like, ugh, you know? What are we gonna do here? So, there are some oncologists in that situation who would say, well now I'm gonna go to the Mammprint, and if the Mammprint is very high, I'm gonna go with the chemotherapy, and if it's not, I'm not. We have no evidence on that. I'll weigh in with personal opinion. This is totally personal opinion. I wouldn't necessarily represent all oncologists, but I kind of figure that there ought to be one per customer, you know? They, we ought to try to pick the single test that we think is the best for this situation and then go with that information.

Sheila Rege: Thank you. At least, from what I remember on the staging, the Oncotype Dx was considered level 1 and the Mammprint was considered level 2 evidence, but I don't think just for us to know that, just because of Oncotype Dx having more studies.

Nancy Davidson: I think they're... I haven't looked at that exact question for Mammprint recently, but it does have a very large randomized trial and knowing the [inaudible] which was pretty definitive.

Emily Transue: Then, looking at prostate, we would recommend for Oncotype Dx and Prolaris that these be covered with conditions, again, early stage disease and a situation where the test results would impact treatment decisions. For Decipher, coverage in men who have had a radical prostatectomy who are deciding between active surveillance and adjuvant therapy in a situation where either would be reasonable and where the test results would impact treatment decisions.

For colon and multiple myeloma, we recommend noncoverage at this time based on there just not being sufficient evidence to support coverage at this point.

Gregory Brown: So, would you be interested in an addendum to that. I don't know, my perception is this may change very quickly. So, your last point under breast at cover at agency discretion in the future, can we put that on all four?

Emily Transue: That'd be great.

Gregory Brown: Is that opening a can of worms or, it still allows you the option, right?

Emily Transue: Yep. That would be fine.

Gregory Brown: Okay.

Emily Transue: We would, yes.

Male: [inaudible]

Emily Transue: So, defining validity as saying that these do add substantial prognostic information beyond what you can get from existing staging data.

Male: [inaudible]

Emily Transue: The testing for that typically looks... many of them are done retrospective and sort of look at testing a sample and then seeing how that... a historical sample and seeing how the patient did. So, if you look at what the likelihood of a patient who had a sample ten years ago was of having a recurrence, how likely were they to have that based on the result of the test, and is that more information than you would get from having done just a clinical assessment at that time. Does that make sense? I don't think I described it very well.

Kevin Walsh: Yeah. I understand what you're saying. I have some problems with some of your suppositions.

Josh Morse: Do you care to use the microphone, please.

Kevin Walsh: Thank you. I understand what you're saying, but I have some problems with some of the suppositions, but I can... I'll discuss that later. Thank you.

Emily Transue: Okay.

Tony Yen: Question about... since these tests have become along, and I think the agency has paid for some of these tests, I think, since was it 2014?

Emily Transue: Yeah, 2014.

Tony Yen: Have you noticed any decrease in the cost of care for breast cancer for what the agency pays for? My gestalt about some of these tests is they are actually tending towards recommending less chemotherapy if you look at the aggregate.

Emily Transue: Right.

Tony Yen: And just intuitively, it feels like would that be less costly and with better outcomes?

Emily Transue: And I think intuitively, I agree that that makes sense. We've only seen the tests done in a couple hundred people out of the overall population. So, at this stage, we don't have the data to back that up.

Tony Yen: Thank you.

Gregory Brown: Okay. Thank you. So, next we are on the scheduled and open public comments. So, we have two people scheduled.

Josh Morse: Yes. We have two individuals scheduled.

Gregory Brown: Okay.

Josh Morse: And these are, they're both from Myriad, and they've agreed to pool their time.

Gregory Brown: Okay.

Josh Morse: To present.

Gregory Brown: We may begin. I'm sorry? Yeah. Actually, while we're waiting for those, if you'd like to introduce yourself and where you're from.

Karen Heller: I'm Karen Heller, and I am representing Myriad Genetics.

Gregory Brown: Just a reminder, do you, Myriad Genetics, represent one of the tests being used, and which test?

Karen Heller: Yes. I am going to be speaking about EndoPredict, second generation breast cancer prognostic. Thank you.

Karen Heller speaking about EndoPredict, second generation breast cancer prognostic introduced in the U.S. in 2017. A 2016 publication by Buus

compared the prognostic ability of EndoPredict, or EPclin and Oncotype RS using archive samples from the prospective ATAC trial. Based upon the long-term outcome data from the trial, Oncotype’s hazard ratio was calculated as 2.73, and EndoPredict was 5.99. You see that in the grey box, reflecting EndoPredict’s stronger ability to separate low and high risk patients with EndoPredict providing a bimodal result with no intermediate result.

In this slide, this is a more recent publication by Sestak who compared several breast cancer gene expression assays using the same ATAC cohort. Based on the C-indices you see highlighted here, EndoPredict’s prognostic ability compared favorably to the other assays for both node negative and node positive patients where they’re considering one to ten years in the top section or just years five to ten in the bottom section.

The 2016 ASCO evidence review concluded that EndoPredict has clinical utility according to the well-recognized framework for review of biomarkers put forward by Simon, Paque, and Hayes in 2009. Level 1 evidence can be achieved by a prospective randomized control trial, such as the types sought by the evidence review of the CEBP. However, such a trial is often not possible for biomarkers. On the other hand, previously randomized trials may have archived samples available. If the biomarker assay is run retrospectively on samples that represent the intended use of the test blinded to the outcomes, then it is essentially simulating a prospective study. Simon calls this level 1b evidence and suggest that this proves clinical utility. You see the requirements listed here. What is missing is where the clinicians will use the results of the test to impact decision making, and that has been confirmed separately.

In summary, EndoPredict’s prognostic accuracy is at least equivalent to other breast cancer assays and clinical utility has been confirmed based on a similar level of evidence 1b. EndoPredict is currently broadly covered by Medicare, most commercial payers, including AETNA, Humana, United, Anthem, and almost all Blue’s plans, including Premera and Regence, as well as numerous Medicaids, including current Washington policy. I would just like to clarify that EndoPredict does currently have expedited pre-authorization status. Thank you for the opportunity.

Gregory Brown: Thank you.

Devki Saraiya: And I guess while the slides are getting loaded, my name is Devki Saraiya, and I also represent Myriad Genetics, and I’ll be talking specifically about the prostate cancer gene expression assays, and Myriad offers the Prolaris test. So, we would like to support the agency medical directors’

recommendation for coverage of Prolaris to aid in prostate cancer decision-making, given its strong validation and demonstrated impact on treatment decision-making, and we would like to provide the following information.

So, as you're aware, there's widespread concern that early detection of prostate cancer, through screening programs, has led to the overtreatment of localized prostate cancer with about 90% of all men receiving treatment. Studying the clinical utility of gene expression assays in prostate cancer using the standard approaches is particularly challenging, given the long natural history of the disease and low event rate. Therefore, the alternative biomarker framework, such as that proposed by Simon et al and Karen just walked through, it is particularly helpful in assessing the prostate cancer biomarkers. So, if we look at the Simon framework and apply it to Prolaris, Prolaris' clinical validation studies meet a level of 2 evidence requirement for clinical utility, and this level of evidence warrants a change in practice, when there are compelling circumstances. We propose that the overtreatment that occurs in prostate cancer with its associated morbidities and the significant challenges posed by the long natural history of the disease qualifies as compelling circumstances that warrant a change in management.

Additionally, a chain of evidence can be applied. So Prolaris has been shown here in column two to have robust clinical validation studies and has been shown to be one of the strongest predictors of disease-specific mortality, as well as providing improved prognostic information, looking at oncologic endpoints beyond that achieved from the standard clinical features. In addition, Prolaris has been shown to decrease treatment intensity in a manner that is directionally aligned with a Prolaris result and increase the decisional confidence for patients and physicians, as was noted in the evidence report by the CEBP. This reduction in interventional impacts, the short-term patient experience by reducing impact, or reducing associated morbidities and their impacts on quality of life. This, combined with a long-term randomized data from the Pivot and the ProtecT studies, so, in column four, which have shown that treatment of low-risk localized prostate cancer does not improve mortality demonstrates that Prolaris can be used to safely better risk stratify patients and reduce overtreatment without increasing mortality. So, providing coverage for Prolaris would allow for consistency of care for Washington Medicaid members, as it's in alignment with the Medicare LCDs, and also the very recently updated 2018 NCCN guidelines, which make a stronger recommendation for the use of tumor-based biomarkers to help in the standard risk stratification. Thank you for your time.

Gregory Brown: Thank you.

- Mika Sinanan: Excuse me, can you please comment about the cost of the study?
- Devki Saraiya: The cost of the test?
- Mika Sinanan: Yes.
- Devki Saraiya: So, I believe that the Medicare rate currently, they just came out, it's about \$3800.
- Mika Sinanan: And, which is... there's a little difference in the way you're presenting relative to the breast cancer... Emily's prior presentation where when there was ambiguity or it would change treatment, that's when we're recommending.
- Devki Saraiya: Mm-hmm.
- Mika Sinanan: Or she was recommending that it be deployed. What you're recommending is that it be used and then a decision might be made to change treatment, which is a different question. Is that right or are you not...
- Devki Saraiya: No. I think it's similar to what she is saying. So, the idea would be, if you have a low-risk or a favorable intermediate... basically an early stage localized prostate cancer patient who was trying to determine whether to pursue active surveillance or definitive treatment or prostatectomy or radiation therapy, they would utilize the results from the Prolaris test to determine which direction they would go. So, it would be for the same... that patient who is trying to make a treatment decision.
- Mika Sinanan: So, the 90% overtreatment value that you gave is because there is no data about what the... whether or not higher or more treatment is helpful, and this study would provide that. Or is it because people have made treatment decisions absent this, and they wouldn't change their plan?
- Devki Saraiya: So, the 90% treatment, it's actually greater than 90% of men currently just receive treatment. So, it's not necessarily the 90% are over-treated. It's 90% of men with low-risk prostate cancer, according to the data, currently pursue treatment, and that's in the absence of having a result like the Prolaris result or gene expression assay. That's based on them making a decision based on just the clinical features, and currently, if you look at the NCCN guidelines, the vast... if you look at the options for an early stage patient, they could choose after surveillance or treatment and currently the vast majority choose treatment, and what the studies have shown, in

terms of decision impact with the Prolaris result is that when a clinician and patient have that additional gene expression information, which is shown to have improved prognostic information, they are more likely to choose active surveillance that is directionally aligned with the results. So, if the result came back saying that they have a low risk of disease specific mortality, ten-year disease specific mortality, they're more likely to choose active surveillance than treatment. Does that help clarify?

Mika Sinanan: Thank you.

Gregory Brown: Next, we have Dr. Valerie King from the Oregon Research Center. Thank you.

Valerie King: Good morning. So, in your packet, you have a full slide set and because Emily has covered guidelines and policies fairly well, I have moved those to the back of the slide deck. We can certainly discuss any of them, but I'm going to be skipping the guideline and policy slides and one of the background slides that she covered very well.

Gregory Brown: Thank you.

Valerie King: So, just to give you a little bit of an idea of what order we're going in here, I'm going to be discussing a bit of background, what we did in terms of the methodology to do this evidence review, and then, I will be reviewing the evidence by test, giving you a grade summary of each one, and then again, the clinical practice guidelines and payer policies we've moved to the back that we can go into with time and questions. The four conditions under consideration in the key questions were breast, prostate, and colon cancer, and multiple myeloma.

There are certainly a growing number of gene expression profile tests for cancers that do help inform treatment decisions after a cancer diagnosis. The theoretical benefits of this kind of testing are more appropriate treatment decisions and improved patient outcomes, and the Holy Grail is really improved survival and avoidance of treatment that you didn't really need. So, the purpose of this evidence review was to review the clinical utility and the cost-effectiveness of these selected gene expression profile tests for the four cancers.

Gene expression profile testing identifies genes and cancer tissue that make messenger RNA, that carry genetic information that encode proteins. So, they are designed to provide additional information beyond clinical pathologic information so that if a cancer is judged to be not

ultimately going to recur or be dangerous or impact longevity, that active surveillance or decreased intensity therapy could be undertaken.

Just to give you a little bit of background about how these tests are regulated, I know this is something that the medical directors think quite a bit about. All tests are ultimately regulated by the FDA, but the FDA has discretion in its requirements for how they regulate these particular tests. So, these tests are developed and validated often by in-house laboratories, and a specific reference laboratory is generally the one that's putting out these tests. So, those are really regulated under CLIA, the Clinical Laboratory Improvement Amendment, and then the FDA clearance can be asked for by a test manufacturer and approval is not actually required for these lab developed tests, or LDTs. So, Mammaprint and Prosigna, two of the breast cancer tests have received FDA premarket approval, but the other tests are marketed as LDTs. So, LDTs have to meet sort of the general regulatory standards of CLIA, but the standards do not place any requirement regulation or standard on test validity.

The scope of this particular evidence review was for adults with any of these four cancers. The intervention were the specific gene profile tests that we listed. The comparator was care without the use of one of these tests or with an alternate test.

These are the lists of the tests that we considered. These six for breast cancer, three for prostate cancer, two for colon cancer, and two for multiple myeloma.

I think, importantly, the outcomes that we were looking for were hard clinical outcomes, morbidity, mortality, quality of life, impact on patient or clinician decision-making, harms, such as the consequence of a false-positive or a false-negative that would really be false reassurance or false alarm, and then cost-effectiveness or other economic outcomes.

You have the clinical questions, the key questions in your packet. I'll just point out that the point of the evidence review is to look at clinical utility rather than clinical validity. We were asked to consider whether there were particular subgroups or subpopulations that would have more benefit or harm from these tests. I'll give you just a little bit of background, because I think these terms are confusion and overlapping, and how we used this language in the vernacular is not necessarily the way that we will be talking about it today.

So, I think you can think about prognostic biomarkers and predictive biomarkers and roughly this equates to clinical validity and clinical utility.

The FDA NIH working group defined a prognostic biomarker as one that is used to identify a likelihood of a clinical event or a disease recurrence or progression. For example, that would be the likelihood of a distant metastasis at some point in the future. On the other hand, a predictive biomarker is one that's used to identify individuals who are more likely to have a favorable or unfavorable effect based on exposure to an intervention or something else. So, an example of that is that predicting a positive or negative outcome from the use of a particular treatment.

There is a hierarchy of clinical utility outcomes, and we talk about all of these in this evidence review. So, analytic validity is really the base here. This is can the test actually detect a genetic variant, and that is sort of a baseline requirement. The next level above that is, does that detected variant relate to disease presence or absence or risk. So, Emily talked quite a bit about the clinical validity of these tests, and there is a review of that in your evidence report. Then, at the top of the pyramid here, we're looking at, are these actually useful? What is the clinical utility of these tests? At that stage, you're looking at whether the test can provide useful clinical information, particularly about treatment or management of that particular cancer for that particular patient.

Mika Sinanan: Can I ask a question before you move off of this?

Valerie King: Sure. Yeah.

Mika Sinanan: I don't use these myself. So, when you develop a panel of 21 or seven or eight, is it that they've developed a database of 10,000 different genes and done a data analysis and figured out that this batch of 21 or seven or eight correlates with a certain outcome, a black box sort of thing? That's one option. Or are they choosing those 21 specifically because they know that those are active in cancer generation in colon cancer or breast cancer and therefore, specifically targeting those. The former means you have to have the whole batch to have significance. The latter means you could have two or three that potentially still have value, even if not all of them are valuable.

Valerie King: Sure. So, when these tests are developed, typically they start with a whole bunch of genes and they look at which ones are most strongly correlated to disease recurrence or metastasis or some outcome to assure clinical validity. So, in...

Mika Sinanan: Combinations of them that are associated with those.

- Valerie King: ...yeah. So, as Dr. Davidson pointed out earlier in a question, these can be totally different sets of genes from one test to the next that still predict recurrence. So, you can have different recipes that sort of get you to the same result.
- Mika Sinanan: So, as a consequence of that, you really have to have all of the 21 to draw any significance from it. It's the batch. You can't look at individual elements of it and abstract value from looking at two or three of the 21?
- Valerie King: Right.
- Mika Sinanan: Is that correct?
- Valerie King: Yeah. That, it, it's the whole soup together, and if you had a Holy Grail of a particular gene, well, they would use that, but that's not the way these tend to work.
- Mika Sinanan: Thank you.
- Sheila Rege: So, Mika, what's always been interesting is the studies where they look at the concordance between the two tests, and I don't know if you're going to address that, then I'll wait, but each of these tests, you know, like you say, EndoPredict or Oncotype Dx, or MammaPrint, they're not 100% when you look at how they predict, and that always confounds me as a clinician.
- Gregory Brown: What percent are they, though, concordant?
- Sheila Rege: I think high 60s, like 70-75 is what I remember. So, that always... I mean, just instinct, you use one Oncotype Dx until somebody gives you great data, maybe MammaPrint.
- Valerie King: Yeah. So, the concordance piece really was out of scope for this particular review. It's an issue of clinical validity, which we weren't really tasked to look at. There are some studies, at least in breast cancer, that look at concordance for clinical validity, and they all have overlapping confidence intervals.
- So, let's take a look at the top of this particular pyramid and drill down a little bit on clinical utility outcomes, because that's what we're focused on. So, the most basic one would be that the treatment recommendation changes. So, as a clinician, with this particular test result, I would have a conversation with a patient and say, really, you're at quite low risk of recurrence, and I think you could safely forgo chemotherapy. The patient may choose or choose not to take me up on that, but the actual treatment

received, based on patient choice after discussion with the clinician, is that middle level, so what did the patient actually do? Then, at the top of the pyramid here, you have these longer-term, some longer-term outcomes, some shorter-term outcomes of morbidity, mortality, and quality of life. Ideally, we would like to know that the treatment recommendation results in an actual change in the treatment that's received, and the treatment that's actually received is correlated with a better prognosis, in terms of survival, a better prognosis in terms of fewer side effects, or less interference with your life, or that you just feel better about it, and that your quality of life is good.

I see a light on. Is that just a light on? Dr. Walsh? Okay. So, turning to the methodology a bit. For key questions one, two, and three, these are the effectiveness, efficacy, harm, and subgroups questions. We were willing to accept randomized control trials, but also nonrandomized studies that were comparative in any degree, both prospective and retrospective designs, and systematic reviews of any of those study types. For the economic outcomes, we were willing to accept cost-effectiveness studies or other comparative economic evaluations, and systematic reviews of those.

We searched a whole bunch of databases, and a lot of great literature sources and guideline sources. We, additionally, looked at trials registries to see if there were ongoing studies that might be influential in coming along. We looked at a whole bunch of guideline sources and the directed payer policy sources.

At the end of the day, we looked at almost 3000 studies, about two-thirds of those are in breast cancer with quite a few in prostate and colon cancer, and some in multiple myeloma. We had independent rating of two researchers for risk of bias using standardized instruments, and we classified those as high, moderate, or low risk of bias based on standard features of the methodology of those studies. Then, at the end of the day, we looked at the overall quality of evidence based on the grade system. This is grading or recommendations, assessment development, and an evaluation framework, and that is an international standard that is used.

The definitions that go along with grade ratings are here, and they range from high, meaning that we're quite confident that this finding is true, that the estimate that we give you lies close to the true effect. Then, that ranges all the way down to very low where we really think that we have no confidence at all in the estimate of effect, and that future research really could substantially alter that finding.

So, we'll go into the part of the presentation now where we'll go cancer by cancer. We're starting with breast cancer. Again, there is the most stuff here. So, this will be the longest section.

This slide just details for you the number of studies that we've found to populate the evidence review for each of these six particular tests. So, there were the largest number of studies for Oncotype Dx, with 38, and then MammaPrint had seven. Really, there was only one primary study each for Prosigna, EndoPredict, BCI, and Mammostrat. I just want to underline the fact here that the subject in these studies are basically women with HER-2 negative, estrogen receptor positive, early stage breast cancer. Most of the studies really studied women who were lymph node negative, but some also included women who had minimal node positivity, generally one to three nodes.

So, turning to the tests, in turn. First, with Oncotype Dx. There are three systematic reviews, and I will go through those first and then the additional studies that were found in the search that would contribute. So, first of all is the Blok systematic review with a moderate risk of bias. This particular systematic review did not rate the risk of bias of included studies at all, but most of the studies were of patients with lymph node negative tumors. There were 22 before and after studies with a total number of patients of 3700 and change. Then, the basic thing that they reported in the Blok review is, after testing, the proportion of patients who either had a more... a recommendation for a more intensive or a less intensive treatment after application of the test. So, for Oncotype Dx, they found that there was generally decreased treatment intensity recommendations, so about 50% of women had a change after testing with a recommendation for a less invasive treatment.

The Augustovski systematic review was assessed as having a very low risk of bias. It only looked at Oncotype Dx. The Blok review looked at several tests. It included 15 before/after studies of women with lymph node negative and early stage breast cancer, but they only put into meta-analysis seven of the studies that were at the very lowest risk of bias, and that was because they used a rather universal way of enrolling patients in those studies rather than selective enrollment. So, again, they sort of give you the idea that the proportion of patients whose treatment decision was altered and that could be as high as almost 29% in the meta-analysis. Then, they looked also at patients who were then assigned to get chemotherapy after the test, and that decreased by 9%, although I will point out that the I^2 , which is a measure of heterogeneity, was very high on that second meta-analytic result, which indicates that probably those studies for that result should not be pooled, but I think you can see in the one above it,

that the I^2 is zero. So, there is, at least, some evidence there that the treatment decision changes.

Then there is a systematic review by scope and colleagues. We did assess this as having a very high risk of bias. It included 28 before and after studies that described changes in recommended treatment after Oncotype Dx testing. The authors, I think, rightly did not present pooled meta-analytic results, because there was concern about heterogeneity, but Oncotype Dx use, across these studies, did lead to treatment recommendation changes in between 21 and 74% of patients, and in general, that was a recommendation to a less intensive or invasive form of therapy. I will say just in comment here that these before/after studies are actually particularly problematic from an epidemiologic standpoint. They are either looking at a group of patients compared to a group of historical controls. So, in my hospital, five years ago, ten years ago, this is what was happening to these patients versus this group who got the test now. Historical controls are particularly problematic because they've been well recognized as generally overestimating the benefit of new interventions. There is a second kind of before/after study that used patients as their own control. So, those kind are fairly common in this literature base. They look at a group of patients who have tissue diagnosis and a clinical pathologic recommendation for treatment. Then, they get the test and you look at whether the treatment recommendation or the actual treatment received changes. Those are also kind of at risk of bias, mostly from the fact that the intervention is not experimentally applied, but there is selection bias, commonly, in these studies, especially of clinicians I would say in this case, and that oftentimes these studies are really only looking at patients whose clinicians already have use of or a favorable attitude towards these tests. So, the case mix of both patients and clinicians can be quite different. They are also quite prone to outlier findings, and as you get more data, and multiple repeated measure, and not just a single before and after, you tend to see regression to the means. So, those more extreme values go away. There are also some issues, like Hawthorn effect, but I just wanted to say that this whole literature base is full of these kinds of studies, and I think they're a bit problematic. That's why you see low or very low quality of evidence on most of these.

Now, let's go into some individual studies. There actually is one randomized trial on Oncotype Dx, although it is not a very good study. It only has 33 patients in it, and the outcome that they looked at was response rate based on response to either new adjuvant hormone or chemotherapy. There was a difference, so that the clinical response rate was a bit lower for women who received chemotherapy, but that's quite a poor surrogate for survival.

Then, there were quite a few retrospective cohort studies. There were about six of them, and they were assessed as either having a moderate or high risk of bias, but overall, patients who had the Oncotype Dx test ordered did receive less chemotherapy or received chemotherapy less often than patients who did not have the test, and patients with the intermediate or high risk Oncotype Dx score were more likely to receive chemotherapy than those with low risk scores, exactly what Dr. Transue described.

Let's turn to the MammaPrint test.

Mika Sinanan: Sorry. Quick question about the Oncotype Dx. More studies for that than any of the other tests. Is that because it's been out longer or industry funding or both?

Valerie King: All of the above. Yeah.

Nancy Davidson: It's been out the longest. Also, I don't know that it matters or not, but Oncotype Dx was developed in the United States. MammaPrint was developed in Europe. So, they were studied on either side of the Atlantic.

Valerie King: So, MammaPrint was developed in the Netherlands, came later to the U.S.

MammaPrint in the Blok systematic review, there were four studies of almost 800 patients. Again, they looked at the change in proportion of patients with a recommendation for a more or less invasive treatment after testing, and you do see that difference in favor of less invasive treatment.

In the scope review, you again see treatment recommendation changes in 18 to 40% of patients and most of those do tend towards less invasive treatment.

I think it's important to discuss the Cardoso study. This is really the one high-quality randomized trial that you see in this literature base. It had a little more than 6.5 thousand women with early invasive breast cancer. It's really a combination of two things. It's both the MammaPrint gene expression profile test, but it's also the use of a particular risk scoring system called Adjuvant! Online, or a modified version of that. I think you really have to see those two things together, because they were used together. So, it's not just the test. It's the test with the scoring system.

Although there were more women in this study, the part that was randomized that has been reported thus far is about 2000 women who had discordant results on these two parts. So, they had either high clinical risk with a low genomic risk or the other way around. For women who had high clinical risk and low genomic risk, the rates of five-year survival without distant metastasis were similar whether they were treated with chemotherapy or no adjuvant chemotherapy. In the opposite situation with low clinical risk and high genomic risk, again, the risk was quite similar for chemotherapy and no chemotherapy. You can see the numbers there in the first situation, it's about 96 versus 95% and the second situation, it's about 96 versus 95%.

Tony Yen: Can I ask you on that last bullet point over there on the slide, could I interpret that as being that MammaPrint in this very particular setting with clinical risk could not really discriminate between those who would benefit and who would not benefit?

Valerie King: In that type of a situation where you've got... this is somebody who had quite low clinical risk based on the Adjuvant! Online scoring system. So, probably would not normally be recommended to get chemotherapy but then had a high genomic risk, and they were randomized there to chemotherapy or no chemotherapy. So, it probably didn't matter. Yeah.

John Bramhall: So, it's fair to say then, that in that last pool, the theoretical prediction of high genomic risk does not translate to any real risk. I mean, is that a fair statement, and this is the one study that really is done to the high level, right?

Valerie King: Yeah, so Dr. Davidson may want to say something as a breast cancer expert, but I don't see much discriminatory ability there, yeah.

Nancy Davidson: Short-term follow-up, right? These trials, it's not a matured trial yet.

Valerie King: And there are a ton of publications that are going to come out of this trial. We have just begun to see it.

Then, let's look at other types of study designs beyond that one randomized trial that are available for MammaPrint. There is a retrospective cohort study by Kuijer looking at 2000 women who were surgically treated in the Netherlands, and they compared women who had MammaPrint to inform treatment decisions in addition to the standard clinical pathologic factors that were normally used. The use of the test, MammaPrint, was associated with just slightly under 10% absolute reduction in the use of chemotherapy. That particular study group also

has a before/after study of 6.5 hundred women in the Netherlands, same sort of population. They estimated that after the MammaPrint test was applied, that treatment recommendations changed for about half of them and that chemotherapy actually administered did tend to comport quite well with that which was recommended. So, in about 10% of the cases, the patient had a different decision, but often they followed the treatment recommendation.

Tony Yen: Could I ask you about those two studies done there in the Netherlands. I'm sorry, I can't pronounce the Dutch last name over there, but what do you think about the applicability of those studies with that population in the Netherlands, how would that apply to the U.S., which is, I think, a little bit more heterogeneous?

Valerie King: Yeah, it's probably a little more heterogeneous in the U.S., particular I would think racially, but also socioeconomically. I do think that we have probably the impression of European countries being largely Caucasian. That's probably not all that true anymore, and that there are subpopulations, but in these studies, the vast majority of women were white, and it's a very different healthcare system. People have different access. There are differences, yeah.

Mika Sinanan: This study has to follow the organization you had earlier, it has clinical validity, but it does not have any utility, because there's no outcome.

Valerie King: Yeah. So, if you consider the outcome to be a change in treatment recommendation or treatment receipt, then it is evidence of clinical utility. It isn't that highest level of evidence of survival or quality of life.

Mika Sinanan: Or disease recurrence, or anything about their disease?

Valerie King: Yeah.

Sheila Rege: I'm interested in either our clinical expert or your comment on, it just came out in JCO, the article on community practice, that the results may not be as good as what we would theoretically. Any comments on that? And that may have been too late for your report. It just came out in February, and I can summarize, but if you wouldn't mind. I'm going to read from it. It says, gene test to predict breast cancer recurrence less cost-effective in real world practice, only one study, and I know England is also looking at it, because of all that. I wouldn't propose going backwards, but I just want the committee to know and they were interesting. They just looked at community practices 2005 to 2012, chemotherapy use was 30% and testing was 24%. They said it should have been lower, and they even

looked at before these tests came out. So, I'm just kind of curious. It's one study. I think Fred Hutch was involved.

Nancy Davidson: That I can't speak to, but I do think that you're right, that it's one study, and I think it would be a truism, certainly in oncology, and I think probably across maybe some other specialties, that when we do these trials, when we do these studies, we do them in relatively defined populations. Then, when we bring them out into the community, we're going to see some erosion, perhaps, in the findings, but I guess I would not personally think that the trial that you're talking about would change the evidence review that we're hearing about now, nor the conclusions that were drawn.

Valerie King: Yeah. It's always hard to tell when you put something into real practice what's ultimately going to happen. There was a study in Medicare that looked particularly at when they opened up payment for the breast cancer tests, what happened, and it was included in this review, because it was non-comparative, but I will just say that in actual application, there was much less impact in the Medicare population, and that probably reflects both clinicians and patients who are 15 or 20 years older than I am. So, I think you're going to see changes, as people are trained and are more used to using these tests in a real-world way, and that typically happens with diffusion of innovation.

So, this last study in this section by Tsai and colleagues. Again, before/after type of study and did look at whether the use of MammaPrint effected treatment decisions, and in this particular study, they only applied the MammaPrint test to women who had an intermediate Oncotype Dx score. So, this was the joint application of these two tests, or serial application of these two tests. So, for women in this intermediate risk with an Oncotype Dx score, the treatment recommendation changed with the application of MammaPrint about 34% of the time, and the odds of treatment went down. Then, in this study, they also surveyed clinicians about whether the application of MammaPrint influenced their decision, and they said that it increased their confidence in the final treatment plan for about three-quarters of them, but a few had the opposite effect.

Turning to Prosigna, again, this was a test that was looked at in the Blok systematic review, but there was only one before/after study on a single group of patients, and 12.9% of patients had more invasive treatment and about 37% less invasive. There were then two additional studies beyond the Blok systematic review, one by Hequet and one by the West German study group. By Hequet, about 200 patients, again, high risk of bias. Treatment recommendation changed for about 18% of women, and in this particular setting, the recommendation for no adjuvant chemotherapy

changed to the recommendation for adjuvant chemotherapy for about 13% of them, and a recommendation to no chemotherapy for 5%. This is sort of going in the opposite direction of what some of the other studies have said. So, this is actually more chemotherapy after the test than before it.

In this West German study group, again, about 200 patients, also at high risk of bias. Also, very similar results to Hequet with treatment recommendations changing for about 18% of women. Again, no adjuvant chemotherapy. Recommendation initially changing to recommendation for chemotherapy for the majority of those.

For EndoPredict, also covered by the Blok systematic review, but again, only one study available for this in that review; 34% with more invasive or intensive therapy, and 53% with less, and there were no additional studies that were located on clinical utility for this particular test.

Breast cancer index, again, this is a slightly different kind of test. So, really, looking to inform decisions about adjuvant endocrine therapy that is extended. There is one additional study, almost 100 women, U.S. based, with 26% of women having a change of treatment recommendation after application of the BCI, and that really was for recommendations for extended adjuvant therapy decreased. So, about 74% of women were recommended extended therapy before the test, and that went down to 54% after the test.

Gregory Brown: Sorry. I didn't interrupt fast enough on the previous one for the EndoPredict. Did I see in the public presentation that there was a publication in 2018? So, was that outside of your capture, I guess is my...

Valerie King: Yeah. It was out of scope for our review, and...

Gregory Brown: Okay.

Valerie King; ...we did get it in public comment, but it would not have met inclusion criteria.

Gregory Brown: Would not. Okay. Thank you.

Valerie King: It's really a comparison of clinical validity.

Gregory Brown: Okay. Thank you.

John Bramhall: Excuse me. Do you mind if I take you back one more...

Valerie King: Absolutely.

John Bramhall: ...study to the Prosigna? Do you happen to know... so 5%... on your slide, it said that 5% of women, there was a change in the type of chemotherapy that was offered, as a result of the testing.

Valerie King: Yeah.

John Bramhall: Can you explain how that is informed by the test? How does the test inform the type of chemo? Is it, are you... have you got any details on that? So, as I understood it, the test is an array test. It gives you basically a plus/minus kind of result.

Valerie King: Yeah. So, if the risk was judged to be quite a bit higher, then they may have changed the particular chemotherapy drugs, and that's just what was reported. Dr. Davidson may have more clinical detail on that.

Nancy Davidson: I don't know the details of this study, but I think you're probably right that I'm gonna hypothesize that if it came out with an especially high risk that maybe the oncologist decided well, you know, now I'm gonna use anthracyclines, as part of my chemotherapy regimen, and I wouldn't have, necessarily, otherwise, but I haven't read that, and I can't tell you that for a fact. That's a guess.

Gregory Brown: It's not a plus/minus. It's a score, right?

Valerie King: Yeah.

Gregory Brown: So, it's not plus, so if it's a low risk or, you know, if it was a really high risk, then I think that's the hypothesis.

Valerie King: Yeah. And some of these tests are plus/minus, you know, bimodal, and some of them are scored without so much of a cutoff, yeah.

So, going ahead to Mammostrat, there was only one study of this particular test in the scope systematic review. It's one of those prospective-retrospective studies, about 700 women, and they looked again at distant recurrence free intervals when treated with tamoxifen. So, this is really informing the use of adjuvant endocrine therapy. So, for women who had a low risk score, they had improved recurrence free intervals, and for the high risk group, they also tended to improve with chemotherapy or with the use of the hormone therapy. This was the study that Dr. Transue alluded to where it has this really paradoxical finding that

women in both the low and high risk groups benefited from chemotherapy, but women in the intermediate risk group did not, and nobody really knows what that's about. It shouldn't be that way, but it is.

So, just summarizing where we've come to on breast cancer, most of these studies do have a high risk of bias, but the findings are quite consistent. There is an association between test use and changes in recommended or actual treatment based on the test result, generally in favor of less intensive therapy. The largest body of evidence is on Oncotype Dx. There is a moderate amount for MammaPrint and Prosigna, but very little for the other three, and the evidence is limited to mostly treatment decisions and actual treatment received, and really, the only thing that we can say about survival is limited to MammaPrint and the results of the MINDACT study.

In terms of direct harms, no studies really reported anything related to false reassurance or false alarm of these tests. These are generally considered to be clinically valid tests. So, this is maybe less of an important question, but studies that did report on patient decisional conflict, anxiety, patient function, or patient perceived usefulness of the test all found small differences in favor of testing. Similarly, physicians tended to perceive the testing when they were asked to be useful, and that increased their confidence in their treatment recommendation.

So, looking at subpopulations...

Gregory Brown: I'm sorry.

Valerie King: ...yep. Go ahead.

Gregory Brown: Given your earlier comments, would you say that's a false sense of confidence?

Valerie King: As a clinician, I'm always looking for something that will help a patient, and I think that this is a bit of a hard thing, because some patients just want information, and some patients want information that's going to change what they will do.

Kevin Walsh: So do providers.

Valerie King: So, if you ask me do I think that these tests provide information, I think they do that. If you ask me to make a firm prediction about whether a patient will choose or not choose a particular course afterwards, I think many do but some will not.

Kevin Walsh: Isn't there an underlying supposition to all this that more information is better, and that more information leads to better decisions? It seems like that's what all of these studies are based on.

Gregory Brown: I agree. I also think that the difference, though, is most of the information you're getting is based on population averages, and this is, at least, patient specific information. So, I agree with you, it's based on that supposition. I'm curious, because I had two grandparents with multiple myeloma, and there's no evidence here, but in terms of looking at outcomes in all other aspects of healthcare, I mean, the whole concept of patient-centered care, this is really getting at that, because it's their patient-centered information.

Kevin Walsh: Filtered through the provider who is offering them the treatment.

Sheila Rege: As always, yeah.

Valerie King: So, with the caveat that we're already looking at a subpopulation of breast cancer, so these are women with estrogen receptor positive, sometimes progesterone receptor positive, HER-2 negative, early breast cancer with, at most, minimal node positivity. So, we're not looking at the entire universe of breast cancer already. There was some evidence that I will just say that some groups were less likely to receive testing. So, older patients were less likely than younger patients, African-American women were less likely than women of other racial groups in America, and women without insurance were, not surprisingly, less likely to be tested.

Nancy Davidson: Your slide says older patients were more likely to receive testing.

Valerie King: I'm sorry, more likely, okay. You're right. Yeah. So, these tests probably don't get applied incredibly evenly, and that doesn't really say whether the people that they're applied to have more or less information or a change in their treatment recommendation. It was just an interesting finding. These studies are a bit all over the map. So, for... if you were looking at differences based on subgroup for treatment recommendation change or actual receipt of treatment or morbidity or survival or quality of life based on a patient subgroup. There are really very sparse data here, and I don't think that we can make a firm conclusion about any subgroup.

Gregory Brown: So, just to clarify that, so older patients are more likely to receive the test?

Valerie King: Yes. Sorry. Currently, in America, older patients, maybe because Medicare, many local coverage areas do cover it.

Nancy Davidson: I think another possibility would be that for many younger patients, I'm giving the chemo. So, I don't need the test, right? We've already made the decision, and so it's an irrelevant piece of information.

Gregory Brown: That was going to be my question is, is it more of the younger patients, theoretically, premenopausal, more aggressive, full court press. So, I'm not going to? Okay.

Valerie King: Yeah. I think you've got this group between probably 50 and 65, so postmenopausal, pre-Medicare age group where we don't have a lot of data.

Gregory Brown: Thank you.

Sheila Rege: For our clinical expert, are you ...the... is there an age-cutoff you would do on any of these testings for breast cancer?

Nancy Davidson: So, since most of them are designed to try to think about the use of chemotherapy or not, I don't have any pre-existing chronologic age. I obviously have a lot of interest in comorbidities. So, if I'm not going to give chemotherapy, if I'm not going to give chemotherapy and you're 35, I'm not going to order the test. So, I think it is more based on general health and on patient preference.

Sheila Rege: Mm-hmm.

Nancy Davidson: Turning to economic outcomes, the Blok systematic review did summarize the results of cost-effectiveness studies for MammaPrint, Oncotype Dx, and EndoPredict. Then, there were some economic studies that were published after that systematic review by Hall and Loncaster. Then, there was one decision analysis on the BCI test.

So, Blok found two direct studies. So, there were two studies that compared testing to not testing, and they reported directly, not on the basis of modeling, but direct evidence from studies published in 2015 and 2016 that the cost per patient in U.S. dollars was \$400 to \$1367, increased with the use of Oncotype Dx. Then, there were 26 modeling studies that looked at cost-effectiveness results and cost per QALY or quality adjusted life year. In U.S. dollars, they found for Oncotype Dx with lymph node negative tumors that the cost/QALY ranged from \$3800 to \$43,000, a really wide range. Five studies looked in lymph node positive women and found a similarly wide range from almost \$2000 to almost \$50,000, U.S. dollars. There were five studies on MammaPrint, and the cost/QALY there

was \$10,000 to \$43,000. I would just say that all of those estimates are below what would be a generally accepted threshold for cost/QALY.

Additional economic studies beyond the Blok systematic review, Hall was a study that was done for the U.K.'s National Health System, and it was a feasibility study for looking at the addition of Oncotype Dx to their national testing program. Important to say here that they were using a cutoff score for low risk of 25 rather than the test originally designed to use a cutoff of 18. Then, this was compared to either standard clinicopathologic risk assessment or alternative tests. What they were trying to do here was decide which of these tests they would put into a trial within the NHS. That's why you see Oncotype Dx, MammaPrint, and Prosigna listed in the table, and you'll see very indistinguishable QALY estimates. Then, the cost ranges from negative to positive, but with highly overlapping confidence intervals, again, in U.K. dollars here.

Loncaster was a modeling study looking at the use of Oncotype Dx, U.K. dollars, budget savings of a little over £1000 per patient. Gustavsen looked at the BCI test for newly diagnosed women with estrogen receptor positive lymph node negative breast cancer, cost savings of around \$4000. The estimates of both the costs and the cost/QALY vary really widely among these kinds of studies. The quality of the economic evidence for Oncotype Dx and MammaPrint is low, and for everything else, it is very low.

This is everything we've talked about in breast cancer. So, for clinical utility, very low evidence for Oncotype Dx, moderate for MammaPrint. For clinical utility of patient management decisions, moderate for Oncotype Dx, low for MammaPrint, very low for everything else. Clinical utility for quality of life, very low for Oncotype Dx, Prosigna, and BCI, and no eligible studies for any other tests. For harms, very low for Oncotype Dx, no evidence for anything else. For cost-effectiveness and other economic outcomes, low for Oncotype Dx and MammaPrint, very low for everything else.

Skipping guidelines. Skipping payer policies. We are turning to clinical utility of the prostate cancer tests. I will say here that although we identified a couple of systematic reviews, they weren't very up to date, and we ultimately decided just to give you the studies that were included in those, and the newer ones together, but they weren't really able to be meta-analyzed, because of the way the outcomes were reported or salient clinical heterogeneity differences.

We did identify eight individual studies. They were all assessed as having a high risk of bias. They were all these before/after designs. Half of them used a single group of patients and half using a historical control group.

These tests, as Dr. Transue pointed out, are used in two different clinical scenarios. So, for Oncotype Dx and Prolaris, they are used after biopsy or resection to look at the risk of distant metastasis and aggressiveness of the tumor, and then Decipher is really only used after radical prostatectomy and to inform treatment decisions about adjuvant radiotherapy in general, or salvage radiotherapy, and there were fewer studies on Decipher.

So, now we'll turn to Oncotype Dx. Three studies used a historical comparison group, Albala, Dall-Era, and Eure. In general, these all indicated that there was increased use of active surveillance after application of the test. Badani was a single group of patients and found quite a similar result.

For Prolaris, there were two before/after studies, one of each type. Again, Crawford found that 37% of men, the recommendation for and interventional treatment was changed to one for active surveillance or watchful waiting after the test, and in short, that proportion was about 47/48% of subjects had a treatment recommendation, and three-quarters of those treatment recommendation changes were to a decrease rather than increase in treatment intensity.

For Decipher testing, these were two before/after studies using a single group of patients of men who had already had a radical prostatectomy. Gore found that the test use was associated with treatment recommendation changes, and this is really about the decision to pursue either radiotherapy or salvage radiotherapy, and I will say that although these odds ratios are statistically significant and have reasonably tight confidence intervals, the decision was ultimately much more influenced by the surgical pathology than it was the test. So, while you see odds ratios of about 1.5, 1-1/3, the odds ratio for positive margins, for example, was almost 2.5. So, the clinical features in this particular cancer really trump that of the test. Michalapoulos found quite similar things. So, for 42% of patients who have a recommendation of any active type of treatment, they were changed to a recommendation of observation or active surveillance only, and then 18% who had an initial recommendation of observation were recommended to have an active treatment.

There really were no studies that talked about false alarm or false reassurance, and absolutely nothing that talked about subpopulation with

the exception that these tests are used in sort of different clinical situations.

For economic outcomes on prostate cancer, there was sort of a province wide budget impact analysis done in the Canadian province of Ontario, and they really felt that they couldn't do a formal cost-effectiveness analysis, but they were trying to determine what the overall impact would be to the provincial budget. When they looked at the time horizon of 2016 to 2020, they determined that the total impact in Canadian dollars would be about 50 million, and most of this was due to the cost of the test, about 42 million of it. So, there was about 8 million that was due to increased use of services or more visits to physicians or things like that. Lobo looked at the cost-effectiveness of Decipher found that test based care increased on a per-person cost basis by a little more than \$5000 but also increased the mean QALY per individual a bit. The incremental cost-effectiveness here was a little more than \$91,000. Albala looked at Oncotype Dx, and this was a study that was done in a single insurance carrier in the state of New York and found that for that commercial carrier, that the total cost of care was a little more than \$2000 less for men who had received Oncotype Dx testing.

So, in summary, study findings based on kind of low high risk of bias studies for the most part, do show a consistent association between the use of these tests and recommendations for decreased treatment intensity, increased decision confidence on the part of patients and physicians, the quality of evidence is very low for these findings, and the quality of economic evidence is also very low.

Skipping guidelines. Skipping payer policies. We will turn to colon cancer. I can't tell you anything about ColoPrint. There were no systematic reviews, no individual studies that were eligible. For the Oncotype Dx colon, there was no systematic review. There are two individual studies, both of these assessed as having a high risk of bias. Srivastava did pretty consistently find that the use of the test resulted in changes in treatment recommendations, increased for 11% and decreased for 33% of patients. Brenner looked not at recommendations but actual treatment received and compared, found that there was increased intensive treatment for about 10% and decreased for 28%, quite similar to the Srivastava results. So, you see a little bit of a decrement between treatment recommended and treatment received, but it is fairly consistent.

Nothing about harms. Nothing about subpopulations. A tiny bit about economic outcomes. So, this is only for Oncotype Dx and this is in the setting of MMRP tumors. These are mismatch repair proficient tumors,

which have a worse prognosis, and it tends to be the population that these tests were developed for. So, using the Oncotype Dx colon test to guide therapy for resected stage 2 MMRP colon cancer, slightly lower lifetime costs of a little bit under \$1000 U.S.

Gregory Brown: So, the results on the Oncotype Dx are similar to what you saw in breast and...

Valerie King: So, the...

Gregory Brown: ...it's just the number of studies are smaller, so...

Valerie King: ...yeah. So, this company makes... so think of it as Kleenex, right? It's Oncotype Dx, but they've got one for breast cancer, one for prostate cancer, one for colon cancer. They are very different tests, very different genes.

Gregory Brown: Sure, very different genes, but...

Valerie King: But the same brand name.

Gregory Brown: In terms of, but, I mean, in terms of outcomes that you've said, they're very consistent with the...

Valerie King: In terms of what's available, what's published, it's consistent in that way with many fewer studies. The quality of evidence is nonexistent for ColoPrint, very low for Oncotype Dx for both clinical and economic outcomes.

Skipping guidelines. Skipping policies. Moving to multiple myeloma, I wish we could provide you more information, but there were absolutely no studies that were found for either clinical utility or economic outcomes. One of these tests is actually not even available in the U.S. yet. So, I think as Dr. Transue presented, there's some language in clinical guidelines that would suggest maybe in certain particular clinical circumstances, but they are certainly not in [inaudible].

Then, just wrapping up here, this whole evidence base, as I'm sure you've gotten the flavor of, is a bit limited. The risk of bias of these included studies, it did vary, but it was often quite high, and it's limited in terms of the types of outcomes that were reported. The clinical utility measures are largely limited to the influence on decision making for nearly all the tests, and there really isn't firm evidence about clinical endpoints. The populations included across the studies were generally not very diverse, in

terms of race, ethnicity, or socioeconomic factors. Many of the studies were conducted in Europe, which may or may not limit generalizability. Certainly, the health systems are quite different, and given limited evidence on effectiveness, economic modeling studies are a bit unfair, because they all adopt a certain input that assumes clinical effectiveness, but that is a guess and not based on firm studies. No real high quality evidence of clinical utility to guide decisions about any gene expression profile test with maybe the exception of MammaPrint in breast cancer, and then based on that one RCT by Cardoso, there is probably moderate quality of evidence for women with early invasive breast cancer who are also at high clinical risk by the Adjuvant! Online assessment tool that they could probably safely forgo adjuvant systemic chemotherapy if their MammaPrint score was low.

Moderate quality of evidence supports the use of Oncotype Dx for breast cancer, because of its impact on clinical treatment recommendations, but not on those other clinical utility features. Based primarily on modeling studies, low quality evidence, for both Oncotype Dx and MammaPrint in breast cancer, that they are cost-effective at rather conventional thresholds of cost/QALY, and for prostate cancer, colon cancer, and multiple myeloma, very low quality evidence or complete absence of evidence to support the use of those tests to improve clinical decision making and impact patient outcomes.

Gregory Brown: So, we are four minutes over our time. May we take a break and then ask you to come back and answer questions after the break?

Valerie King: Absolutely.

Gregory Brown: Okay. Then, before we do that, actually, we did not ask if there's anybody on the phone for public comment. So, that was my fault. So, do you know of anybody on the phone or on mute? Okay. We're on? Yeah. This Greg Brown, chair of the Health Technology Clinical Committee. We're reviewing genetic expression profiling. We are wondering if anybody is on the phone for public comment? Okay. Not hearing any, I think we have our answer. So, we will take a 15-minute break. We had 20 minutes, and we'll be back on time at 10:30. Well, actually, no. I take that back. I miscalculated, how about 15 minutes?

Okay. I think we mostly have our quorum. Dr. King, I want to thank you for a nice presentation and particularly focusing on what has not been covered and skipping over when it had already been nicely covered. So, this is our opportunity to ask you questions. Anybody have any questions that they'd like to start with?

Seth Schwartz: Yeah. This is Seth. I'm still struggling a little bit about our main clinical outcome being an alteration of a decision, as opposed to an actual clinical outcome. Yet, these tests seem to have been fairly widely adopted. So, I'm trying to really understand, sort of, how that's happened. The only slide I'm really seeing that shows us anything looking like a clinical outcome is on the MammaPrint. I think it's slide number 34. So, maybe you can go back to slide #34 with us. The Cardosa paper, and I am trying to understand this, because to me, this basically... well I'm trying to understand how this is used, because what this is telling us is that if you have patients, women with high clinical risk but low genomic risk or the reverse. There is basically no difference in their outcomes, but what I'm trying to understand is, was there treatment affected by this choice in saying that if you use... is this telling us that if you use the MammaPrint to guide treatment so that you are categorizing low risk patients as low risk and high risk patients as high risk, then there's no difference? Or is this just saying there's simply difference?

Valerie King: Yeah. So, I apologize. I think I explained that really badly on that slide. This was a randomized trial. So, the treatment decision was out of the hands of either the clinician or the patient. So, it didn't affect that. So, you've got randomized to either chemotherapy or not in these circumstances. I think what you can take away from Cardosa for this roughly 2000 women who were in this discordant clinical and test results situation is that for women who are at high clinical risk who normally would get chemotherapy, because they are at high clinical risk, if you then have the test that gives you low genomic risk, those women really have the same outcomes, and they can safely defer and not have chemotherapy. I think that's what you should take away from that particular study.

Gregory Brown: But it's really not a group that we would be looking at here. It's the discordant group.

Valerie King: So, it's the subset of women who, based on the pathologic characteristics of their tumor and their own characteristics would be judged to be at very high risk of recurrence and without the test you would basically always recommend that they get chemotherapy. What that study adds is to say okay, for that group of women, if you then do the test... if the test says yes, you're at high genetic risk, then it doesn't change anything, but if the test comes back and says you're at low genetic risk based on this test, then you really have the same outcomes with or without chemotherapy in that scenario, and you could safely avoid.

Gregory Brown: Okay.

John Bramhall: Well, the additional problem is when the genetic test suggests a high risk, there's no difference with and without chemo apparently. So, in other words, the result that comes out of the genetic test could be either high, or it could be low, but neither of those results have a connection to the reality of response to chemo.

Valerie King: Yeah. So, they only... again, they only, in this study, looked at women who had discordant situation. They will be... there are probably three papers in the pipeline right now, over the next one to five years, that will... so, this is a third of the population in this study.

John Bramhall: And do we... I know it's not in the study, but do we have a feeling for those women who presented with a high clinical risk and a high gene expression profile risk, they would show a difference when they were, in five years survival, when they were given chemo. That's not in the study.

Valerie King: They were not randomized.

John Bramhall: But do we know that from other information? High risk clinically, high risk supportive information from the test, get chemo, is there a difference between 95.9 and 94? Is there a bigger risk?

Valerie King: I've got the study. Let me look it up. Let me see if it's in there.

Nancy Davidson: So, I would say that our standard practice, you know, has been pretty routinely to consider adjuvant chemotherapy for people who have clinical high risk, and we have decades of randomized clinical trials that would support that. So, these genomic tests are only relatively recent in that the whole goal of them is to try to figure out whether you can do, as somebody said, try to go from these population randomized clinical trials to trying to individualize therapies for the specific patient, whether this added information would help with that.

Seth Schwartz: I guess I'm trying to understand. So, when I look at what this, what this paper shows me is that if you have discordant testing and clinical presentation, chemotherapy is irrelevant. So, nobody in that group should get chemotherapy, because everyone has a 95% chance of survival.

Nancy Davidson: So, I would say that these are pretty early results. Again, 95% is pretty good, isn't it, with or without the chemotherapy. The adjuvant therapy trial, I'm interested in a decade of results, and this is much earlier. So, I think we're gonna have to look at that question that you're asking over a longer period of time.

- Seth Schwartz: I understand that question, but at least... but what this paper is showing me here is that chemotherapy is irrelevant in anyone in that indeterminate group?
- Gregory Brown: I'm interpreting...
- Seth Schwartz: Am I misinterpreting that?
- Gregory Brown: ...it differently. I think I asked my other question improperly. So, to me, the second or the third bullet point is that if they were low clinical risk, high genetic risk didn't matter. So, if they were low clinical risk, don't even order the test, because you're not gonna give them chemotherapy.
- Valerie King: Yeah. I think that's fair.
- Gregory Brown: Right.
- Seth Schwartz: But it's randomized, so that doesn't make sense, because they randomize who got it. So, if you were low clinical risk, you might or might not have gotten chemotherapy.
- Gregory Brown: No, but... so I'm just saying practically, low clinical risk, so you've got low-low, low-high, high-low, and high-high. So, the... if you've got low clinical, you don't need to do the genetic test, because it's going to have the same outcome, at least based on early results.
- Valerie King: Yeah. So, based on the Adjuvant! Online scoring system. So, the low clinical risk is determined with a very specific tool.
- Seth Schwartz: But I thought the whole question for us is, if you have someone who is low clinical risk, should we be using it in that group?
- Gregory Brown: No. No. No. It's test results will impact treatment decisions. So, I mean, to me, again I would interpret it as if your clinical risk is low, you don't... it's not gonna change treatment decisions, because it's probably gonna...
- Valerie King: Right, but if it's high, it, it well might. So...
- Gregory Brown: Right.
- Valerie King: ...if your clinical risk is high, but your genomic risk is low, then it should change your treatment decision.

- Seth Schwartz: But we don't have any data to say that.
- Valerie King: Right.
- Nancy Davidson: So, may I? I'm just looking here at the abstract just to remind ourselves that the primary goal of this trial, and I'm going to read it to you. This is the abstract from the paper in the New England Journal of Medicine. The primary goal was to assess whether among patients with high risk clinical features by that model that she talked about and a low risk gene expression profile who did not receive chemotherapy, the lower boundary of the 95% confidence interval for the rate of five-year survival without distant metastasis would be 92% or greater. This was a noninferiority boundary. So, it's a very complicated trial design. So, what's been picked out is here is one element of it, but their goal was to use this to say that you had a 92% rate of five-year survival without metastasis, and they showed that.
- Valerie King: Yep. They absolutely met their primary endpoint and if 92% for you or your patient just isn't good enough, then the study doesn't apply.
- John Bramhall: But again, I just want to get a feel, it's not my area, but what would the number be, what's the percentage five-year survival with high clinical, end of story, high clinical presents and you start, presumably, the decision would be to start adjuvant chemotherapy. What's the five-year survival in all populations?
- Valerie King: Better than 90%, but Dr. Davidson can probably improve on that. It was not reported in this study.
- John Bramhall: Because your point, Dr. Davidson, is that five years is irrelevant.
- Nancy Davidson: I don't think it's irrelevant, but I think that it's not as mature as we'd like to see. It's certainly a common endpoint.
- John Bramhall: But, do you have a feel for the percentage survival at five years for high clinical treated with chemo?
- Nancy Davidson: I think it's going to depend, a certain amount, on how you describe... you define the clinical risk, right? So, I'm just going a little further here in this abstract. Again, I'm encapsulating for you what they reported. So, they were really focused on 1550 patients who had high clinical risk and low genomic risk, alright? Then, they say at five years, the rate of survival without distant metastasis, this group was 94.7% among those not receiving chemotherapy. The absolute difference in this survival rate

between these patients and those who received chemotherapy was 1.5 percentage points. Yeah. Thank you. You can go ahead and finish up then. Do you want to go ahead and finish up what I was saying? I was just reading the conclusions there. I guess, actually, I was going from results to conclusions.

John Bramhall: I know it's putting you on the spot, because it's taking you outside the study, but my human question is, if the endpoint was one week survival for everyone, you wouldn't see any result that was of any value, correct? And you take it to one year survival, five-year survival, are we, are we looking at anything clinically meaningful at five years in any way.

Valerie King: So, you're looking at a group of women who have early breast cancer and who by and large have quite good survival. So, if you're asking at five years for a high clinical risk group defined in this way, what is their five year survival with or without, then you're looking at probably 91 to 93%. This trial was designed at 92% as the cutoff for a reason. It was done in the Netherlands and other European countries in which this trial was done. They needed to show that it was at least as good as that, as what was happening anyway. So, survival is going to be better than 90% for high risk women who are treated with conventional chemotherapy at baseline.

Seth Schwartz: So, do we have any information about the group in this study, or were there any patients in this study who were high clinical risk and high genomic risk?

Valerie King: They are in the study but not reported in this paper. That is... and they were not randomized.

Seth Schwartz: What I'm struggling with is, we have a lot of papers that say to us, these tests are clinically useful, because they're going to change what you're going to do for patients, but we have a study right here, which says, that it doesn't really matter... that the testing doesn't really matter, 'cuz patients are going to do the same whether they receive treatment or not.

Valerie King: There's a group...

Gregory Brown: That's not what it says at all.

Valerie King: ...there's a group for whom this is, it would really change. So, for women who have a high clinical risk but a low genetic test based result, they will do as well without chemotherapy as they do with chemotherapy. Therefore, why take on the additional burden and adverse effects of the chemotherapy?

- Seth Schwartz: Well, that makes sense if I know, but I don't know what's happening in the group that's high and high. So, that's what I'm trying to figure out.
- Valerie King: You don't know from this paper, because they were not randomized.
- Seth Schwartz: So, this doesn't...
- Nancy Davidson: So, high-high would be in our many, many, many randomized trials of adjuvant therapy over many years.
- Seth Schwartz: ...okay. So, maybe help us out. So, what are we looking at in the high-high group at five-year outcomes? Chemo versus non-chemo.
- Nancy Davidson: For most of those patients, we're going to know them as high risk by clinical criteria and adjuvant chemotherapy in these populations might increase the recurrent... or decrease the recurrence rate by, like, 10% in absolute terms. So, it'd be pretty standard to give it...
- Seth Schwartz: So, it would be, like, 85% five-year survival without distant metastasis without treatment versus 95%?
- Nancy Davidson: Something like that. Remember that high risk, it may be the number of those. I mean, there are a lot of variables there. Could I read the conclusions to this study, because I think it might help with one of the questions you're asking about?
- Valerie King: Absolutely. Do you want me to...
- Nancy Davidson: Or do you want to read them?
- Valerie King: ...I'm happy to, since I've got a bigger...
- Nancy Davidson: Okay.
- Valerie King: ...piece here. So, the conclusion on the Cardoso study reads, among women with early stage breast cancer who were at high clinical risk and low genomic risk for recurrence, the receipt of no chemotherapy on the basis of the test led to a five-year survival without distant metastasis that was 1.5% percentage points lower than the rate with chemotherapy.
- Nancy Davidson: Then, given these findings, they estimated that 46% of women with breast cancer who are at high clinical risk may not require chemotherapy. That's their last sentence.

Seth Schwartz: So, that's the group that we're talking about is the high clinical risk.

Valerie King: High clinical risk.

Seth Schwartz: Got it.

Valerie King: And maybe as many as about half of them would not benefit from chemotherapy.

Seth Schwartz: Okay, but we've talked about... so, we've talked about two things that will happen with this testing. One is sort of downgrading those women so that you can get by without offering chemo. We've also talked about upstaging or patients who were in the low clinical risk group that you then might offer chemo to, because they're different. In that group, this paper seems like it's saying it doesn't make a difference.

Valerie King: That's my interpretation.

Seth Schwartz: Okay. Thank you.

Valerie King: And again, as these data mature, as you get ten-year outcomes, you might see a spread of those survival curves, but we don't know that yet.

Tony Yen: Dr. King, did you find a paper that was kind of similar for Oncotype Dx. It seems like this MammaPrint paper is probably the better one, at least...

Valerie King; It is.

Tony Yen: ...in terms of a, okay.

Valerie King: There is nothing similar. There is one randomized trial for Oncotype Dx breast. It's the Bear RCT, and it's tiny and does not look at an outcome that's really meaningfully.

Nancy Davidson: I actually would take a little issue with that. I think that there actually, as we talked about earlier, two incredibly large randomized trials of Oncotype Dx that have been performed. The one in node negative breast cancer, the first arm has been reported, and that's the women whose tumor clocked in with a very low recurrence score and who received only endocrine therapy, and they're doing just great. The randomized part of this trial has not yet been reported, and the trials that looked at this in node positive patients have also not been reported. These are randomized trials

supported, again, by the National Cancer Institute for many thousands of women. So, they're coming.

Valerie King: These are really important studies. Again, they did not... the one thing that's been reported was not included, because it's not comparative.

Tony Yen: Okay.

John Bramhall: So, it seems like oncologists in the field are placing a lot of... they're placing a high regard on these tests. Why?

Valerie King: I'm not an oncologist. You should ask one. Yeah.

John Bramhall: What's the basis for the faith in the test?

Nancy Davidson: I think one of the things we didn't talk about at all here is, the evidence base that led to the development of the test, and I'm going to go to Oncotype Dx, because that's the one I know best. So, in that particular case, as we talked about earlier, there was a really major attempt to go out and look at the collection of genes that you and I would be thinking would be important in cancer, you know, proliferation genes, metastasis genes, invasion genes, genes of hormone response would be important in breast cancer. Then, looking at them and trying to come up with algorithms in the context of tissues that had been acquired from women who went on randomized clinical trials of adjuvant hormone therapy and chemotherapy in our country, so the trials that led to the development of our practice guidelines for how we give therapy. So, the beauty there was what we had was randomized trials, right, where the doctors and the patients did not choose the therapy. We have tissues that were acquired at the time that the patient went on the trial, and because they're old trials, we have very mature follow-up. So, that test was devised on a set of tissues, and then it was validated in these trials from the... from these tissues, from randomized clinical trials. So, I think when we look at that, we think that's a pretty powerful data set. It's not the top level evidence, because it is, of course, not a prospective trial, and that's what these other two trials are, but when you look at the curves from these well regarded clinical trials in the U.S., people in our practices, right, the folks that we take care of, I think that we think that the data is very strong and that's what led to the prospective trials that are being done, but it also means, in the interim, I think, that most people would feel pretty strongly about having the opportunity to apply those tests when it seems to be clinically appropriate.

Valerie King: So, in that case, you'd say, Oncotype Dx is a quite prognostic test. So, it has really good discrimination of people who are likely or not likely going

to have metastatic disease at five, ten, or more years, and that's really a measure of clinical validity. That's largely the basis under which these tests have been recommended in guidelines.

Nancy Davidson: I think that clinically the way people use the Oncotype Dx test is both prognostic and predictive in the sense that a high recurrence score would suggest that a patient is probably going to have a worse outcome natural history wise, and that she may also be somebody who is more likely to respond to chemotherapy. So, it's going to have both the prognostic and the predictive qualities that were discussed earlier.

Seth Schwartz: This is Seth again. I think this is a situation we struggle with sometimes when oftentimes it's sort of presupposed that something is effective, and then we're asked to make a decision without actually seeing the data on the effectiveness of that, and we're kind of at the next step without really understanding the first step. So, clearly, it's been compelling, because it's been put in the AGCC guidelines. I mean, this is obviously something that people believe. It's just hard for us not to have that understanding or have any of that evidence here.

Gregory Brown: I think it's a little different that we struggle... I'm an orthopedic surgeon, the American Academy of Orthopedic Surgery has an evidence-based medicine workgroup, and developing clinical practice guidelines, and the problem we have is just what you outlined is, how do we get level one prognostic evidence. It's observational. It's not comparative. So, RCTs and comparatives for efficacy, effectiveness, not for prognostic value. So, grade throws out every observational study no matter how good, how prospective, because it's noncomparative. So, is that the same problem here? Is that... I mean, what I'm hearing that we can't... I mean, we've got to be able to get prognostic evidence, because that's what it is, it's evidence, into these reports and as soon as you say it's noncomparative, we throw it out, it sounds like.

Valerie King: So, this really is how the scope of the review is determined early on. If what you're interested in, on these kinds of tests, is really their clinical validity, then that should be included in the scope, and...

Gregory Brown: I guess my question, I think, is different. I mean, how does grade incorporate observational evidence, I guess, is my question.

Valerie King: Yeah. So, um, so most of the evidence in this review is observational, but there are very few prospective studies, and even fewer randomized trials. So, it gets downgraded for some issues with that, but given that you've got several tests where the evidence, the overall quality of evidence is low or

very low, I will say that it's tremendously consistent, particularly in breast cancer, at least on treatment decision and treatment received. So, I don't think we've got those higher quality outcomes to look at, but I do think that you have evidence of clinical utility. The evidence could be changed in the future, as mature studies that are prospective and randomized come along, but that's less likely when the findings of these observational studies are very consistent.

Gregory Brown: Okay. Thank you.

Sheila Rege: I have a question, and this is more for the agency. Looking at Medicare or the private insurances, this is an evolving field. When I go on the private commercial payers, they kind of go, you know, especially for prostate cancer, these are investigational, but they're going to look at it again in a year. What is our charter or guidelines? Is it looked at, at the certain period of time, or not unless it's brought back to us?

Josh Morse: We would look for new information, or if somebody brought us new information. Then it would be reselected to come back to you.

Gregory Brown: I think that's why you put in here under breast cancer, and whether we want to include it under more is, covered at agency discretion in the future, if developers can show prognostic equivalence or superiority of the above tests. So, because it's fast... we don't want to, every time a new test comes out, we don't want you to have to bring it back. So, that's kind of your out to be able to... a new test comes out, good evidence. You can adopt it, don't need to come back to us.

Sheila Rege: Yeah, and...

Josh Morse: I'd like to say, I have a little concern with that language, and I do have a query in to see if you can actually do that, because that's...

Gregory Brown: Okay.

Josh Morse: ...kind of... I'm not sure you're able to do that, push that decision back to the agency.

Gregory Brown: That's the request.

Valerie King: The other thing that I would point you to in the evidence report is one of the appendices. It's Appendix F, and this is studies that are registered at clinicaltrials.gov. What you really see in breast cancer is one, two, three, four, four pages of ongoing trials. So, just a tre- ... this is just a

tremendously active area of research. I think the most important things in there are the Taylor Rx study that Dr. Davidson alluded to, but there are others, as well. So, there's more coming.

Gregory Brown: So, Josh, how are we going to resolve that if you have a query in?

Josh Morse: We'll get there.

Gregory Brown: Okay.

Josh Morse: You haven't made a decision, so.

Gregory Brown: Okay. Okay.

Josh Morse: And I think the concern is, if you came up with a framework and said tests that looked... meet this threshold or meet this threshold, I think if it was a criteria based threshold that the agencies would follow based on your assessment of the evidence, I think that is different from just giving them the authority to make the determination without that criteria.

Gregory Brown: No. There is. It says show prognostic equivalence or superiority of these tests, of the above tests.

Josh Morse: Okay. Yeah.

Mika Sinanan: Can you, on the basis of your analysis, review the value of doing multiple tests or repeated testing?

Valerie King: There's really only one study that directly addressed that, and it's the study that looks at women who are in that intermediate zone, Oncotype Dx situation then have another test applied on top of it. So, that is not a situation that really is covered by this evidence base, the multiple testing issue.

Seth Schwartz: And just to echo that. So, have been there any head-to-head trials looking at people get two different tests, are they categorized in the same way?

Valerie King: Yes. There have been, and it was out of scope for this particular review. So, I probably shouldn't comment, but in terms of their categorization of patients, yes. There have been studies that use tissue banks that applied multiple tests to the same tissue sample.

Seth Schwartz: Part of the reason I'm curious about that is, we've been told that these tests can range in cost from \$500 to \$5000, and if you have a \$500 test

that's equivalent to a \$5000 test, we may not want to be approving both, but I'm not seeing any of the evidence to be able to...

Valerie King: Hm-mm.

Seth Schwartz: ...allow us to discriminate those. So, it is available, we just don't have it? Is that what I'm hearing?

Valerie King: It has been published, but I can't describe it to you. Dr. Davidson may be able to give you a better idea.

Nancy Davidson: I don't feel like that's strong enough that we would be able to help you with that. I could tell you that's a big goal in the field, the desire to come down to some very small streamlined test would be everybody's Holy Grail, but at least, at this point, we haven't gotten to that.

Valerie King: Mm-hmm.

Seth Schwartz: And then, maybe you can help me with just how these tests are currently used clinically. I think we talked a little bit about this earlier, but if you have a patient, how are you making a decision between whether you use the Oncotype Dx or the MammaPrint or how are you making that determination clinically.

Gregory Brown: If I may interrupt for just a second. If we have any more questions for Dr. King, we can ask those and then let her sit down. Then, we can have our group discussion. She doesn't need to stand for that. Any other questions for Dr. King? I mean, we can certainly still ask her, but. Okay. Well, thank you. We will certainly ask if we have other questions, but then, so if we, yeah. So, let's open it up for the committee then. Thoughts, questions for our expert.

Seth Schwartz: Again, I'm just trying to clinically understand how these tests are used in terms of... when I think about us making a decision, are we simply going to approve all of these based on whatever the evidence is, or is there some guidance for how they're used clinically? Are there differences between them that are meaningful and things like that?

Nancy Davidson: As somebody who has now practiced in three different parts of the country, I'll start by telling you there are regional differences between how people use these things. I think that the two most common tests would be the Oncotype Dx and the MammaPrint. We discussed the fact that MammaPrint wasn't quite as common in this country for a long time, because it was developed in Europe. It actually... the other thing I forgot

to mention to you is that originally when it was developed, it required fresh tissue. That's not the practice too much in this country. We do most of our testing on paraffin tissues. So, only when they refined their methodology to make it paraffin based did it make it easier to think about doing it. Even within the practice I work in, I'm an Oncotype person. I'm used to it. I've used it for a long time. I like it because I think that it helps with the two things we just talked about. It helps me with prognosis, and it helps me to try to predict who will or will not benefit from chemotherapy, and that's a really important question for me. It is, as you saw in that report, it's a continuous variable. So, that's sometimes complicated to think about and to explain to patients. The MammaPrint is kind of more black/white. You're either high risk or you're low risk. So, sometimes, that's easier for doctors and patients to conceptualize. They're also a little bit different in terms of the patients that they allowed into the trials. So, they might have slightly different scope about how you want to do it. I think those would be the most common ones that we would run into. We heard, and I actually agree with your assessment, that I think it would be reasonable to consider all of the ones that we discussed in the breast cancer world. The BCI test that was mentioned is one that is often used for a second clinical decision, which is in somebody you give hormone therapy to, for a long time it has been our standard practice in the United States to stop the therapy at five years. In the last few years, we've seen new randomized trial information that suggests that maybe we should give these therapies for longer periods of time, but again, we're sort of stressed, because it's, like, a long period of time, and does everybody need this, and is there a way that we could actually try to refine it a little bit more. So the BCI group has tried very hard to suggest that their test is especially useful to think about who would need the longer-term hormone therapy. So, I think folks do choose their tests a little bit based on the question that they are trying to answer and the kind of data that they think that they and the patient will find useful to make the decision.

Sheila Rege:

I would agree with that. There are regional differences. I was with a patient in Los Angeles and I was surprised to see they really like the MammaPrint. In Washington, we seem to do more Oncotype Dx. One of my worries, and I'd like us to keep this in mind, is given that they're not 100% concordant, there is a discrepancy, that we consider whether we should say what your personal opinion was one patient one test. I don't know if you say one test per year or how you put that, but just in my mind it doesn't make sense to do an Oncotype Dx and then go, well I have a gut feeling and then do a MammaPrint. It's just a little worrisome, because these tests are expensive. It's nerve wracking for the patient. The patients

are, okay. The Oncotype Dx was good. Oh, my doctor doesn't believe it, or, you know? It's really hard.

Nancy Davidson: Saying that would be, I guess, it would be evidence based in the sense that there's virtually no evidence to support that practice.

Tony Yen: Dr. Davidson, can I get your opinion on EndoPredict and Prosigna? It seems like there's very little data on those two types of tests, and...

Nancy Davidson: Yeah, newer... I think the data are emerging right now. So, you know, we're left making a decision at a time when this is a rapidly changing area. There are folks who are major fans of Prosigna because they would say that one of the things that that does is to actually subtype breast cancer into some pretty well-defined molecular subtypes and that maybe that would be more useful information over time, but I look at it as was pointed out at the very beginning, it is a really rapidly changing area. So, I liked your recommendation or the agency's recommendation that all of these things in the breast world would be considered as rational strategies and that based on varying degrees of information, but that would give latitude to doctors and patients to make the selection of the one that they think is the most useful to that patient.

Mika Sinanan: In that regard, we have, as one of the agency recommendations, the Mammostrat and BCI, covered with conditions, but in the Mammostrat presentation, low risk and high risk appeared not to have any... did not change the outcome with tamoxifen. There was an improvement for both low risk and high risk. It was only in the intermediate risk group where there was any difference. So, does Mammostrat actually have enough evidence to support inclusion?

Nancy Davidson: I'm looking for where you and I are in the book here.

Mika Sinanan: Slide 46.

Nancy Davidson: Slide 46 in?

Mika Sinanan: Dr. King's presentation.

Gregory Brown: It's page 24, slide.

Nancy Davidson: I'm lost. I'm probably in the wrong presentation. Which presentation was it again? In Emily's?

Valerie King: So, we only found described one study in one systematic review.

- Mika Sinanan: Right. That's from 2008. And that showed low risk improved by 5%, high risk improved by 21%. So, both improved. The risk... the evidence of risk by Mammostrat did not seem to have any effect on the benefit of Tamoxifen. It was only in the intermediate, right, your third bullet point down there? I'm just wondering why that's included in our approval recommendation.
- Nancy Davidson: I'm thinking, this is also a trial that has to do with the pros and cons of adding chemotherapy, right?
- Valerie King: This was on tamoxifen. So, this...
- Nancy Davidson: It says, these patients are treated with tamoxifen, and I thought that what we were looking at here is the benefit of chemotherapy when added on. No?
- Gregory Brown: Well, but the last line says benefited from chemotherapy.
- Nancy Davidson: Yeah. Most of these tests wouldn't be looking at the pros and cons of adding hormone therapy. I think that we would already be giving the hormone therapy. So, what we're trying to sort out is whether there's a role for chemotherapy on top or for some of the tests there is also a question about whether you can use it to think about the duration of the hormone therapy, not yes/no.
- Valerie King: Can I just in for a sec?
- Nancy Davidson: Please.
- Valerie King: So, on this one, it was Mammostrat and randomized to either tamoxifen or not, and there was a small response to tamoxifen in the low risk group, 5% absolute reduction and 20% absolute reduction in the high risk group, and none in the intermediate. So, the thought was there that that difference might be enough, again, to impact the patient's treatment decision. So, if someone said for a 5% improvement, I'm not going to do this, but for 20% improvement I would, then in that setting, it would be a reasonable test to do.
- Nancy Davidson: Thanks for correcting me. I appreciate it.
- Sheila Rege: In my mind, just clinically, and I'm going to ask you, Oncotype Dx, and MammaPrint seem to have the most data and seem to be most used. The rest are new to... newer studies.

- Nancy Davidson: I think they're emerging. We'll see what happens.
- Sheila Rege: Emerging. So, I don't know when we're making decisions if we... I think definitely cover Oncotype Dx and MammaPrint. We've included EndoPredict and Prosigna in the same category, and I don't have an opinion on it, but I'm kind of curious what your take is on them, and the agencies' recommendation.
- Nancy Davidson: I think that you're right that the information that's available right now is smaller in quantity. I guess as a practicing physician, I like to think that patients and I can have a choice and that if we have a really compelling reason in our minds for why one test would be superior to another, that we would be able to take advantage of that.
- Mika Sinanan: In that regard, you had commented that you had practiced in three areas, saw significant different practice differences. Are those evidence based or are they custom?
- Nancy Davidson: I think that in some cases they are custom, and then sometimes it might have to do with... oncologists are often very active in the clinical trial sphere, right? I mean, one of the things we're trying to do in life is to improve our outcomes for our patients and so many oncologists in many spheres will participate in trials and often these things will be the subject of trials, as we just talked about. So, that might be because you're participating in this national trial, you'll become accustomed to using this test and thinking about it, and it might be something that's easier to absorb into your own practice.
- Kevin Walsh: In the past, we've talked about effectiveness, safety, and cost comparison before we make cover with condition criteria. I feel like we've jumped 15 moves down the board. I would like us to maybe go around the table and offer our analysis of what this evidence is showing us, in terms of effectiveness before we start detailing the conditions of coverage.
- Gregory Brown: So, I think that's a good idea. I think effectiveness is all over the board, and what are you measuring? So, if the request from Health Care Authority is for clinical utility, then the measure of effectiveness is how effective is it for clinical utility.
- Kevin Walsh: Maybe we should talk about people's interpretation of that, because...
- Gregory Brown: Sure. Yeah.

- Kevin Walsh: ...when I look at the key question on page two of the final questions and background at the end of the packet, it talks about, is there evidence the test results effect treatment decisions, do treatment decisions guided by gene expression profile testing of cancer tissue result in clinically meaningful improvement in patient outcomes. Those are both effectiveness questions. Clearly, there is a lot of evidence offered about the first question, and there is virtually no evidence offered about the second. So, I'm interested in people's opinion about where does that take us?
- Gregory Brown: Go around the table. Seth? Tony? Who wants to start?
- Tony Yen: I'm happy to start. I think there is clinical utility over here from my interpretation of the literature and how I sort of see that is that it actually helps people make decisions with their provider to determine if they want to proceed with chemotherapy or not, if they're in the high clinical risk category. That's really kind of how I sort of see it, and I derive that from really looking at the MammaPrint literature from the New England Journal. I think it's 2016 or something like that by Cardoso, but that's really where I find the highest clinical utility, and for people who would normally proceed to chemotherapy, normally proceed to chemotherapy, about 50% of them can actually forego chemotherapy and actually have the same outcomes. From that, I feel that we're decreasing morbidity significantly. You're, if you're forgoing clinical chemotherapy and having the same outcomes, you're decreasing morbidity and from a... and maybe kind of looking forward to the future, you would have better cost-effectiveness, because these people are not going through a lot of stuff that they don't have to go through that's both expensive and quite frankly harmful. In that same paper, it also shows that people who have low clinical risk, they really don't benefit from undergoing this sort of gene expression testing, because even if they have high clinical sort of high genomic risk, looking at the randomized studies, at least of the five-year point, there is no difference. So, that's my interpretation.
- Kevin Walsh: Am I correct, Dr. King, that this was... there were kind of two arms to this, to the Cardoso study, one was using MammaPrint but the other was using a specific risk stratification tool.
- Valerie King: So, not arms. They were applied basically concurrently. So, the whole design of the study was to, the randomized part of the study, was to look at discordance. So, high clinical risk, low test result risk, and vice versa, with MammaPrint.

Kevin Walsh: So, I just want to be clear that what you're advocating is, yes, there is benefit to MammaPrint.

Tony Yen: The MammaPrint.

Kevin Walsh: But there's benefit to MammaPrint with this scoring tool.

Tony Yen: So, there's two, I think maybe I'm not communicating clearly, but I think there's... the genomic risk is what's given by MammaPrint, right. The clinical risk is done by kind of the standard calculate you would find online, and you will put in, like, I forget the exact society that actually has this clinical calculator, but I think the magic number is, like, 88% or something like that, in terms of, like, determining whether you're high or low clinical risk. So, this is just my interpretation that I think that there is clinical utility over here, particularly in those folks with kind of, in this very specific category of having stage 2b breast cancer or below and HER-2 negative, I want to make sure I'm saying this correctly, and ER-positive. So, it's a very specific category of folks, and their clinical risk calculator that we can just, and I apologize again, if they're a high clinical risk by the clinical calculator that we just kind of munch through over here, this can actually help us determine, hey, do these folks, do they benefit from chemo or not? I think it would be great if we can offer something that tells our patients that hey, you know what, you don't need to go through chemo. You're going to have good outcomes, or equivalent outcomes I should say, than not having chemo.

Gregory Brown: Laurie?

Laurie Mischley: I largely agree with what Tony just said. I just keep going back to the data that I want aren't going to be available anytime soon. I think that in terms of... in my clinical role, I am seeing patients distraught over the increase in provider confidence, oncologist confidence is relevant to me. I think that... I trust that oncologists know this field well. I'm impressed by your testimony, and I think that when patients have additional tools... I'd say the thing that concerns me most is, I was joking around that if it were me, I would want a snapshot from every angle. I would want every one of these to make an informed decision. I like data, and the more data I have available to me, the more confident I would be in my decision making. So, I get that the data that we have is limited. There is no question it effects decision making. We don't have the data we want and won't have the data we have any... that we want anytime soon, as to whether it impacts outcomes, as much as we'd like. For me, the bigger concern is patients overusing this. I think right now, it hasn't been over-utilized. So, I'm not too afraid of what that means. I think that when you look at the cost

utilization over time, I suspect it will actually decrease costs, improve savings over time by decreasing chemo and morbidity, but I actually am afraid of over-utilization depending on what we do with this recommendation. I mean, just in terms of if we just say yes, we'll pay for all of these. I know that as a patient, I would be an over-utilizer.

Sheila Rege: So, in terms of key questions effectiveness, is there evidence that test results effect treatment decisions? I'm only speaking for breast and would advocate for leaving it up to the physician, the oncologist, about which one, based on regional differences, etc., and comfort level. I think the evidence we've seen, yes. It seems to effect treatment decisions, maybe not as much as was originally forecasted, but it does. In terms of do these decisions result in clinically meaningfully improvement in patient outcomes, that, I think, is the evidence we don't have today, just very concrete evidence of how much is significant, but I would be in general agreement on the effectiveness, and I am only speaking for breast cancer. I don't know if we should take breast cancer different than prostate, different than the others.

Gregory Brown: I think right now, it's just the general philosophy. I think when we get to the voting, we'll take them one at a time, probably, but, yeah.

Sheila Rege: But that's what I focused on was breast.

John Bramhall: I don't see... so, I have difficulty, I can see a lot of evidence in the data that we are working with of clinical effectiveness at the level of which I understand it, which is the decision that's made is the right decision over a long course of time, and that's partially result, as you both pointed out, the lines haven't had time to diverge yet. We're looking at two years, three years, and five years. What we really are interested in is looking back in 50 years' time to say the decisions that we made were valid, or they were not valid, and we won't know that, obviously. It's just sort of an existential issue. My questions to you earlier on about why do oncologists use these tests. We're rhetorical, I accept, as a scientist. There's a clinical validity to the test, and it's backed up by an immense amount of superb work and very sophisticated sets of statistics, molecular biology, clinical correlation. I don't disputed that. I think that points to the structural problem of our table here, that we're not being asked to make a decision on the basis of those data, which oncologists believe in. We're being asked to make a decision on the basis of this sort of poorly-organized massive trials with arbitrary selection of tests, presumably then, information based on arbitrary... essentially arbitrary in the context of the ten different tests, arbitrary selections of RNA profiles. I use the word arbitrary not to mean that it was random. I use it to mean that there seemed to be

nonoverlapping, relatively poorly-overlapping, subsets of RNA that can be used equally effectively to make decisions. So, what I'm reduced to is, I think it's very clear to me from the data that we have, that the decision process is heavily influenced by these tests. Oncologists in the field put great score on this, and I think patients likely put great score on this, probably filtered through their oncologist presentation of the data, and I think that's immensely valuable. I'm not convinced that I know the decision that's informed by the test is in fact the right decision, because I think it's that temporal issue that we just can't overcome in 2018. So, I am a bit conflicted, really. I think I accept the tests are valid clinically. I accept that, because ex cathedra, the community of oncologists and researchers say it's valid, but that messes up our whole model of using randomized control trials to inform our decision.

Gregory Brown: Again, that evidence exists. I think Dr. Davidson explained that in terms of all the chemotherapy trials and RCTs and everything that have gone on. It's just out of the scope of putting all that in this report. So, I don't think we're violating any principles of evidence here. Again, there is a scope, and you can't put everything in the report. So, anyway, Mika?

Mika Sinanan: So, we know that even patients with early breast cancer progress, and it can be a lethal disease. We know that chemotherapy is effective at reducing the rate and incidents of development of metastatic disease. There is evidence in the literature that we've looked at that supports validity. There is only one study that supports utility, and that's the limitation we have. We know that there is broad utilization in the market already. So, there's a political and a use dimension to all of this of doing something that is out of step with where the market is. The accuracy of this testing in predicting whether treatment actually influences the natural history of the disease is lacking. I think that's the angst that we've heard about. It certainly affects treatment decisions, but whether or not that actually changes the natural history of the disease is something we don't know. I, to get back to Tony's original point that for many of these diseases, early stage breast cancer and prostate cancer, in particular, there are probably a lot of people, because of fear of the disease, who get or choose to have excessive treatment, treatment which is at our current level of technology not helpful, and perhaps no treatment would be helpful or beneficial. So, in that regard, if we can reduce the number of people who get unnecessary or unhelpful and potentially harmful treatment, that would be a very strong positive. That's where the validity argument, I think, is probably the strongest.

Gregory Brown: I would echo that last sentiment. If there is, I think, reasonable evidence that it helps people avoid harmful overtreatment, that that is a huge

benefit, and looking at some other decision aids and things in other areas and one of the things you look at breast cancer of the number of women that are opting for bilateral mastectomies because of a very famous movie star that had it done with no evidence to support it, out of fear, largely. So, if we can give those people, I think, better information, patient specific information, to help them make that decision and avoid that overtreatment, that's a huge advantage to me. Do you have any comments, doctor? We don't want to skip you, but if you have a comment or?

Nancy Davidson: No. I think the discussion has been really good.

Gregory Brown: Kevin?

Kevin Walsh: Mika, I think you gave a great summary, thank you. I'm struggling with the, first of all, with the agencies', I think, lowering the bar for this decision from outcome to does it affect treatment decision. It takes me back to about ten or twelve or fifteen years ago, and Dan probably can remember this, when the American Diabetic Association came out very emphatically saying that we had to get A1c down to below 6.5. It was not based on evidence, and over time, we learned that those people who were driven down below 6.5 were having more heart attacks, but in retrospect, they were very emphatic, and everybody was doing it, and that was what the endocrinologists were jumping up and down about. So, people decided to do that. This feels really similar to me. I understand it changes treatment decisions. The supposition that that leads to better outcome is not here. So, I'm struggling on what do we make a decision. I agree that Cardosa shows that in that specific subgroup of women there seems to be benefit to having that specific test. Beyond that, I feel this is wishful thinking, and I am encouraged that there are lots of trials out there that will be, hopefully, very soon giving us some evidence to support this. I can just tell you that I've lived through similar enthusiasm that ended up being shown to be incorrect and even damaging to people. So, while I support the idea that I would love to be able to decrease the use of unnecessary chemotherapy and not effect outcome, I don't see... this just feels like a hopeful effort, and it's not yet demonstrated in reality to me.

Seth Schwartz: I think you guys have all summarized pretty well what the situation is here, and I think the data is pretty compelling that it does change decision making, but there is really only paper that shows that it actually is effective, and we're extrapolating in a large way from that one paper with very little evidence from the other tests that we're asked to approve. So, I think, like Tony, it's fairly compelling that there is an opportunity here to reduce the distribution of potentially harmful and expensive therapies, and I'm sort of

swayed to think that this is probably going to allow us to do that, but the data that we've seen today is not super compelling in that way. That's not to say it doesn't exist. I think that's the problem, Greg, that we were talking about, which is the data may exist, and it probably would help us tremendously, but it wasn't scoped into this, and that's a just real handicap. It just feels, I think, as John said, it feels wrong to just accept that the data is there, even though the data is probably there. That's just the challenge, not that it doesn't exist, but that our job is to critically appraise what we're given, and if we're not given it, it's hard to weigh that data.

Gregory Brown: I mean, I agree with you completely. At some point, you reduce the evidence based medicine process to absurdity by having to go back every step, you know? You have to build on something, and you keep building forward and you... it feels to me like we're questioning the effectiveness of chemotherapy and all the cancer treatments and [crosstalk].

Seth Schwartz: I don't think that's the case at all.

Mika Sinanan: We're questioning whether or not the tests accurately predict the risk of development of future metastatic disease and death. That's what we have...

Seth Schwartz: That's exactly right, and I think Dr. Davidson has kind of assured us that that is the case, and I believe it. I'm not really questioning it, but it's just challenging when we're expected to make evidence based decisions, and we have to make a very big assumption that we were not told to make before we got here. So, that's the challenge.

Gregory Brown: No, I agree, and I think that's the tightrope that Josh tries to walk every time when we're scoping these. You actually pointed out very clearly is there clinical validity versus clinical utility, and the difference, and this was for utility. So, I agree with you completely, yeah. Any other discussion, comments? Do we want to start looking at writing our...

Seth Schwartz: Do the nonbinding voting?

Gregory Brown: Yeah. Should we do the nonbinding voting, because just to see that most people are interested in looking at covering with conditions or not covering. Then, obviously if we're not covering, then we don't need to do the conditions, but if we, see where we're at. This is just a straw vote. This is not a...

Mika Sinanan: For all types of diseases?

- Gregory Brown: Should we do them one at a time?
- Group: Yeah.
- Gregory Brown: So, breast cancer.
- Josh Morse: May I ask before we move onto this vote, have you... can we go through the nonbinding vote on safety, efficacy?
- Gregory Brown: Oh, sure.
- Seth Schwartz: That's what I was talking about.
- Josh Morse: That's usually the first step we go through.
- Gregory Brown: Again, it's the same, sure.
- Josh Morse: So, you've taken your temperature as far as...
- Gregory Brown: Yep.
- Josh Morse: ...which direction you're heading on the decision, but...
- Gregory Brown: Yep. Okay. So...
- Josh Morse: ...I would ask that you.
- Gregory Brown: So, safety outcomes, adverse events, really the ... if I encapsulate everybody else's conversations, this is about preventing adverse events from chemotherapy. That's how I view the safety issue is that.
- John Bramhall: No. It is also the dimension of the safety element if you avoid chemotherapy inappropriately. I mean, that's part of the equation, right?
- Gregory Brown: Otherwise, there's no real... is there harm with the testing? I mean, again, if you have a false-positive or negative, distress over that, anxiety. Any others? Is there any difference between any of them? Did anybody see a difference between the safety outcomes in any of the four conditions? Not seeing any? Efficacy, effectiveness, and so just so we're all on the same page. I'm sorry. Yes, correct.

- Josh Morse: Yes. I'll be the historian and say on page 5 of your decision document, your discussions in the past, you've gone through this page. You've talked about whether these are outcomes you wanted to...
- Gregory Brown: And then we vote after we've gone through all of them.
- Josh Morse: ...and then, you turn the page, and we vote on those [inaudible], yep. Okay.
- Gregory Brown: So, efficacy, effectiveness, our measure of that, as requested by Health Care Authority is decision, effect on decisions. Okay? Do we... yep. No. Again, no. There's clinical utility, morbidity, mortality, and I think we all agree there's no evidence. Is that correct?
- Sheila Rege: And are we taking it all together or...
- Gregory Brown: Well, I mean, again...
- Sheila Rege: ...would you like to separate it into ... in my mind, the effectiveness especially is different for breast or prostate versus colon cancer and multiple myeloma. That's just the way I'm thinking about it.
- Gregory Brown: Okay. Well, are those the... I guess the first question, these are ... are these the... if I understood your suggestion, Josh, is that these are the questions. So, are these the appropriate questions? Are there other questions we need to ask? Then, when we get to the voting on the next page about evidence, proven, unproven, then we can do them disease by... cancer by cancer. Is that... everybody agree to that? Okay. Are there any other questions that are missing that we feel like we have evidence for? I mean, again, I think from our discussion, really, we don't think there's evidence on clinical utility or quality of life or morbidity/mortality or quality of life. It's really just the patient decision management.
- Kevin Walsh: Well, no. I think that, I think we're all... I think we've agreed that Cardosa is the only study that demonstrates the potential benefit to using the test in a certain subgroup of breast cancer types. So, there is that one outlier.
- Gregory Brown: Okay. So, that would be on morbidity and mortality.
- Sheila Rege: And it's just in January that the U.K. and National Institute against all oncologists said that they reversed endorsement for even Oncotype Dx based on effectiveness and outcomes. So, I think they over-reached, but that's personal. That's not evidence based.

- Gregory Brown: Well, and again, at the end, once we make our coverage decision, we'll review other guidelines. I don't know that that affects our vote on the evidence. Okay. So, if I'm hearing correctly, you think there is evidence for breast cancer under morbidity and mortality.
- Kevin Walsh: Under that specific subgroup.
- Gregory Brown: Breast cancer only.
- Kevin Walsh: And for a specific test.
- Sheila Rege: I'm just broadly, I think that's what he's looking for.
- Gregory Brown: I mean, again, if there's at least one study on breast cancer but nothing else for colon cancer, prostate cancer, or multiple myeloma. In terms of patient decisions, there is evidence in breast, colon, and prostate but nothing for multiple myeloma. Again, we can say stronger or weaker evidence, but at least there's some evidence.
- Sheila Rege: Would you prefer it being broken down? Is that what... into different cancers?
- Kevin Walsh: Well, in the past, I think the way that it's been proposed, if it was... that if there was benefit in any, you had to say either some or all, and if there was no benefit in any, then you could say none. That's kind of the way it was...
- Gregory Brown: Correct.
- Seth Schwartz: So, I think historically the way we've looked at it is, these are the outcomes of interest. Are we accounting for all the proper outcomes? Not, do we think there's evidence for them. At this stage of the game, we're essentially saying are there other outcomes than what's listed here that we should take into account when we're doing our voting on the next page.
- Gregory Brown: Well, I think the other thing that's unique to me, I don't remember being asked to choose between which specific test we'll approve versus not. I mean, for example, in hyaluronic acid, you didn't say Synvisc versus Euflexxa. We did it as a class. So, and again, this was just the Health Care Authority's recommendation. We can say we agree that genetic expression profiling is appropriate in breast cancer under these conditions, but we're not going to... but we don't think the evidence is strong enough to specific out each individual test, which we want or not.

- Seth Schwartz: I think that's fine. I think just from a protocol perspective, we're sort of doing several things at once here, where historically what we've done, I think, as Josh is pointing out, is we're not even talking about that. We're simply saying are there other outcomes we should be thinking about, and then we'll go to the votes, and we can decide if we want to break down the votes however we want to break them down.
- Gregory Brown: Yep. Okay. So, we've got our questions for efficacy. Cost outcomes? I mean, I think we've got the right cost of testing, cost of effectiveness. We've got some weak estimates.
- Mika Sinanan: Cost of indicated or avoided treatment is implicit to the fact that it's being used to guide the next step of therapy, right? So, it's not just the cost of the test. It's the chemotherapy and the morbidity or the lack of chemotherapy and the lack of morbidity, and as John has pointed out there's the risk of missing.
- Kevin Walsh: Right. Logically, that's true, but none of that was presented in studies.
- Seth Schwartz: Well, we're just talking about what other outcomes we want to look at. I think cost averted is a real thing to look at.
- Gregory Brown: And that's the point of effect... cost-effectiveness is... overall, some may help, some may worsen, and the overall balance is what's the... so I think...
- Mika Sinanan: So, you're rolling it into that. Okay.
- Gregory Brown: ...I think that's the cost-effectiveness. Okay? Special groups? We certainly had a question for the expert under age.
- Sheila Rege: And comorbidities.
- Gregory Brown: And it's really more comorbidities and that's number five here, race, ethnicity. We saw some at least discussion of certain races having less testing than others.
- Kevin Walsh: It's consistent with the rest of healthcare in America.
- Group: Yeah.
- Gregory Brown: No, I agree with you. I don't know that that...
- Seth Schwartz: You know, the gender issue is an interesting one. I mean, I know that breast cancer is dominantly a disease in women. We saw nothing about

this disease in men. I don't know if any of the data holds. Does this hold for men, or is it ever used in men, or is that just totally such a small subgroup that it's not really even thought about.

Gregory Brown: 1% of the population.

Nancy Davidson: It's never been tested. It's less than 1%. We tend to think of men with breast cancer as the same as postmenopausal women, because hormonally that's what it turns out to be, but I think when people develop these things that data set is so tiny.

Mika Sinanan: The stage of the cancer is included under clinical history? Because that's... we're talking about a special population.

Sheila Rege: Age would be a good addition.

Mika Sinanan: Well, that's the question is, is that part of clinical history or not?

Gregory Brown: I would say we can do it separately.

Sheila Rege: And the other thing is, I guess clinical history whether hormonal type or HER-2 and ER, whether you want to list that out or not or just assume it's part of clinical history, the ER status and the HER-2 NEU status.

Seth Schwartz: One more question, so maybe Dr. Davidson, you know the answer to this one. Are we presuming that these women who are diagnosed with breast cancer already had surgery to remove the breast cancer or is that... so this is all postsurgical?

Nancy Davidson: Yeah. These tests are all really for people who are looking at adjuvant therapy as only described. So, they've had their surgery. They'll have their radiotherapy if they need it, and then it's the therapy after that.

Gregory Brown: You guys have to get the tumor tissue to review, the biopsy tissue, but it's from the actual tumor, itself, correct? Yeah? Okay. So, we added staging and then I'll call it tumor characteristics of receptor positives or whatever. Okay. Anything else? Okay. Page six. Do we want to do it by different cancers individually? So, is there sufficient evidence that the technology is safe for the indications concerned? So, we'll start with breast. You're being... I was going to say, you're about to be influenced, huh, Seth?

Josh Morse: Okay. I see one more, four some, one equivalent, and two unproven, eight. Okay.

- Gregory Brown: And then prostate?
- Josh Morse: Five unproven, two some, one equivalent.
- Gregory Brown: Colon?
- Josh Morse: Seven unproven, one equivalent.
- Gregory Brown: Multiple myeloma?
- Josh Morse: Seven unproven, one equivalent.
- Gregory Brown: We must have a different... definitional difference.
- Mika Sinanan: I'm thinking that I must. I'm trying not to be influenced by the crowd.
- Gregory Brown: Okay. Okay. Efficacy. So, a meaningful impact on patients and patient's care. So, in our earlier discussion, we thought under breast cancer that there... we thought there was evidence regarding outcomes in terms of survival with avoiding chemotherapy in the one study, and then in terms of treatment decisions. So, is there sufficient evidence this treatment makes a meaningful impact on patients. So...
- Kevin Walsh: For breast?
- Gregory Brown: Sorry, breast. Yes.
- Josh Morse: Six some, one more, and one, wait. I'm sorry. Can you hold your cards back up, those of you who are not some? I have to ask you your individual vote, because I think we have some mixed cards here, perhaps. So, more and all. I think more and all is the same category.
- John Bramhall: We're just talking about breast, correct?
- Gregory Brown: So, more and some and more and all, so some and all.
- Josh Morse: Right, but your cards aren't distinguishing more and some.
- Sheila Rege: Oh, I see. There's not... we don't have some here.
- Gregory Brown: We've got more in some and more in all.
- Josh Morse: Tony, what is your vote for? Is it more in some or more in all?

Tony Yen: My vote is more.

Gregory Brown: Which is all. Oh, yeah. It's more in some or more in all.

Tony Yen: I'm sorry. I thought that by putting more, is more in some.

Josh Morse: So, it's seven more in some and one in all. Okay.

Gregory Brown: Okay. And so that was... I'm sorry, that was prostate?

Josh Morse: Breast.

Gregory Brown: I'm sorry, breast. So, prostate.

Josh Morse: Six more in some, one unproven, and one less.

Gregory Brown: Okay. Then colon, efficacy. Seven unprovens and one some.

Josh Morse: Seven, yep. Thank you.

Gregory Brown: Then, efficacy for... no. I said some. Yep. Then, multiple myeloma, eight unproven.

Josh Morse: Eight unproven, thank you.

Gregory Brown: Okay. Cost outcomes or cost-effectiveness. So, breast cancer.

Josh Morse: Let's do the unprovens, one, two, three, four unprovens; one some, two some; one less. Thank you.

Gregory Brown: Okay. Cost outcomes, cost-effectiveness for prostate. One less? Oh.

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

Gregory Brown: Cost outcomes, cost-effectiveness for colon.

Josh Morse: Eight unproven.

Gregory Brown: Multiple myeloma? Eight unproven.

Josh Morse: Okay. Thanks.

- Gregory Brown: Okay. Since we voted by disease, should we do recommendations by disease? Does that make sense? Do we want to start with the Health Care Authority recommendations, or do we want to write our own?
- Tony Yen: I think that would be great. It's a good start.
- Gregory Brown: Do you want to pull... can we pull up the Health Care Authority recommendations on breast cancer? So, we're going to hold lunch hostage. No lunch until we have a vote. Okay. Well, I ask do we want to be test specific or do we want to... I mean, what's the feeling of the group? Do we... it's such a dynamic area to say this... to be test specific or not. I guess the question is, is since the healthcare's recommendations were cover with conditions but then they were very specific about early stage cancer 1 or 2, estrogen receptor positive, human epidermal growth factor receptor negative, lymph node negative, or 1 to 3 lymph nodes. So...
- Mika Sinanan: I think we have to be test specific, because the data is not... is test specific.
- Sheila Rege: They're not interchangeable, it seems like. I would ask, though, on the recommendation only for a woman with stage 1 to decide what hormone treatment, there was some discussion about whether that was appropriate, and I'm kind of looking...
- Nancy Davidson: You're looking at the Mammostrat and the BCI?
- Sheila Rege: The Mammostrat and the BCI, any comments on that wording there?
- Nancy Davidson: I think what's being suggested is that two tests are not necessarily going to be useful to select for chemotherapy, right? I don't personally have any problem with it, but from a simplicity point of view, if you wanted to follow what some of you said, which is these tests are, right now, potentially interchangeable, and you want to go back to the first guideline there.
- Sheila Rege: I like how it's done. I just want to make sure it wasn't inaccurate.
- Gregory Brown: So, do we, under the second condition, or the second there, the Mammostrat and the BCI, cover with conditions, don't we also want to add the test results will impact treatment decisions to that also?
- Nancy Davidson: Absolutely.
- Gregory Brown: Yep. So, basically, yeah. So, under the Mammostrat and BCI, if you could add the same phrase, test results will impact treatment decisions.

- John Bramhall: So, there must be a clinical subpopulation of women presenting with a tumor profile that lends itself to hormonal therapy rather than chemo. Is that true?
- Nancy Davidson: It is.
- John Bramhall: So, the clinical diagnosis, would you suggest tamoxifen is going to be beneficial, not beneficial, and then you would augment that with this specific test?
- Nancy Davidson: I think these tests are being used a little bit more pragmatically right now for duration of therapy and a little less for selection for or against therapy. That's just what's going on in practice, but I think we looked at one trial that you talked about where it actually was used to think about using tamoxifen or not.
- Gregory Brown: It says that under the conditions, deciding about hormonal treatment.
- John Bramhall: Right. I'm just wondering whether women present in the Oncotype and Mammostrat, because the decision is being made, should they get chemo, should they get hormonal?
- Nancy Davidson: I think in practice right now where that might happen is that somebody might have an Oncotype at the time of initial diagnosis to think about whether she should take chemo or not. Then, five years later, after she's finished her hormone therapy, there are oncologists who might say, well, I'm trying to think about whether I'm going to extend the hormone therapy. I don't think the Oncotype is as useful as the BCI test. So, that would be what's going on in practice in some cases. You've seen the evidence that supports that, which isn't as robust as we would like, but that's what people are often doing.
- Gregory Brown: The other... I think Laurie, you brought it up, do you want to list as one test per year so that if... in that situation five years later they ordered another test if they need it but not all at once or? Kevin your jaw dropped.
- Kevin Walsh: Well, it's a process question. I mean, usually we vote on these with conditions, and then we start the process of deciding the conditions.
- Gregory Brown: Okay.
- Kevin Walsh: We've agreed that we're going to go cancer type by cancer type. I would prefer that we vote up and down on each of the cancer types. Then, if the

decision is that we cover with conditions for one of them, we proceed to define the conditions and then vote on that.

Gregory Brown: That's fair.

Seth Schwartz: I recall you would normally do a straw vote just to see... is that what you're saying, not a...

Gregory Brown: Sure. I'm still learning. Thank you for assisting me. So, right. So, a straw vote on breast cancer of cover, cover with conditions, or not cover. So, eight cover with conditions. Okay. How about prostate cancer? That's pretty enthusiastic there, Sheila. Seven to one.

Sheila Rege: I was kind of going to not cover.

Gregory Brown: Seven to one.

Sheila Rege: I was kind of... I wanted this.

Gregory Brown: What about colon cancer? It's a straw vote. It doesn't matter. So, okay, and then multiple myeloma. Not cover. So, I think it was 8-0, 7-1, 1-7, and...

Josh Morse: We don't record the straw.

Gregory Brown: Oh, wait. No. I know. I know, but I'm just [inaudible]. So, I mean, from that, we're going to, it looks like we want to cover breast and prostate with conditions and not cover colon or multiple myeloma. Okay. Do we want to, although we're not covering any specific tests, do we want to add the covered by agency discretion in the future, or do we not want to... for colon and multiple myeloma?

Josh Morse: Can I weigh in on that?

Gregory Brown: Yeah.

Josh Morse: So, the challenge here, for you, in that regard is, you're asked to make one of three decisions, cover, no cover, cover with conditions. If you say, so what you would be saying is really two things. You'd be saying, don't cover it now, which is no cover, but change that in the future, and that presents a challenge.

Kevin Walsh: Really, the only choice we can give them is to change the conditions. So, we could say at agency discretion if we decide to cover something with

conditions, because the conditions we could anticipate or project or wish that the conditions change with additional evidence, but I think what Josh is saying is, we can't really give the store away to say, well we're saying don't cover it now, but if things change, you can go ahead and cover it without asking us. That's not consistent with the process.

Josh Morse: Yeah. It's a little [crosstalk].

Gregory Brown: Well, I guess, another way to do it is if we say cover with conditions and say early stage breast cancer, you know, ER positive, HER-2 negative, or lymph node negative, or 1 to 3, or we say women with stage 1 to 2 deciding about hormonal treatment, but don't specify the test. To me, we're part of the artificiality of what we're running into is that we're only going to approve specific tests. So, if a new test comes out that's shown to be just as effective as what's already out there, that doesn't seem to me to require... should require a review by us again.

Mika Sinanan: But the other situation is that the evidence in support of these tests might change. So, we're... maybe Josh you can comment about this, is the interpretation of new evidence as it comes out and how that impacts the coverage decision.

Josh Morse: So, you're looking, in my opinion, at a number of different unique tests. You're not looking at classes, unfortunately, which is, as you've talked about, with hyaluronic acid, they seemed to each have and demand their own evidence base. That's one problem. So, if you say cover for breast cancer but you don't say which ones, I think that presents a challenge. Then, if you say, cover these ones in the future when the evidence gets good enough, that's really your decision to determine if that evidence is good enough, and I think you've seen today the variability in the evidence. So, what is... how are... how is the agency supposed to make a rational arguable defensible decision based on this discussion.

Gregory Brown: So, I'm sorry. I wasn't being clear. So, my intent is to say, take out the covered at agency discretion part, but instead of specifying the tests, we say cover with conditions early stage cancer 1 or 2, or only women with stage 1 to 2 deciding about hormone treatment, but we don't specify the test. So, in other words, if another test comes out, I mean, the agency says we think this is an appropriate test, and it meets these conditions, they can authorize it. In other words, we're not being prescriptive in saying you can only have these four tests.

Valerie King: Actually, I have sort of a process question for you, Josh. Since this review is really about these specific tests, presumably, we're not making a

determination about any tests that aren't reviewed here. So, it might be considered that it would essentially be... if a new breast cancer test came on the market that was equivalent, it would be up to us, the way it always is up to is if there isn't a decision, and that would probably be the way we would make it. So...

Kevin Walsh: We don't have to specify this, because if we're limiting ourselves to the evidence that we were given, we're only going to decide on the test that we were given. The agency can decide in the future if another test comes out, and they think the evidence is overwhelmingly positive, they can decide on their own without coming to us to authorize it.

Gregory Brown: So, what I'm hearing then is, we get rid of the other breast cancer tests. We drop that. We have added the test results will impact treatment decisions for the second one. Then, are we in agreement? Is that...

Kevin Walsh: Well, I think that's...

Gregory Brown: ...because then we're just doing these four tests. So, if some new test comes out, again, it's not covered by this decision. So, this allows the agency, or authority, to accept the new test, yeah?

Mika Sinanan: Or choose to bring it back here.

Gregory Brown: Well, right. Or they could say, you know what, there's new tests out. We want you to make a decision about these new tests. We'll keep these four, but we're going to add three more or whatever, or there's new tests out for multiple myeloma. We're going to bring that to you. Is that?

Josh Morse: So, all of the tests... so, let me ask you this clarifying question, because I don't think I'm all caught up with you on this. So, are you saying, for those tests that don't meet your evidence threshold today, they will be not covered. Is that... you're going to vote on that. You can't wean them out.

Gregory Brown: Correct. Yes.

Josh Morse: Okay.

Gregory Brown: Yeah. Yeah.

Josh Morse: Okay.

Gregory Brown: Yes. Yep. So, that's for breast.

Mika Sinanan: Can I just ask, Dr. Davidson, are there conditions where we would do these kinds of testing for higher stage cancers?

Nancy Davidson: No.

Mika Sinanan: We didn't talk about evidence for that, but...

Nancy Davidson: No.

Mika Sinanan: Are we limiting that then if we only say stage 1 and 2?

Nancy Davidson: Well, I certainly can admittedly envision clinical situations where I would do it for higher stages, but I would have to say that the evidence is not there for it. I mean, there are some people who would have four positive lymph nodes where I would decide I want to do it because I would see the difference between three and four isn't very great, and I am thinking the biology is a very favorable one. Since the question I would be asking is, does chemo help or not, I can envision I would do that, but the evidence is based on these areas, and the large clinical trials that I told you about that are going on in the U.S., those areas.

Mika Sinanan: Is there a way to capture that issue in the language that's here that doesn't create a problem for a patient or oncologist who has four lymph nodes?

Sheila Rege: I don't think there is evidence for that, though.

Seth Schwartz: Now we're stretching it a little bit. I think we already have limited evidence for what we're talking about approving here. If we're going to stretch to a clinical situation where a clinician might choose to do something differently...

Mika Sinanan: Okay. Alright.

Gregory Brown: Any other questions or comments? Chris? I'm sorry? No. Leave them. You've got it right. Yeah. Perfect. Okay. Are we ready to vote on breast cancer?

Kevin Walsh: I would like to propose a separate set of conditions.

Gregory Brown: Okay.

Kevin Walsh: I would like to propose that we limit breast coverage to the Mammaprint for the specific breast cancer type that was demonstrated to show benefit in the Cardoso study, and that be the only breast cancer test that we cover.

John Bramhall: I don't think we're using the evidence base before us to make our decision. I just don't. At least I'm personally not. I'm not using the evidence base that I have here in this folder and in the background literature to make my decision. I'm not. My decision is primarily based on faith in oncologists in the field who believe in the core base pure academic studies. They say these are valid. There is clinical validity. It helps them with their interaction with patients. It's helpful to patients to have something a little bit more definitive. That's what I'm going on, and I don't know, I have no idea whether foregoing chemotherapy as the result of a test result is beneficial or not beneficial over a 10, 15, 20 year period. I have no way of knowing that, certainly not from these data. So, to constrain artificially on the basis with that one test, none of the data here are very helpful with the core decision, should the State pay for this or should it not? I'm actually looking at the situation, if we said as a group, no. These are not covered at all, it would cause such a problem for practicing oncologists, for physicians in the field, and patients, and for the State, that I think that that's a decision that I wouldn't be willing to take, and that's not a scientific decision.

Kevin Walsh: I was going to say, it's not only not a scientific decision, it's not what we're charged with doing.

John Bramhall: What we're charged with is not supported by the database that we're presented with that's here today. That's the problem.

Gregory Brown: Actually, I disagree. I think when we come up... virtually every one of these we don't have enough evidence to make a definitive... I mean, if they did, they wouldn't bring it to us, you know? It's part of the answer, but again, if the endpoint, if the outcome is, does it affect patient treatment choices, that's... and again, it's clinical utility not effectiveness, or not validity, and we're assuming that the clinical validity is all there based on Dr. Davidson's...

John Bramhall: Also on the basis of this information.

Gregory Brown: Right. Well, again, that was the scope of the report. So...

John Bramhall: I understand that.

Gregory Brown: ...we have, so... but I don't think we're... I think we do have evidence that it effects patient decisions and treatment. So, that is evidence. I'm not saying it's strong evidence, but it is evidence. It's a form of evidence. So, I don't think we've abandoned our charter to use that as our evidence.

- John Bramhall: It's such a narrow...
- Gregory Brown: I agree with you. I mean, I agree with you to tell oncologists that you can't do these at all, it just... that's not fair to patients.
- Kevin Walsh: I'm sorry, but that argument has been used by paid physician proponents of Medtronic for the last eight years I've been on this committee, and it's not been accepted by committee members. So, I would just ask you, again, I would, yes. We might be rocking the boat a lot. The charge, again, is to look at the evidence, not to look at the political climate or the fact that this test is being used by everybody because they all hope it's going to work.
- Nancy Davidson: So, may I... I don't perfectly understand the scope of the review that was done, but I don't think that you heard the results... the first results of a trial on Oncotype, that big trial I told you about that we're all paying for as taxpayers, of these 10,000 some odd women who had early stage receptor positive HER-2 negative breast cancers, 10,253 eligible women, 1626 had the very low recurrence scores, and this is reported in the New England Journal of Medicine, and at five years, those individuals have a rate of invasive disease-free survival of 94%, rate of freedom from recurrence of breast cancer just to cite, 99%, rate of freedom of recurrence for breast cancer at a distant or local site, 99%, and rate of overall survival of 98%. So, I think that's pretty good data, and I can't imagine that we're going to be able to improve that with chemotherapy. It is true they didn't randomize those women, because I think that people felt that would be unethical.
- Kevin Walsh: With all due respect, that's not part of the evidence that we were given to consider. We can continue to wait for better evidence, but the scope of what we were given was defined.
- Gregory Brown: So, the... I personally go back to the definition of evidence-based medicine, and evidence-based medicine is the evidence. It is the provider's experience, and it is the patient's preferences, and it's the synthesis of those three. So, we have the evidence from the report. We have the... Dr. Davidson's experience, since she is the only oncologist among us, and how she would use these tests. Then, we are to consider the patient preferences that's in their decision making on how to be treated. So, I hear what you said about saying, well, patients have a right to this, but I don't buy that either. I'm saying there is evidence that these change decisions. There is experience that this is beneficial to patients, and a whole body of evidence of cancer treatment, and there are patient preferences that

clearly in these trials show that they've chosen not to have chemotherapy and all the side effects. So, I don't think we've abandoned anything there.

Kevin Walsh: So, I trust and respect everybody at this table. I am offering a different set of conditions, and I will respectfully submit to the decision of the group if people think this is not acceptable, and we can move on.

Sheila Rege: So, you're suggesting on the first one, just MammaPrint only.

Kevin Walsh: Yes.

Sheila Rege: And taking off Oncotype Dx and EndoPredict.

Kevin Walsh: And taking off Mammostrat and BCI, taking off everything except MammaPrint.

Sheila Rege: And also taking off Oncotype Dx?

Kevin Walsh: Yes.

Sheila Rege: Which has the most studies, but not one study that just showed this prospective.

Kevin Walsh: It had a lot of studies that showed that it effected treatment decision and no studies that it effected outcome.

Sheila Rege: I think it has had studies that show it effects outcome, but perhaps not a recent one with a prospective, because it's an older... I mean, it's been used for years in the U.S. I would advocate ... clinically, just in the real world, Oncotype Dx and MammaPrint are the most used.

Gregory Brown: So, if I heard you right, Kevin, what you're saying is, you've proposed this, if we say we're not comfortable with...

Sheila Rege: Yeah, we could...

Gregory Brown: ...so basically, what you're asking for is a straw vote of...

Kevin Walsh: I was just asking for the chance to offer a different set of conditions and then have people thumb up or thumb down.

Gregory Brown: I think that's appropriate. So, who would... so, the two options are Kevin's proposal or what we have up there. Who is more leaning towards what we have up there.

- Tony Yen: So, is there room for another proposal. I'm sorry about this. I feel like I'm throwing, like, another gasoline on the fire over here, but...
- Sheila Rege: Maybe we should... there's a motion on the floor, though. Maybe we should...
- Gregory Brown: Well, let's just see whether we want to...
- Sheila Rege: ...we want to do this first and then...
- Gregory Brown: ...right. Is it...
- Sheila Rege: ...and then move to your proposal?
- Gregory Brown: ...is it preferably what we have or Kevin's. Let's do that first. I agree with you, Sheila.
- Kevin Walsh: Well, so people... I respect the fact that I'm the only person that supports that condition. So, let's drop that, and let's move on and hear Tony's.
- Gregory Brown: Yeah, Tony, what's your?
- Tony Yen: I think the data really shows the best for Oncotype Dx, at least from the papers I can see, and the MammaPrint. That's pretty much it. Well, at least that's my interpretation of the data. That's why I was asking questions of our clinical expert over here about those other tests. I just had no greater understanding behind them. So, that... if we were going to narrow down to specific tests, I think we should use those tests with the most data and the most experience behind them. The Oncotype Dx data is not prospective, but there is a wealth of data. Whether or not that's meaningful is another issue.
- Kevin Walsh: So, your proposal, Tony, is to cover Oncotype Dx and MammaPrint for those conditions and then not cover EndoPredict, not cover Prosigna, Mammostrat, or BCI?
- Tony Yen: Yeah, and that's because I just don't understand kind of the supporting data behind it, as well. That's all. I'm willing to be convinced. That's all.
- Gregory Brown: Well, we've got the evidence, I think...
- Seth Schwartz: Well, yeah. I think that's right. I think I'm struggling to separate these tests out. Again, I come back to this cost question of we've seen a lot of data

for Oncotype Dx and for MammaPrint. Again, it's primarily about clinical decision making rather than outcomes. We've seen very little data on the EndoPredict and the Prosigna, and I'm curious if those studies are... if those tests are drastically more expensive than the other two. I don't necessarily feel like... I kind of would mirror what Tony says. I don't see why we have to include two tests that have much less evidence in support of them or almost none if they happen to be more expensive than the others. I don't know if we have that information. Do we have any information on costs of these tests or?

Valerie King: Very little.

Gregory Brown: I guess the... I guess my perspective is, is we don't have evidence enough to say one is better than the other. I mean, there's more evidence in some than the other, but it's not... it's more of a historical. They've been around longer. So, there's more studies using them, but none of the studies show that it's superior to the other tests.

Seth Schwartz: I totally agree with that. So, I'm not necessarily saying that we should do that, but I think it's an important point. I think we've had situations where we have two things that are... we have one thing we have really good data for that is inexpensive, something else that we have really lousy data for but may be about equivalent, but cost ten times more, and we're not going to support that thing, as one study where the other has 13, because they're different situations, and I have not heard anything to tell me that the oncologist couldn't function with only access to Oncotype Dx and MammaPrint. That they need EndoPredict and Prosigna. If they do, maybe they do. I don't know. I haven't heard anything to say those two tests are critical.

Nancy Davidson: My only experience is largely with the two that you've already talked about. That's probably because the other ones are newer. So, again, information is emerging. It also may be partly the regional stuff that we talked about and partly the clinical trial stuff that we talked about that people have familiarity with one or another based on the experience they've been involved in, in a research setting.

Sheila Rege: I actually agree. I think I would personally be comfortable with just Oncotype Dx and MammaPrint, because that's got the most of the studies. I don't know if we've got coverage decisions by other insurance companies. I mean, you don't want us to be ahead of all the data. I understand giving the clinician the choice, but if one is much more expensive, I mean, if one's much cheaper, that's different, but if the newer

tests are much more expensive, then I worry. We don't have that data. Can we get that data in time?

Josh Morse: We don't know that information. Dr. King, do you happen to know the market cost for these tests and if there's any difference?

Valerie King: I don't know the market cost. I could check the Medicare fee schedules and really quickly and see.

Josh Morse: Do you need codes?

Valerie King: Some do, some don't. That's another problem with this.

Josh Morse: One of the problems we ran into is you can't distinguish one code from another... one price or billing code from another.

Valerie King: I will say, in the cost-effectiveness studies, they were roughly priced the same, but you can't do that. The other thing I would point you to is there is information in the report on the slides that we didn't do in detail on guidelines and private payer policies. So, we can tell you what others do and don't cover in your region.

Gregory Brown: Well, I don't feel like I have enough... I don't think the evidence drawing enough to just throw some out and not others. I mean, again, this means the State cannot cover them moving forward. Again, I think to some extent, the market will find the best test for the appropriate cost, and we don't have the evidence now to pick that. To me, it's not clear that one is much better with a lot less cost. So, I would prefer to go with what we have here. I see your hand. I'm sure you can give us your costs.

Female: [inaudible]

Gregory Brown: So, there's not going to be a cost difference then? Okay. So, we had a suggestion by Tony to just keep those two and eliminate the other four. Vote on that? Stick with...

Mika Sinanan: Can I ask just a clarifying question? The sense I have is that the normal process and decision making is being stretched because of the limitations of the data, that we're being asked to make a decision, which in your prior experience, is not something that we would have done. I'm looking at both Seth and Kevin. I don't have the experience for that. So, is that what you're... is that underlying this, or?

- Seth Schwartz: I don't think that's true. I think as Greg said earlier, we're always... our data is always bad trying to answer these questions, and we're trying to sort out the best answer with the limitations that we have.
- Mika Sinanan: Okay.
- Seth Schwartz: I think that's why the important aspect of having us as clinicians here is important, because we're trying to look at this through the clinician's eyes, which, I think, sometimes prevents us from making rash decisions that could have implications for clinicians everywhere, even though the data may be challenging to assess.
- Gregory Brown: We use the word limited instead of bad. [laughs]
- Seth Schwartz: Well, it may be both. I think here we're a bit more limited than we are bad. That's fair to say.
- Mika Sinanan: So, John's comment earlier that the decisions that we make, we incorporate all the available data that's been presented, but the decision doesn't need to be driven only by the data. There are other considerations that we can bring into it and do on a routine basis? Is that correct? That's your understanding?
- Kevin Walsh: I think there have been different camps at different times, depending on the makeup of the group about whether that's reasonable or not.
- Seth Schwartz: I think that's fair. I don't think our specific charge dictates how we handle it, and there have been very significant differences of opinion about how much people weigh the data versus the clinical scenario and vice versa.
- Gregory Brown: I think our charge as individual committee members is to make what we feel is our best decision. Not that... and we're all going to weight different factors differently and everything there, and that's the point of essentially a consensus approach. So...
- John Bramhall: The problem with that, though, is that decision-making becomes opaque. So, I've confessed to you that the outcome studies are not here. So, I can't make a decision, I can only make a decision to turn all this down. Stop it.
- Kevin Walsh: Correct.
- John Bramhall: On the basis of outcome studies.
- Kevin Walsh: Correct.

- John Bramhall: And in the past we've often thought that if the intervention was going to be successful or unsuccessful, it was on the basis of the ultimate outcome of the test or of the intervention or what have you. So, fine. I say, well I can't make a decision on the basis of these data that makes sense to me. I'll make a decision that makes sense to me in other ways, but those other ways are not laid out before the public. So, I'm saying that I have confidence in the oncologist. I have confidence in our expert witness. That's just personal confidence. That's not scientific.
- Seth Schwartz: John, I don't think that's totally true. I think you're seeing it through the eyes of the data, which is... there is data on MammaPrint. There is some data suggesting there's effectiveness. It may not be super compelling, but there's some data to suggest it's effective, and we have numerous different testing options, which we can't discriminate. So, we have something with some data suggesting it may be beneficial, clear data that suggests that it changes decision-making, and no big difference between any of these tests. So, that's not... that is very muddy waters, but it's not fair to say that that's not influencing your decision. I mean, that's what we all see. It may... we may interpret it differently and weigh it differently to make an ultimate decision, but I think there is data here that we're not going to disregard. It's just... it's hard to make... it's not conclusive enough to make a definitive decision on what to do, but you have to look at our own... whatever decision we're going to make, through the eyes of what we have seen.
- Sheila Rege: This is Sheila. I'm actually comfortable with that suggestion of Oncotype Dx and MammaPrint, because that has the most data. I mean, even with everything else. Also, looking things up, in our state, it looks like Medicare also for EndoPredict is doing very limited coverage. They are not doing this broad coverage, and that just happened in January it sounds like. Somebody can correct me. Is that true? It says postmenopausal women only. So, that's the patient population. And it says only for treatment with adjuvant endocrine. They are not looking at chemo, according to the? So, it says... well, I'm just, I'm looking it up, 2/2/2018. I feel either way on that, but that's... I just...
- Gregory Brown: I hear you. Again, the point is, what this is telling me is this is evolving, and to say the State is not going to cover it and in six months Medicare say we're going to cover it for this, this, and this, and we have, you know? So, again, I'm not... I don't think that... for me, the data is not compelling enough to say we're gonna throw out those other tests. That's just me. That's not... Dr. King?

- Valerie King: Yeah. You know, I went back and looked at the evidence tables, and I do want to highlight something. That's that you've got, in the clinical decision impact realm, you've got 48 studies on Oncotype Dx, 11 on MammaPrint, including the only really high-quality study, and then you've got one on each of the other four tests, one, none of which were high quality. So, it's just... there's great disparity in the amount of evidence available.
- Gregory Brown: And I understand that. I guess my point is, if the next ten studies on EndoPredict are poor, clinicians aren't going to use it, but if they're good, but we say no, you can't use it, then we're stuck. So, to me, again...
- Kevin Walsh: No. Then the State says, we need to reevaluate this. We've re-reviewed several technologies when studies have come out that are distinctly at odds with the existing studies at the time that we made the first decision.
- Gregory Brown: I agree. Again, we review classes. We don't review individual products in my experience. So, again, we review hyaluronic acid. We don't review each individual hyaluronic acid injection. We review fusion. We don't review every single possible method of lumbar spine fusion, you know?
- Seth Schwartz: We have.
- Gregory Brown: We review it as a topic.
- Seth Schwartz: I don't think that's true. I think we have reviewed different ways of doing things. I think... the question is, how do you view these? Do you use two different forms of hyaluronic acid that are effectively the same thing, or tests that are quite different, and we've been told that they're looking at different genes and they, theoretically ... well, they presumably have different evidence for how they discriminate patients into the risk categories, which we haven't seen. So, I don't know that I... that we can lump these in the same way that you'd lump, like, that you lump a product that's the same.
- Gregory Brown: Well, so here's... we're developing a new clinical practice guideline for knee osteoarthritis, and there's a lot of dissatisfaction about a recommendation to not use hyaluronic acid, which is consistent with this committee's, but there are so many biologics out there, and what's being done to patients with absolutely zero science, but the problem is, is the field is changing so fast, if we put it in a clinical practice guideline, it's effective for the next five years. So, I agree they can bring it back, but to have to come back for an individual test, I don't... I personally don't see the advantage there. We've beat this up. We need to move forward. So, do we want Tony's...

- Sheila Rege: Um...
- Gregory Brown: ...so who wants to vote for Tony's suggestion of just the two?
- Kevin Walsh: Yeah. Let's vote on Tony's, straw vote.
- Seth Schwartz: So, it'd be just the Oncotype Dx and the MammaPrint?
- Sheila Rege: One, two, three, four, oh God. I'm undecided.
- John Bramhall: It becomes self-fulfilling. That's the problem is that then you never collect the data.
- Kevin Walsh: There's seven of us at the table, or eight of us. I'm sorry. So, it's four and four. Thanks. I couldn't count. Thank you.
- Sheila Rege: Four and Four. That's why I'm, like, struggling with this one.
- Kevin Walsh: Let's, then I would propose that we... so we've done that. It's split. Let's vote on the one that's on the screen. Straw vote.
- Sheila Rege: I do... before that, though, I would like to... us to consider something that was discussed that we've not put in that you only get one of these tests. You don't... you can't go down the list. I got this. Okay. I'm going to go do this next. Oh, I'm going to go do this next.
- Gregory Brown: So, a third point, one genetic expression profiling test per year.
- Sheila Rege: Per 12 months, because what if you get diagnosed in December?
- Gregory Brown: Sure. Sure. Well...
- Sheila Rege: For 12 months or something like that.
- Gregory Brown: Again, you run a calendar year, right? So, you're not going to...
- Female: We can do it either way.
- Gregory Brown: Okay.
- Female: We do make an exception if someone had an independently diagnosed second cancer.

Sheila Rege: We need to propose wording.

Gregory Brown: So, only one genetic...

Sheila Rege: Only one test...

Gregory Brown: ...expression profiling test...

Sheila Rege: ...per 12 months...

Gregory Brown: ...per diagnosis per year, 12 months.

Sheila Rege: Per, per diagnosis, right. That's good.

Gregory Brown: So, that way if you get a second diagnosis you've got a...

Nancy Davidson: And will that permit, if somebody has synchronous cancers, you know, if they have two cancers, can I get it on each, because I would?

Gregory Brown: Yeah.

Nancy Davidson: Okay.

Gregory Brown: I think so. I mean, that's... per cancer diagnosis.

Seth Schwartz: So, say one genetic per 12 months per index cancer, or something like that.

Gregory Brown: Per diagnosis [inaudible], um, is index more technically correct?

Nancy Davidson: Yeah, that works.

Gregory Brown: Okay.

Nancy Davidson: I like it.

Gregory Brown: So, did you get that Chris? You're at the bottom of the page, we can't... Okay. Yes, one per indexed cancer, cancer diagnosis, indexed cancer diagnosis.

Sheila Rege: For all of them.

Gregory Brown: Is it indexed or index?

Sheila Rege: I just...

Valerie King: Index.

Gregory Brown: No E-D. Take out the E-D.

Mika Sinanan: It goes to the very top. It's not for each of those.

Gregory Brown: Cut, not copy, I guess is what you're saying.

Mika Sinanan: Yeah. Yeah. That's fine.

Female: I think even higher up above.

Gregory Brown: Right below cover with conditions.

Female: Above when we differentiate. It's a little higher. Nope. Higher. Okay. I don't know about that. You'd be the only one listening to me. Okay. I think so, but...

Sheila Rege: Don't you need it for the...

Mika Sinanan: I think our...

Sheila Rege: ...[crosstalk] above the MammaPrint?

Mika Sinanan: ...intention was that it's...

Sheila Rege: For both?

Mika Sinanan: ...at the very top.

Sheila Rege: Yeah. The very... before the thing.

Mika Sinanan: Before even the title.

Gregory Brown: Oh, oh.

Sheila Rege: Because we want it... we want it to apply to both.

Gregory Brown: Oh, I see.

Mika Sinanan: Yeah. It's supply everything.

Gregory Brown: Oh, yes.

Sheila Rege: Does that make sense? Do you agree, Dr. Brown?

Gregory Brown: Yes.

Mika Sinanan: Right.

Gregory Brown: Well, then, I mean, the cover with conditions is in the wrong spot, too, I guess is what I'm... so breast... yeah.

Sheila Rege: Oh, yeah. The cover with conditions should be there on the top, too.

Gregory Brown: So, breast genetic expression profiling cover with conditions, and then...

Female: [inaudible]

Gregory Brown: ...delete that. No. No. Keep that. Yep. No. No. No, not...

Kevin Walsh: Can I ask for... I want to make a process suggestion. Rather than wordsmithing this right now, let's get the straw vote and then decide if we need to wordsmith it or not.

Gregory Brown: Perfect.

John Bramhall: By the way, with respect to Tony's suggestion, it's paradoxical, [inaudible] and Noridian, those are the only two that you would suggest, messing out the only two that they cover.

Tony Yen: So, I was trying to do that rationally rather than just kind of arbitrarily.

Gregory Brown: Anyway, so...

Sheila Rege: Were you aware of that Noridian coverage?

John Bramhall: We have the LCDs for [crosstalk].

Kevin Walsh: It's the third coverage with condition proposal. So, we're going to do a straw vote on this one, right?

Gregory Brown: Yep. So, all in favor of this one. Do you want to vote for this one or no?

John Bramhall: For this?

Gregory Brown: Yeah, Sheila is from Chicago. She's voting both sides.

Sheila Rege: Yeah. I'm voting both sides.

Gregory Brown: Vote early. Vote often. Did you... are you voting for it or no?

Sheila Rege: For.

John Bramhall: I'll vote for it.

Gregory Brown: So, we have five. Okay.

Kevin Walsh: Now, we can wordsmith it.

Gregory Brown: Now we can wordsmith it. Thank you. So, yep? I think we got it. Anybody have any wordsmithing else, or are we good? Okay. Are we ready to vote ... real vote? Breast cancer.

Seth Schwartz: So, you're going to vote for each condition separately?

Sheila Rege: I think it was reversed, yeah, because they just started covering.

Gregory Brown: No. We're going to vote for that. Oh, yeah, each cancer separately. Yeah. So, breast.

Josh Morse: Seven cover with conditions, one not cover.

Gregory Brown: Then, next is prostate. Can you save that one and bring up prostate, Chris? Okay. So, do we want to put in that same line about one genetic expression testing or profile testing per 12 months per index cancer?

Sheila Rege: Yeah.

Gregory Brown: And then, you can get rid of the cover with conditions after those two, yep. Okay. What do we... is this acceptable or do we want to modify this one? Not hearing any modifications, should we do an official vote? Are you going to vote for Tony in his absence?

Mika Sinanan: And early stage, do we want to say stage 1 and 2, or is early specific enough?

Nancy Davidson: I thought it would be the... early is great wording.

Mika Sinanan: Pardon?

- Nancy Davidson: I think early is very good working for this.
- Mika Sinanan: Okay.
- Gregory Brown: Okay. Any other?
- Josh Morse: Emily, is early implementable?
- Emily Transue: I think it would probably be more easily implementable if we set a definition.
- Gregory Brown: And a hyphen, too, like on breast or, what's the definitely of early?
- Nancy Davidson: I don't actually know the information on that. That's why...
- Seth Schwartz: Wouldn't it make more sense to look...
- Nancy Davidson: ...I think it says early.
- Seth Schwartz: ...at who was included in the studies? I mean, do we have... do we know what the inclusion criteria were for the studies?
- Valerie King: Yeah. They were really mostly 2a.
- Sheila Rege: But they... but we don't do... we mostly look at a favorable risk with not just the 2a. It has to be biopsy proven, low Gleason score. I mean, we don't just... I'd be a little uncomfortable just saying 2a.
- Valerie King: Oh, I wasn't thinking prostate. I was thinking colon.
- Sheila Rege: Yes.
- Valerie King: For prostate, I...
- Nancy Davidson: So, you could...
- Valerie King: Early describes the studies. The Gleason scores were actually all fairly much all over the map.
- Sheila Rege: Favorable intermediate risk maybe Gleason score not to exceed 3+/4, but that's getting... wordsmithing it, you know, percentage of positive biopsies being less than 50. I mean, those are the kind of criteria we use.
- Emily Transue: I think early is okay.

Nancy Davidson: I think early is probably the easiest.

Sheila Rege: Yeah. I think you know how... you'd be looking at the study, so...

Emily Transue: I think we can use that. I'll change my...

Gregory Brown: Okay. Are we ready to vote? Food is a great motivator, huh?

Josh Morse: Seven cover with conditions, one no cover.

Gregory Brown: And then, I think for colon, we already had our straw vote. Everybody was pretty much...

Sheila Rege: Covering with conditions?

Gregory Brown: Oh. Actually, that's what I voted the first time, but yeah. Actually, yes. No. I'm not gonna let you change me. I am going to...

Sheila Rege: I just wanted to make sure you saw it.

Josh Morse: Seven not cover, one cover with conditions.

Gregory Brown: Then, multiple myeloma. Eight not covered.

Josh Morse: Eight not covered. Thank you.

Gregory Brown: Hey, thank you, everybody. We will...

Josh Morse: Do we need to check the National Coverage Decisions and guidelines...

Gregory Brown: Yep.

Josh Morse: ...concordance.

Gregory Brown: Okay. So...

Sheila Rege: Which page was that on?

Gregory Brown: So, for Medicare, coverage guidelines, we had ... there is no Medicare National Coverage Determination. It says Noridian coverage for EndoPredict, Prosigna, BCI. I don't see the other two.

Josh Morse: There is no NCD. So, that...

Gregory Brown: Oh, okay. Yeah. There's no National, so...

Josh Morse: No National coverage.

Gregory Brown: So, we don't need to worry about the State one with Noridian, the local?

Josh Morse: No.

Gregory Brown: And then...

John Bramhall: Well, except Noridian, the LCD does not cover the endo, right?

Sheila Rege: The Noridian LCD...

John Bramhall: I don't know if those are anchored or not, thought, but...

Sheila Rege: ...yeah.

Josh Morse: You just... it's okay. The national coverage determination, if you differed from that, then you would... we would have to do a little bit more.

Gregory Brown: But we don't have to worry about local coverage. Okay? Prostate cancer, there is also no Medicare National coverage decision. Colon cancer, no Medicare National, and multiple myeloma, no Medicare National determination. So, clinical practice guidelines, how about we shortcut. Can we ask our expert and say [crosstalk].

Josh Morse: Well, if you look at the table.

Gregory Brown: Oh, there we go.

Josh Morse: You'll see there is some variability.

Gregory Brown: So, all six of them...

Sheila Rege: I think we're within the...

Gregory Brown: ...sure.

Sheila Rege: ...the guidelines.

Gregory Brown: And prostate cancer, guidelines on prostate cancer, men with clinically localized prostate cancer considered tumor based molecular assays and

make specific recommendations, Decipher, Prolaris, and Oncotype Dx. So, those are the three that we approved. So, I think that's consistent there. None for colon cancer, no clinical practice guidelines regarding that, and multiple myeloma. They did not make any recommendation about the use of these tests. So, I think we're consistent with the guidelines.

Josh Morse: Okay. Thank you, very much.

Gregory Brown: Thank you. So, it is, I have 1:00. A half hour lunch, and then we'll do bylaws? Does that work? Okay. Thank you, everybody, and thank you to Dr. King and your presentation.

Josh Morse: Christine, if you could also dial back in, in case anybody wants to comment. So, you'll see on your agenda that we put review the proposed bylaw changes and comments. We will have a public comment period if anybody wishes to comment. We'll check if there's anybody here, anybody on the phone. It looks like there is nobody here now, as required. Then, you can go to ratify if you are accepting the changes.

Why did we update the bylaws? We updated the bylaws because two years ago, there was a change to the Health Technology Assessment law that made the clinical expert a voting member of the committee, I mean, I'm sorry, a nonvoting member of the committee, as opposed to just... we didn't have anything official about clinical experts previously, and that was passed into actual revised Code of Washington RCW to change to make that person a 12th nonvoting member. So, we've added information about that to the draft bylaws. You might also remember that a couple of years ago, you were briefed on a lawsuit a few times. That lawsuit led us to make some administrative changes. It resulted in a settlement agreement that we would do some administrative updates, which we did. Those rule changes went into effect in September of 2016. So, we started the process of updating the bylaws in response to those two events basically, the law change and then the rule change. Last spring, we stutter stepped when the previous chair left, because he and I had started work on that, and we moved that to the end of 2017. So, that's what brings us here. So, you have, I believe, a copy of the draft bylaws and a copy of the previous version. Fortunately, we restructured these, so they're not in the same order. So, it's hard to do a one-for-one crosswalk, because we did reorganize.

Gregory Brown: Josh passed the bylaws onto me, and I did a little wordsmithing, quite honestly. We don't have a track changes. So, I can't remember what all the changes that we made.

- Josh Morse: Right. So, Kris and Christine have put together these slides.
- Gregory Brown: Okay. There we go. So, we just incorporated the clinical expert, as we... there was some... did we add, we add the Department of Corrections, or did we say we didn't add them, because they do it voluntarily, but it's not part of the law? That was the... I thought that was the gist of it somewhere when I asked that. I don't recall that change.
- Female: [inaudible]
- Gregory Brown: No. I think I just asked a question.
- Josh Morse: So, we added the not... so, the legal change from two years ago also said, so make the clinical expert a nonvoting committee member, and it said at least one member of the committee must be appointed from nominations received from the WSMA or the WOMA. So, I believe we've made that clear in your bylaws just under who the committee membership are. The organization here is, we have the purpose, the committee authority... we had a good some... the previous version, you will see, has mandate and purpose, and we thinned this out to just put really what your authority is, is to make coverage determinations. We don't want to extend beyond... you can't make up authority... what the law says is what's in your bylaws now. So, there is a little less language there. We then organized... at the top is the committee membership and terms, and the terms did change in the rules a little bit. So, that... the terms were edited to reflect what's actually in the rules now. Then, following along, voting members versus nonvoting member. Those are defined in the bylaws whereas previously, there was no cause to do that. The committee support section, which is what Health Technology Assessment staff do, I believe, remained the same. Committee roles and responsibilities, I think there was some minor editing here, just around kind of how things were phrased, but it does not change the substance of the rules and responsibilities. Committee officers, which are now established in rule... as part of the rule changes, it's in the law, it's in the rule, I believe. So, that would... that follows next. I don't believe this language changed at all. Key operations remained the same, except for, perhaps, some grammatical changes in the operation. Then, at the very top, this is the section I was looking for. At the very beginning of your new draft, there are two paragraphs. The first paragraph existed previously. This is the background on the committee. The second paragraph comes from your new rule about establishing bylaws. So, we added that. That's your authority to make bylaws, which didn't, wasn't previously written anywhere. So, that's a new rule, as well.

- Gregory Brown: Quite honestly, most of the things were just some wordsmithing, I think, kind of like under committee roles and responsibilities, just getting the same tense of all the verbs or something, but nothing major.
- Sheila Rege: If I can ask a question. I saw this, the advisory group, and I... during my time, we haven't had that. How do, how does this committee decide on whether an advisory group is needed? I actually Googled it. It seemed like you had an advisory group at some point for cardiac stents years and years and years ago. So, how does that process work?
- Josh Morse: It's the Chair's authority to establish an ad hoc advisory group and it only happened the one time. My recall when the committee was... when the [inaudible] started when the... actually prior to the committee starting, when the legislation was drafted, I think there was a greater belief... I don't know if intent is the wrong word, that that would be a more regular occurrence. Then when it actually began, the technicalities of actually doing ad hoc committees for every subject was not made into a reality, the complexity of that, because... so, the Robert Bree collaborative does operate that way, but their legislation is completely different from this, but they have subcommittees for every topic, and then they spend time meeting in outside public meetings and then coming back to the main body. That was kind of the, I think, one vision of how this could be done, but now, I think the utility of that is that if you... for example, today, if you had thought there's too much detail here to develop criteria in a meeting setting like this in a couple hours, we need a specialized group that can hammer this out and come back to the main body with more like a guideline. Then, that would be when that would be maybe most useful.
- Sheila Rege: So, we kind of have, it's too complex then the Chair would...
- Josh Morse: Like cardiac stents, my recall is the original cardiac stent decision, there was a lot of question about well, who is most appropriate, and if you look back at that decision, there's a lot of detail about who... I'm looking to see if anyone was here at that time.
- Kevin Walsh: No. It preceded, it preceded me.
- Josh Morse: Okay. So, they needed specifications on the lumen size and [inaudible].
- Sheila Rege: Good to know. Thank you.
- Gregory Brown: It was basically if we didn't feel we could come to a decision, here's a group. You form the advisory committee to then come back and make a recommendation?

Seth Schwartz: I thought they were pretty specific. That wasn't the point. It wasn't to table it. It was only formed to answer a specific question that they thought they needed more expertise than was in the room to answer. So, it wasn't... because I think... and Craig as a former Chair, or I guess the second former Chair, was very clear that it was... that our charge is to answer the question before us today, and you really shouldn't use that in order to get out of what our job is. It's really unless it's a separate issue entirely.

Sheila Rege: So, I'm curious, when that happened, was it ... and I don't see it happening, like, you know, except as an exception, but was that when people were reviewing the data, and they asked for it prior to the meeting, or was it at the meeting that they couldn't decide, and it got asked for? Does anybody remember?

Josh Morse: Dr. [inaudible] is on the phone and would like to contribute, I think, to this. He just texted me, but can... can somebody else.

Seth Schwartz: So again, I wasn't here, but we had talked about this a lot, right actually after I came on the committee, and my understanding was that it happened at the meeting. It was not preordained, and it was only in regard to one aspect of the decision. So, the majority of the decision was made, and it was only in regard to one aspect of the decision that they couldn't ... they didn't have enough information on. So, that was tabled and then brought back in the next meeting, but it was not the entire thing.

Josh Morse: Gary, are you on the phone?

Gary Franklin: Yes. I am. Can you hear me?

Josh Morse: Christine, can you turn that up a little bit? Yes. We can.

Gary Franklin: Can you hear me?

Josh Morse: Yes.

Gary Franklin: Okay. So, I actually helped write that original language, and the intent was to do exactly what happened in the stent discussion, which is, you have a topic with a huge amount of data, not like the topic today, where there is enough information in randomized trials to make sort of a higher level decision, but then to get down to the conditions, especially when there's dispute around the conditions of coverage, then the thought was, if you put together some clinical experts that were mixed and blended, some of

them were not... did not have conflicts of interest, that better, maybe better conditions could be come up with. We brought back to the parent committee, yeah, your committee, and then a final decision would be made on the conditions of coverage. So, that was the original intent. I don't really even think the budget is there to do that very often, right Josh?

Josh Morse: I think that depends. I think if it was necessary, the budget might be able to accommodate it, but it would be rare.

Gary Franklin: Yeah, but that was the intent.

Josh Morse: So, we don't have an annual budget anticipating ad hoc committees, to answer that.

Kevin Walsh: I also think that historically, there has been an evolution in the comfort level of the group with making decisions when things are muddy. So, I think there's been... I feel like when I joined the group, there was a little reluctance, sometimes, to make a decision. People were uncomfortable making decisions, and I think that... I think that that has evolved.

John Bramhall: Well, it's explicitly here in our list of responsibilities, I noticed that serving the public interest is A if not THE top priority. I think that kind of phrase there opens the door to a little bit less of a technocratic approach to the problem. I mean, that's just my opinion. So, serving the public interest, it's asking us to look at a few other dimensions beyond the purely technical. That's the way I read that anyway. So, but you've seen an evolution? Is that? Yeah, you sense it.

Kevin Walsh: I feel like that. Gary, do you?

Gary Franklin: Yes. I feel like that very strongly.

John Bramhall: And is that felt with positive glow in your heart or venom?

Gary Franklin: Yeah. Yeah. Positive glow, yeah. The committee has been unbelievably great.

Kevin Walsh: I've become an advocate of the process that we go through, and I've been able to let go of the decisions, because I think the process is really the value. I think that we do this in a different way, and the way that we do it is, I think, credible and conscientious and accountable and transparent.

Gregory Brown: I think that addresses your earlier comment about you feel that it's opaque for you personally. And yes, but again, that's the point of having a

committee and a process. So, we all may be somewhat opaque or very opaque, but as a group, we tend to migrate to the same area.

Laurie Mischley: I have a question about the requirement that there be some congruence with Medicare. Requirements, why wouldn't we take that into account before we spend a whole bunch of time wordsmithing our recommendation? Why do we make our recommendation first and then go to the Medicare coverage guidelines?

Sheila Rege: Where do you see that?

Josh Morse: It just would reverse your process, and it could influence your take on the evidence, I think. The way the law was written was that you base your decisions primarily on the evidence in the systematic evidence review. At the end of the process, you are... it's... you are required to see if you're in a different place from a National coverage determination that was written into the original law, and if you're different from that, then you need to explain why, but it's different from starting with whatever Medicare decision there might be and then looking at the evidence, and, you know, it would have maybe changed your line of thinking.

Seth Schwartz: I think that's right, Josh. We're not supposed to be bound by what that says at all. We just, but if our recommendation is different, we just have to explain why it's different.

Gregory Brown: For example, Medicare pays for HA, hyaluronic acid, and there was a recent award at the, I think, American Association of Hip and Knee Surgeons that half of the treatment in the year prior to surgery for knee replacement is for non-clinical practice guideline recommended treatment, non-recommended treatments, and, like, two-thirds of it was HA costs. You open up the newspaper every day in the Seattle Times, and ads for...

Gary Franklin: Also, Josh, did you mention that only is relevant for National coverage decisions, not for regional decisions?

Josh Morse: Right, and that's how it's framed in your rules. So, the administrative code makes it clear, it's the National coverage determination and not the local, which are different across regions.

Seth Schwartz: Can I move us on? I just had a question...

Gary Franklin: And then we have had, we have had examples of National coverage decisions that were counter to the decision to the committee, but they

were 20 years old and did not include any of the evidence that the committee looked at. So, that was also disregarded.

Seth Schwartz: ...yeah. I just wanted to move on. So, where... under the committee membership and terms of appointment, it says we're appointed to a three-year term, but there had been some talk about whether we can... how many consecutive terms we can serve. Is it two? Is it one? It doesn't say anything about more than one term here. It says you can serve until a successor is appointed, but it doesn't say...

Gregory Brown: Where are you?

Seth Schwartz: On the first page, at the bottom, appointment. It says committee membership term appointment, committee members are appointed by the director in consultation with participating agencies to a three-year term. It says terms of less than three years can occur, and you can serve until someone else is appointed, but it doesn't say... I thought we had talked about there being... you could serve two consecutive terms, or three terms or, I can't remember what it was. So, I don't see that in here.

Female: It's in there. It's nine years.

Group: Where is it?

Female: It should be under terms of appointment. [inaudible].

Seth Schwartz: Yeah. That's what I thought, but I don't see it in here.

Sheila Rege: Maybe it's on a different page.

Seth Schwartz: That's where we are.

Mika Sinanan: No. I don't think it's there. I think it was dropped off. It's not in here.

Sheila Rege: Yeah. We had talked about that. That would be good.

Josh Morse: We'll add that.

Sheila Rege: Okay. I do have a question of when this committee has called an executive session historically, has that ever happened, and is it just, why would it be?

Josh Morse: The committee can go into executive session for... without looking at the... I'll just give you the... my lay perspective on this for two reasons. One is if somebody were to bring you proprietary data that... and you had reason

to see that. Like, if an industry said, hey, we have this data. It's not published yet, but we want to share it with you, you could go into a closed session and do it then. The only other time, and the only time that you... the committee has gone to a closed session is for legal updates from State attorneys, and that has occurred a couple of times.

Laurie Mischley: I don't see it in the new draft, on the PowerPoint, you talked about the importance of justifying why we differ from Medicare, but I don't see that written into the draft bylaws.

Sheila Rege: Yeah, the National coverage decision is not in the...

Female: [inaudible]

Josh Morse: Can we move to approve? Do you want to edit for terms?

Seth Schwartz: I would move to approve it with the edit for terms.

Gregory Brown: Any further discussion?

Josh Morse: We need to ask for public comment.

Gregory Brown: Unmute the... is anybody on... are we unmuted?

Female: We are unmuted.

Gregory Brown: Is anybody on the line and wish to make a public comment regarding the bylaws for the Health Technology Clinical Committee? I'm not hearing any. We can put them back on mute. Okay. Now, we can vote. The fact that we put in that nine-year term, or nine-year limit does that require it to get re...

Josh Morse: No. I'm looking at the rule right now. So, what we will add to the rule, I'm sorry, I'm looking at the committee member requirements and member terms, which is what we will copy part of this in there, and I'll just read to you what I'm going to put in here, so you know what this edit may read, something similar to. So, it is, number three, committee members serve staggered three-year terms to provide for staggered terms. Committee members may be appointed initially for less than three years. Then, the next bullet, number four, a committee member may be appointed for a total of nine years of committee service, but an initial appointment of less than 24 months is not included in the nine-year limitation. A committee member may serve until that member's successor is appointed, notwithstanding the limits of service in subsection three. Midterm

vacancies of the committee are filled for the remainder of the unexpired three-year term. So, we will take those points and make them clear in this, in terms of appointment, terms of appointment section.

Female: [inaudible]

Josh Morse: Right. So, that's...

Gregory Brown: That's what he was reading from.

Josh Morse: The reference is what I'm reading from, but I can make that clearer in the bylaws. Okay.

Mika Sinanan: So, that's a further amendment that we've incorporated in the motion.

Gregory Brown: Just a clarification, I think. It's already in the law. It's just we're adding it to the... we're transcribing it from the law into the bylaws so it's clear. So, there's no change. It's simply a clarification. Okay. Any other? Okay. All in favor of the bylaws?

Group: Aye.

Josh Morse: All approved. Thank you.

Gregory Brown: Any opposed? It's passed. Thank you all for your participation today.