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**Health Technology Clinical Committee Public Meeting**  
March 20, 2015

Craig Blackmore: So, I'm going to call the meeting to order. This is the Health Technology Clinical Committee meeting, and it is a public meeting. So, all are welcome to attend and hear what we have to say. I'm Craig Blackmore. I'm the chair of the committee, and I will ask . . . we are being recorded, as it's a public meeting. So, I will ask everyone who is speaking to the committee, as well as the committee members themselves, to use the microphones and identify yourselves when you're speaking so that we can know, on the record, who said what. The first item on the agenda is program updates, Josh.

Josh Morse: Thank you, Craig. My name is Josh Morse. I'm the program director for the Health Technology Assessment program, and I'll give a brief overview of today's meeting and the program itself.

So, the topic of today is testosterone testing. The next meeting of this committee is May 15<sup>th</sup>. The top scheduled for that meeting are bariatric surgery and imaging for rhinosinusitis. We will have an update later today on the reports on those topics and where they are in the preparation.

So, a little background on the Health Technology Assessment program. This program is located within the Health Care Authority. It was created through legislation in 2006, and it's designed to use evidence reports and a panel of clinicians to make coverage decisions for selected medical procedures and tests based on the evidence of their safety, efficacy/effectiveness, and cost-effectiveness.

So, multiple stage agencies participate to identify the topics and implement the decisions that come from this program, and they include the Uniform Medical Plan and Medicaid, which are managed within the Health Care Authority and the Worker's Compensation Program within the Department of Labor and Industries and the Department of Corrections. The agencies implement the determinations of the program within their existing statutory framework.

So, the purpose of the Health Technology Assessment program is to ensure that medical treatments, devices, and services that are reviewed that are paid for with state dollars are safe and demonstrated to work. We provide a resource

for state agencies that purchase healthcare. We develop these scientific evidence-based reports on the medical devices and procedures that are selected, and we facilitate and provide staff support to the work of this independent committee.

Ultimately, our objectives are better health. We strive for transparency and to minimize bias in our processes, consistency in our processes, to be flexible, and learning from what we do and systematic in that.

A very high-level overview of the process: The director of the Health Care Authority has the authority to select technologies. Nominations are reviewed, public comment is sought, and ultimately the director makes selection of topics for review. Six to eight topics are typically reviewed in a given year. We work with contracted evidence-based review centers to develop the reports. We publish the deliverables that lead to those reports along the way, including draft key questions, the draft reports, and ultimately the final products including the report and the determinations. We bring that information to this committee in public meeting and ultimately the determinations from the committee are implemented by the agencies.

The primary questions that drive these reviews are: Is the technology safe? Is it effective? Does it provide value?

Again, we value transparency. We publish the deliverables along the way towards these coverage determinations. We strive to identify the best evidence and evaluate that evidence in formal, systematic processes for the reviews and this committee of practicing clinicians makes decisions. They are an independent committee. Their primary decision focus is to be based on the evidence that's available.

So, the clinical committee decisions must give greatest weight to the evidence that's most valid and reliable. Objective factors for evidence consideration might include the nature and sources of the evidence, the empirical characteristics of the studies that are included and the consistency of the outcomes across comparable studies. Additional factors might include how recent that information became available, how relevant it is to state populations or the outcomes that are in question and the bias that might be within those research studies.

So, for 2015, these are the topics that are on our project plan. Last month, or pardon me, the last meeting in January, functional neuroimaging and appropriate imaging for breast cancer screening were the topics. Today's topic, again, is testosterone testing. May is imaging for rhinosinusitis and bariatric surgery, and we are working on topics for November right now that include tympanostomy tubes and the lumbar fusion re-review.

There are multiple ways to participate with the Health Technology Assessment program. We maintain a website where all of our information is published. We

maintain a list, an email list, where individuals may sign up and receive emails from the program on various subjects. Anybody may comment on proposed topics, key questions, draft and final reports, as well as draft decisions. Anyone is welcome to attend these public meetings, and all meeting materials are posted in advance on our website. Anybody is welcome to present comments to the committee today or in future meetings and anyone again is welcome to nominate topics for review in the program.

So, reminders, Dr. Blackmore reminded us that this meeting is being recorded. We develop a transcript from each meeting which is ultimately published with the meeting materials on the website. When participating in discussions, please, if you're using a microphone, or you should be using a microphone, please state your name and use the microphone and if you wish to provide public comment today, we do have signup materials out in the hallway. We ask people who sign up in advance to complete a conflict of interest disclosure form, and if you are providing comment today, please state any conflicts you may have. Thank you.

- Craig Blackmore: Thank you, Josh. So, the first item on the agenda pertains to business from the previous meeting, from our January meeting and the first part of that is review and approval of the minutes. So, the minutes for that meeting have been distributed and published and are available to the committee members in their packets. I would entertain a motion to approve the minutes or any concerns or discussion.
- Chris Standaert: Motion to approve.
- Craig Blackmore: Is there a second?
- Michelle Simon: Second.
- Craig Blackmore: Alright. If I could just have a show of hands those who approve the minutes from the prior meeting.
- Josh Morse: It looks like eight approve, or seven approve. Are you abstaining?
- Seth Schwartz: Yeah. I wasn't there.
- Craig Blackmore: OK. Alright, the second item then is to go to the two decisions, draft decisions that were made at that previous meeting and formalize those. At this point, we have had . . . there has been an opportunity for public comment based on those draft decisions and we have received a number of comments. First, we will discuss the functional neuroimaging for primary degenerative dementia and mild cognitive impairment, and there was one comment that we received regarding clarity, not about the decision itself so much as about the scope of the decision and so in the version of the draft findings and decision that's in your packet, we've added text after the number and coverage topic that clarifies that beta amyloid PET imaging is outside of the scope of the coverage decision. That

was not in our scope. It was not part of the evidence review. It's not something we discussed. So, it's not that we are making a finding one way or the other. It's simply not a part of the decision. So, that is one amendment to the draft findings and decision. Are there any other concerns or . . . otherwise, I would entertain a motion to approve this amended draft findings and decision.

Michelle Simon: Motion to approve.

Marie Brown: Second.

Craig Blackmore: Any discussion? Alright. If I could have a show of hands for approve.

Josh Morse: Seven approve.

Craig Blackmore: And abstain? Alright, uh, second is appropriate imaging for breast cancer screening in special populations, and again, a number of public comments were received and one point that's worth clarifying, I think based on the comments we received is that it is part of the Technology Assessment program that if new evidence becomes available that we would consider re-reviewing the topic. That was a concern that was raised in the public comments, and that's . . . that is very much a part of the process that doesn't reflect directly on this decision, but it looks towards the future. Any other comments or concerns or discussion around the draft findings and decision? And if not, I would entertain a motion to approve.

Kevin Walsh: Motion to approve.

Joann Elmore: Second.

Craig Blackmore: Any further discussion? Alright. If I could have a show of hands for approval.

Josh Morse: Seven approve.

Craig Blackmore: And one abstain. Alright. That moves us to the topic of hand for this meeting around testosterone testing and first presentation is the Washington State Agency presentation.

Steve Hammond: Good morning. My name is Steven Hammond. I'm the chief medical officer for the Department of Corrections. Today, we'll be talking about testosterone testing in adult men. Testicular function is normally regulated by the hypo, hypothalamo-pituitary-testicular axis, or HPT axis. Measurement of serum testosterone levels in men has been used for many years in clinical evaluation of HPT function and numerous pathological conditions that disrupt HPT function result in hypogonadism and androgen deficiency.

This is a diagram of the feedback loop of regulation of testicular function. We see here are the testes represented. Their function is stimulated by pituitary gonadotropin secretion luteinizing hormone and follicle-stimulating hormone,

which in turn is stimulated by hypothalamic release of gonadotropin releasing hormone. We see in the diagram there are two major functions of the testes, one to reduce sperm and that is not the focus of today's topic. The other major function is production and secretion of testosterone, which we see has a negative feedback effect at the level of the pituitary and the hypothalamus.

So, hypogonadism has been recognized clinically for a millennia and evaluation of classic hypo gonadal state has been part of clinical medicine for decades. Hypogonadism is classified as being primary, or being primarily due to a lesion of the testes, sometimes related to congenital abnormalities or destructive processes, orchitis/trauma. Examples of secondary hypogonadism include hypopituitarism or mass effects of tumors of the pituitary or suprasellar region, and in these classic hypogonadal syndromes, testosterone levels are typically quite low anywhere from one-half to one-tenth to the lower limit of normal, very clearcut abnormality on lab testing. In these syndromes that are marked by severe androgen deficiency, testosterone replacement therapy results in widely-recognized benefits, including improvements in libido and sexual function, improvements in . . . or maintenance of lean body mass, including muscle and bone.

Now, in recent years, a fair amount of research has been focused on the concept of late onset hypogonadism. At this point, a hypothetical condition characterized by low testosterone levels associated with aging, also associated with decreased libido and sexual function and physical frailty. Late onset of gonadism has not been shown to have a clear pathogenesis. It simply seems to be a correlate of aging. We also know that lower testosterone levels are associated with numerous chronic illnesses, which also are associated with aging but at this point, it's merely an association and in the setting of late onset hypogonadism, the benefits of testosterone therapy are less well established, and in addition, research in treating late onset hypogonadism with testosterone has yielded significant signals of risk, particularly for increased cardiovascular morbidity.

So, for years, treatment of hypogonadism of the androgen deficiency has been accomplished with intramuscular injections of a depo form of testosterone. The injections are typically administered every one to four weeks; however, in the past 15 years or so, new preparations have been developed for transdermal administration, in particular gel preparations. The price of the newer gel preparations is much higher than the injectable form, anywhere from 10 to 20 or higher times the cost of the injectable form. Since these new gel preparations have been marketed, mass media has been used to publicize a condition termed 'low T' standing for low testosterone. Again, a suggested health condition characterized by lower testosterone levels, particularly in older men. Health benefits of testosterone treatment for age related low T have not been demonstrated. Testosterone treatment for low T is not FDA approved, and as such, pharmaceutical companies are not allowed to claim benefits . . . health benefits of such treatment; however, pharmaceutical companies are allowed to support disease awareness campaigns about low T that include

encouraging men to discuss this with their physicians and have their testosterone level checked.

So, in this setting, there has been a marked increase in testosterone testing and prescription of testosterone products in the USA and, to a lesser extent in the United Kingdom. These are data from the Layton Study, which is covered in the evidence report on testosterone testing in the U.S. and the U.K. from 2000 to 2011 and we see a marked upward trend, less so in the U.K. but also there. We also see markedly higher rates of utilization in the U.S. compared to the U.K., and then for . . . on the right hand panel, initiation of testosterone treatment has similarly risen sharply in the USA and much less so in the U.K.

So, questions arise: Is low-T a real clinical syndrome, a pathological entity, or is it a correlate of normal aging? We do know from cross-sectional studies, that serum testosterone levels are lower in older men. What is considered normal by clinical laboratories is related to the statistical distribution of testosterone levels in young men and if there is a predictable decline in testosterone levels in older populations, it's also predictable that increasing proportions of those populations would be classed as having abnormally low testosterone levels using standard laboratory reference ranges and this could result in uncritical diagnoses of hypogonadism, simply on the basis of that laboratory result. The most commonly used lab test is the total testosterone level, which is a rather imprecise test being subject not only to testosterone secretion, but to levels of sex hormone binding globulin, which are affected by many other factors resulting in a great deal of inter-individual variability of sex hormone binding globulin levels and actually intra-individual depending on such factors as fat mass or drug use. The age-related decline in serum testosterone is more pronounced for free testosterone levels than for total testosterone levels. Free testosterone levels are measures of the unbound fraction of testosterone in the serum, which is considered to be the biologically active fraction. Another issue with testosterone testing is that norms are typically developed around morning testosterone levels, typically taken about 8:00 a.m. or before 10:00 a.m., which is the highest . . . the time during the day when testosterone levels are higher, such that if random levels are taken later in the day, they will tend to be lower. Also, we should emphasize that low-T is not an accepted medical diagnosis.

So, this is a chart of distribution of total testosterone levels by age. This is taken by a study published by Bhasin. It is drawn from the Framingham Heart Study sample, a community sample of men not selected for any sort of health conditions. This study is based on very careful analytic . . . lab analytic techniques and, sorry, the font is kind of small but pretty substantial numbers, especially in the decade from the '30s through the '70s. And I apologize, I'm straining to see the numbers themselves, but we see that the lower limit of normal defined by the 2.5 percentile is 295 for men in their 20s, and the 295 nanograms per deciliter, which is pretty close to what is considered to be the lower limit of normal in most laboratory reference ranges. You see numbers around 290 or 300 cited, and a lot of action occurs in this range in terms of putative diagnoses of hypogonadism, and you can see that in subsequent

decades the 2.5 percentile level progressively lowers, such that an increasing proportion of men in these age ranges would be classified as having low testosterone levels based on standard laboratory reference ranges. The effect of age is much more pronounced looking at free testosterone levels, such that in later decades, the mean gets down to about what's the lower limit of normal for men in their 20s, and again, illustrating the point that if the reference range is used in and of itself to make a diagnosis that increasing numbers of older men would be considered to be hypogonadal.

So, what is the clinical significance of lower testosterone levels in older men and I would argue that without other clear clinical correlates of known hypogonadal syndromes, that it is unclear what the clinical significance of lower testosterone levels in older men are. Also, it may be appropriate, given the known decline in testosterone levels for age to have age-adjusted reference ranges in clinical lab reporting. Even late onset hypogonadism is not well established as a clinical diagnosis. There are no ICD-9 or ICD-10 diagnostic codes associated with late onset hypogonadism, and given the growing concerns about safety of testosterone treatment in older men, caution is warranted in making the diagnosis of hypogonadism or treating with testosterone replacement therapy.

So, I want to go through a few studies that give evidence of the risks of testosterone treatment in older men. Most of these studies are not covered in the evidence report, which was not really focused on testosterone treatment but because that is so closely linked to testosterone testing, it's pertinent to look at these data. The first study was a randomized controlled trial of testosterone replacement therapy in men older than 65 with mobility limitations. This was a well conducted RCT that was terminated early because of increased frequency of cardiovascular adverse events in the group treated with testosterone. The number of patients in the treatment and control group were not all that large. It was around 225. You have a copy of that article, I believe, available. The committee does for reference, and the trial was . . . the trial included testosterone replacement therapy or treatment for six months, although in some of the patients the treatment did not last for a full six months because of the early termination of the trial.

It was also noted that the group that was treated with testosterone had higher hematocrit and thromboxane levels and decreased HDL cholesterol levels, all of which have been associated with increased incidence of cardiovascular adverse events. Another study, which was reviewed in the evidence report was a retrospective cohort study of 8700 U.S. Veterans with low testosterone levels and among those treated the hazard ratio for all-cause mortality or hospitalization for cardiovascular events was higher.

Yet another study, this one being a retrospective cohort study of 55,000 men in a large healthcare database showed increased incidence of MI, myocardial infarction, within 90 days after testosterone replacement treatment was prescribed. So, these, anyway, showed the odds ratio for myocardial infarction was elevated in the group that was treated with testosterone and the effect was

greater in older men but was also seen in men under the age of 65 with a history of heart disease. So, one thing to take note of in this and the RCT I described earlier is, these effects don't take a long time to develop in this study within 90 days and the previous study within a six-month period of treatment. Also in this study, interestingly, they looked at patients who had been treated with sildenafil or tadalafil, and there was no increase in MI in those patients.

And then finally, I'd like to review a systematic review and meta-analysis that, again, was not included in the evidence report but I think it's pertinent. This was a study of 27 placebo-controlled RCTs of testosterone replacement treatment that lasted greater . . . 12 weeks or more and that reported cardiovascular events. The trials in the literature are not consistent in reporting cardiovascular adverse events but these studies included 2900 subjects, mostly middle-aged or older, and looking at all of the studies together, the odds ratio for all cardiovascular events was greater than 1 and for serious cardiovascular events was also greater than 1. Further subanalysis looking at the published studies that were pharmacy industry funded versus those that were not, 13 pharmacy industry funded studies showed an odds ratio that was not increased for testosterone replacement therapy but looking at the 14 studies that were not funded by the pharmaceutical industry, there was a higher odds ratio of 2.06 for cardiovascular events. The Funnel plot analysis suggested publication bias with there being fewer reported results of trials with increased cardiovascular events, an adjustment that . . . a trim and fill adjustment for publication bias raised the odds ratio even higher, and the authors also noted that previous smaller meta-analyses of testosterone replacement therapy in older men, while they did not show statistically significant increases in cardiovascular events, did show trends in that direction.

These findings have raised concerns, concerns that were voiced at the Food and Drug Administration to the extent that an advisory panel was convened in September of last year to address these concerns and I'm just going to quote a description of that advisory panel's conclusion that was published in an article in JAMA in February of this year. There was overwhelming support that the use of testosterone replacement therapy should exclude men with age-related testosterone decline. The panel voted 20 to 1 in favor of revising the current indication by limiting testosterone replacement treatment to those with classic hypogonadism and including in the label the potential for cardiovascular risk and a statement that both the safety and efficacy of testosterone replacement treatment in age-related hypogonadism had not been established and at the time I put this slide set together on March 1<sup>st</sup>, at that time the FDA had not added a warning about increased cardiovascular risk associated with testosterone replacement therapy but, as it turned out, on the day that the slides were submitted on March 3<sup>rd</sup>, the FDA did issue a warning that was essentially . . . voiced the concerns that are on this slide.

So, I apologize for the small font, again, but this will at least remind me of some points that I want to comment on regarding agency utilization of testosterone testing. We only have data from the Public Employees Benefits Board database.

We were not able to get the data from the Medicaid program in time for this presentation and will not show the L&I data because there has been very little testosterone testing done as part of Workman's Compensation programs. But for the state employees, we see that there is really a modest amount spent on testosterone testing per year in the range of 250 or \$300,000.00. There's an upward trend. We see that there's a significant amount of testing done in women but more in men, such that 3 to 4% of the public employees covered population of men had their testosterone levels checked each year. We also see a rising trend, again, hard to see here with the small font. I want to also point out that the majority of the tests performed are the total testosterone but a fair amount of the free testosterone tests are also performed. I also wanted to show the data on testosterone pharmaceutical prescribing and utilization, and we see that the costs there are significantly higher, two or more fold higher than for the testing itself.

So, this is kind of a busy, complicated slide, but I want to focus your attention on this panel of showing test utilization in men. The upper panel is in women, which we'll just ignore for now, but we see that, we see a couple of things. We see a steady trend upward and utilization of testosterone testing and we see that the highest utilization is in the, I can't read that, but I think it's around 55 to 65 range, or 50 to 65. Sorry, I can't read the numbers, but anyway, the middle-aged range with a significant amount in the 35 to 50 range and also in the 65 and older. So, that's where most of the testing is being done, and then in the right hand panel of testosterone pharmaceutical utilization we see similar trends rising and with the predominant use in middle-aged and older men.

So, when this topic was first considered without having the data, we had high degrees of concern for safety, efficacy and cost. The cost figures that might be debatable and might be more in the medium range, but really the main concerns are around safety and efficacy in this case.

And so the concerns of the agency medical directors are summarized on this slide, and I'll just read, "Testosterone testing without additional clinical findings of hypogonadism is highly vulnerable to false-positive findings of hypogonadism, especially in older men, especially when reference range is appropriate to men in their 20s or used for older men. Such testing exposes patients to risk of any inappropriate diagnosis of 'hypogonadism' and prescribing of testosterone therapy with attendant risks, particularly of adverse cardiovascular events. Efficacy of testosterone treatment in the absence of clear signs and symptoms of hypogonadism is unproven. Inappropriate testosterone testing is wasteful in itself and also likely leads to wasteful and risky prescribing."

Current agency coverage policy for Medicaid and the public employees plans is covered without restrictions and in L&I and Department of Corrections prior authorization is required for testosterone testing, and so these are the agency recommendations that testosterone testing be covered with conditions, be covered in the setting of clinical findings well correlated with definable HPT axis

pathology, such as objective physical examination or laboratory imaging evidence of pituitary or primary gonadal dysfunction, osteoporosis, sexual dysfunction. Some examples would be finding gynecomastia or testicular atrophy on physical exam, laboratory findings of hyperprolactinemia, or evidence of hypopituitarism, imaging evidence of a pituitary macroadenoma, clinical osteoporosis or sexual dysfunction. Again, the agencies can further delineate and detail what the coverage conditions would be, and also another condition would be that a proper fasting blood draw be used for the initial assessment of possible hypogonadism and that concludes the presentation.

Craig Blackmore: Questions for Dr. Hammond?

Joann Elmore: Is treatment with testosterone covered with any conditions currently?

Steve Hammond: I don't think there are restrictions on it. I think it's simply available on the preferred drug list for Medicaid and is not restricted for the public employees.

Joann Elmore: I ask, even though we are only going to be ruling on the lab testing, but I obviously see the cascade after a test is done.

Steve Hammond: Yes, and I think that may be addressed in the not-too-distant future.

Kevin Walsh: Steve, why didn't you list diabetes in the conditions for testing?

Steve Hammond: I'm not aware of very strong evidence that diabetes causes hypogonadism. I know that it's associated with lower testosterone levels and, you know, maybe we can get the input from our clinical expert on that but, uh, I would be hesitant to include diabetes as a condition for testing for two reasons. One is that, as I say, there's not a clearly-established relationship between diabetes and hypogonadism, and our diabetic population is one that's at very high risk for cardiovascular disease, and I think we should be very cautious about diagnosing and treating 'hypogonadism' in our diabetic population simply based on lower testosterone levels.

Craig Blackmore: Let's, I mean, we can circle back to that after we've heard the full evidence report, etc.

Richard Phillips: Hi, Steve. I had a question. On the state's data, as I read through it. It looked like 34% or a little over that, of the testing for testosterone was done on women. Now, I know that we're only discussing men here, but it, it bothers me that women are getting . . . are not even being brought into this equation number one, and I'm not sure I understand that. Are there conditions that . . . are the reasons to test women and men alike for testosterone for reasons that we're not even looking at? I mean, I would have not thought there would be much testing at all for women. So, I'm having a little trouble getting my hands around the utilization issue.

- Steve Hammond: Sure. No, the reason for testing testosterone in women are much different than for men, and they relate to things such as, well, mainly around ovarian dysfunction and, you know, menstrual abnormalities, infertility, hirsutism, just a different set of clinical conditions.
- Craig Blackmore: So, our decision won't apply to women.
- Joann Elmore: OK, that was going to be my question.
- Steve Hammond: Right.
- Craig Blackmore: Specifically scoped only for adult men.
- Joann Elmore: Adult men?
- Craig Blackmore: So . . .
- Joann Elmore: OK.
- Craig Blackmore: . . . we don't have to go down that.
- Richard Phillips: Right, and there's not those . . . the real question I guess I had was, the conditions for which women are tested are not conditions that men are being tested for, that we're not really concentrating on in this review.
- Steve Hammond: Absolutely. This is totally focused on testing in adult men. Low testosterone levels is not nearly as prevalent a clinical concern in women, as it is in men. Usually the issue in women is higher than normal testosterone levels, but . . .
- Richard Phillips: Thank you.
- Steve Hammond: . . . sure.
- Chris Standaert: So, this is sort of random. What . . . can . . . when reporting a laboratory value, so labs are reporting values, but they're not doing it by age-related norms. So, why would . . . it doesn't make any sense to me on why the state would accept that and why somebody would want to . . . it doesn't make any sense. So, why . . . can the state actually just require that things be given age-related norms, because they exist? My second part of that is the . . . like Dr. Elmore said, we're sort of indirectly trying to get at treatment of low-T or whatever, but I suspect there's no requirement that somebody have a documented low testosterone level to be given a prescription for testosterone.
- Steve Hammond: Well, that's true. A surprisingly high proportion of patients for whom testosterone is prescribed haven't had testosterone testing, at least that can be discovered in administrative databases. I'm sorry, what was the first part of your question?

- Chris Standaert: Why aren't labs required to report age-related norms when such norms exist?
- Steve Hammond: OK, and that's a great question that I asked myself and I think I would ask our clinical expert to comment on that. I understand that there is effort underway through the Centers for Disease Control to actually improve standards for testing and, I believe, to also look at developing age-related reference ranges, but Dr. Matsumoto, I think, can comment with greater authority.
- Craig Blackmore: So, let me take this opportunity to introduce Dr. Matsumoto. We always have a clinical expert at these meetings because the committee members themselves may not be experts in the exact area of clinical content that is under discussion. So, the clinical expert, Dr. Matsumoto, thank you for coming. Your task will be to provide us with support and information when we come across an issue that requires clinical expertise. So, we will call on you from time to time and thank you for being willing to help us.
- Alvin Matsumoto: I don't know the process here. Do you want me to wait until everything . . .
- Craig Blackmore: Whenever something comes up, we'd like you to jump in. I do need you to speak to the microphone and, which, is that on?
- Alvin Matsumoto: Can you hear me?
- Craig Blackmore: I'm not sure it's . . .
- Alvin Matsumoto: Can you hear me now?
- Craig Blackmore: Yes, thank you.
- Alvin Matsumoto: Let me start from the beginning. I think we're all under the impression that testosterone levels measured are uniformly measured the same way in different labs, and as you all know, that's not true, but even . . . for testosterone it's even worse. The actual variability from assay to assay is extreme, and extreme meaning there have been several publications looking at testosterone measurements, total testosterone measurements done by different assays for the same sample. So, the same sample, obviously, should read the same, or similar, in all assays and so the variability in the actual value reported for hypogonadal men is eight-fold difference in the actual level. For normal men, it's about three and a half or two and a half fold difference. So, yes, normals are a little bit closer, but, you know, are you going to accept a two-fold difference in the actual value on the same sample. So, accept that there's a big problem with assay and standardization, part of the CDC program that was alluded to by Dr. Hammond is to actually standardize the assays and as an aside, I think the way we got into this situation is that the quality control, or the way the laboratory is actually allowed to continue doing the assay, is based on the quality and the quality is based on reproducibility of the same number for the same assay. So, a set of labs that do the same assay, if they get the same number or similar to a particular standard amongst the different laboratories, then they pass the

quality control. Then, it's a quality assay. It hadn't been based on accuracy of the test, OK, which is really what the clinician needs. That's what we need is an accurate test. So, the CDC accuracy based quality control program was the first to actually put into place an accuracy-based quality control program. Subsequently, the College of American Pathologists have adopted a sort of 'mini-version' of that. I think that's the first step. You have to have an accurate test before you can make a diagnosis accurately and so I think that goes a long way. Getting to the reference range, that's step two. The CDC program is trying to standardize not only the assay and the accuracy of it, but to try to standardize the reference range, or the normal range of testosterone and trying to come up with age-adjusted normals. Unfortunately, the way reference ranges are established in different laboratories also differs. So, you would think you would use a standard set of community-based normal men without a whole lot of comorbidities to actually base this on. In fact, every lab has a different way of doing it. I just know for a fact that certain labs in this community use blood bank samples, which you could argue are they really normal, and they don't age adjust. Some assays that are used in this community utilize what's in the kit that's used to actually . . . they don't actually do their own reference range. They just utilize whatever the kit says is normal. They just go ahead and adopt that. So, for a clinician, you're kind of confused and the variability in the lower end of the normal range, I think, can vary quite a lot. At the University of Washington, I have had a, I had a problem with this compared to the VA where I do most of my clinical work is that the normal range for total testosterone, I believe, goes down to about 180 or something like that, 180 nanograms/deciliter, where most people's are, as mentioned, 280 to 300 nanograms/deciliter, and that's based on two things. I don't think it's an accurate test, and I also don't think the reference range was established by normal people. They were established with blood banks.

So, there are a lot of problems. And so one of the difficulties in regulating testing is that you're trying to regulate an inaccurate test that probably doesn't have a very good reference range, and I think what I saw here is that the assumption is that in fact more testing leads to more treatment. I think that's partially true, but the other problem with regulating the number . . . or regulating the testing is that in addition to the assay variability, there is a lot of biological variability. So, if you do a testosterone test that's low on an individual, and you find that it's low initially, let's say it's less than 300, and this actually has been published, the next time you measure that, let's say several weeks later, it could be normal, OK, and it could be normal about 30% of the time. So, the biological variability is such that the Endocrine Society guidelines basically call for measuring at least two tests before you diagnose somebody and maybe institute treatment, if it's appropriate given the risks and benefits of treatment.

So, I think by regulating the test, it's also conceivable that you actually might falsely diagnose individuals that had just happened to have a slightly low test at one point and have a normal if they had an opportunity to get a second test, and the final thing I guess I wanted to point out is that we all know that there is

a tremendous amount of obesity in the community, and obesity is one thing that lowers total testosterone level, but free testosterone level can be normal, and in a paper that we published just recently, in looking at the VA population, high comorbidity, high obesity rates, testosterone levels, total testosterone levels were low. So, you take that population, and I can't remember the percentage, but there was a substantial number of people that had low total testosterone levels. Then, you ask the question, how many of those actually had low free testosterone levels and, in fact, only about 40% had low free and 60% had normal free testosterone levels. So, if you would have based your diagnostic testing to confirm hypogonadism on a total testosterone, 60% of the time you would actually have a normal individual. So, it's a terribly complicated issue.

Coming back to the diabetes, and that's why I mentioned the obesity, is that type 2 diabetes is commonly, as you all know, associated with moderate, sometimes actually severe obesity but certainly associated with moderate obesity, and so it's very common to have low total testosterone in diabetes and obesity, but it's less common to have a low free testosterone. So, that's a long-winded question, but I needed to get in at least some of these issues before we get too far along. It's really the testing, I think, that is protective of treatment but also if you over test and misinterpret the test, that's the thing that leads to treatment, which is, from my standpoint, the thing that needs to be regulated is that, you know, there are people out there doing testing, even with a normal value, we'll start testosterone level because it isn't perceived as normal for that individual's age. The testosterone clinics out there are utilizing normals based on an absolute level unrelated to a reference range. It says less than 300 that means you're abnormal, or less than 350 you were 500 when you were 25 years old. You're now 55 years old. It should be higher than that. We can treat. So, it's the interpretation of what the value is that I think is the problem in testosterone testing.

Joann Elmore: I have a questions for Dr. Matsumoto. Within the next hour or so, at the end of this morning, we as a committee are tasked with making a vote on whether testosterone testing should be covered or not covered, or covered under certain conditions, and it's the specificity or perhaps I should say the lack of specificity of these other conditions that has me concerned. As you may have seen, the agency recommendation lists clinical settings in which they might . . . they are recommending we consider covering with conditions. They list here sexual dysfunction, osteoporosis, testicular atrophy. And so, my question for you, I guess is, what percentage of people with sexual dysfunction have a low-T versus a high-T? What percentage with osteoporosis have a low-T versus high-T? Does it even matter? Isn't this just part of general aging and I'm worried because of the lack of specificity of some of these subjective symptoms that are listed here under the possibility of cover with conditions.

Alvin Matsumoto: Well, that's the problem with the symptoms of androgen deficiency. There are no pathognomonic symptoms or signs or clinical manifestations, I guess, except one, that's individuals that have delayed sexual development, obviously, that

are eunuchoidal. That's, you know, a 30-year-old guy that looks 15. You don't almost need a testosterone level for that, but that aside, all the other things that are mentioned are at nonspecific. So, the answer to your question, sexual dysfunction is more common in a normal situation with a normal testosterone, but then are you going to preclude testing in individuals with severe, low libido, but has as sexual dysfunction, erectile dysfunction, has all the others. How do you make that, is it purely on the basis of percentage? Even though it's a low percentage, are you going to withhold testing and possibly treatment for a truly hypogonadal individual if you eliminate that particular symptom. Osteoporosis, I would say that one of the main contributors to bone loss, not the only thing. That's the other thing is that all of these symptoms have multiple potential etiologies, as you all know. As you get older, you get multiple comorbidities. Comorbidities add to the symptoms of an individual that might be consistent with androgen deficiency but might be related to other things, like comorbidities, medications to treat these comorbidities, so on and so forth. I think it's . . . and at the same time, these comorbidities can lower testosterone. So, it's a very complicated issue. If you ask me how many, what percentage, I can't give you the percent right off the top of my head, but it's also a fairly low percentage in the whole osteoporosis area, but if we deal with men with osteoporosis, true osteoporosis either by bone mineral density or by minimal trauma fracture, then you're talking about a substantial number of people will have low testosterone, and I would venture, I guess, maybe about 33%, about a third of those individuals will have low testosterone.

The problem, and that's the answer to your question, but I think it's also well worth pointing out that testosterone is not an approved drug to treat osteoporosis, and that's . . .

Joann Elmore: That was going to be my next question. So, we only want to approve testing . . .

Alvin Matsumoto: . . . yeah, but are you going to . . .

Joann Elmore: . . . if there's an approved treatment that would be mandated by that testing.

Alvin Matsumoto: But do you ignore the other symptoms? If somebody is truly hypogonadal, and they're osteoporotic, do you then not permit them to be treated because it's not an indication if they have low libido, if they have sexual dysfunction, if they have other manifestations of androgen deficiency. It becomes a pretty dicey situation. If somebody has symptoms maybe in addition to the osteoporosis, which is a sort of tagalong with the other symptom complex that he has, would you withhold treatment in that individual, and I wouldn't. Some people might be very strong about that, but, you know, the way I would approach it and the way I do approach it in clinic and run the osteoporosis clinic at the VA, is that I use approved osteoporosis drugs for the osteoporosis, but I do treat the hypogonadism if it's present. So, I think, you know, to actually prescribe something on the basis of known indications, I think, is difficult because there are also some people with hyperprolactinemia that are asymptomatic, OK? So, not everybody with high prolactins will have a low testosterone. In fact, the

majority of folks with high prolactins will be mildly elevated and have normal testosterone.

So, if you want to do the majority rules approach, then you would say that shouldn't be covered either, or the testing shouldn't be covered in that group either because the vast majority of those folks don't have low testosterone. So, again, it's a difficult regulatory issue that you guys deal with. As a clinician, I'd like to think that I use good judgment in actually doing this, but what I'm afraid happens in a large percentage of the population is that they don't . . . physicians and practitioners don't consider these things, and that's a problem.

Craig Blackmore: So, we're . . . this is a very important discussion, and I'm sure we're going to have to get into it in even more detail, but we're also getting a little bit ahead of ourselves. So, I want to break off here, and we're going to go back to our agenda and the next item is for the public comment period. So, I will ask, I believe we didn't have anybody sign up in advance, but is there anybody who is here with us today in the audience who would like to address the committee. This is your opportunity to do so. I assume nobody signed up outside. Is that right, Christine? We haven't had any?

Christine Masters: That is correct.

Craig Blackmore: OK. So, I'm not seeing any show of hands. I'll ask again in a few minutes, and then we have the ability for people to call in. So, we're going to unmute the phones here, and we'll see if there's anybody who has called in who wishes to address the committee. So, the phones are unmuted. Is there anyone who has called in who wishes to address the committee? OK, not hearing anyone we're going to mute the phones again. Alright, and there is nobody else who wishes to address, then I'm going to bring the public comment period to a close, and we'll move on to the next item, which is the evidence report.

Teresa Rogstad: I don't think I've ever presented the evidence report after such a great discussion. So, I feel like you're well primed for this presentation. My name is Teresa Rogstad. I go by Teri. I work for Hayes, Incorporated, and we prepared the evidence report for today's meeting.

OK, I'll start today's presentation with a review of the policy context and some background information, much of which has already been very clearly stated, then I'll describe the scope of the report and how we conducted our assessment. The findings section of this presentation is going to be an attempt to draw some inferences based on indirect evidence because the way the questions were formulated, we did not find any evidence that directly answered those questions and I'll explain that in more detail later on.

Then, to summarize, I'm going to try to pull together the indirect evidence that was available, practice guideline recommendations, and payer policies where available. Hopefully, that will help organize the policy discussion a little bit and then I'll conclude with some final comments.

You've already heard a presentation of much of the information on this slide. There are concerns because the diagnostic criteria for hypogonadism, especially age-related hypogonadism, are not very precise. There is concern about the benefits of treatment unless androgen deficiency is extreme, and concerns about the harms of treatment in older populations. Dr. Hammond referred to this Layton study. Something that was particularly concerning in those findings is that the incidence of new testing, that is a first time test, increased dramatically over that decade but the prevalence of abnormally-low testosterone levels remained constant. We have no national policy that's relevant, other than the FDA approval. The FDA approves testosterone replacement therapy for primary and secondary hypogonadism, and the way they define that is similar to what some authors call organic etiologies of hypogonadism. So, a clear pathology affecting either the testes or the pituitary and the testes. The exact language of the FDA approved indication is in the evidence report. It starts at the bottom of page nine. As you also heard, in 2014, the FDA expressed concern about the safety of testosterone products and announced a decision to reassess its labeling requirements. That decision, as Dr. Hammond stated, did come out a couple of weeks ago, and I'll return to that later.

The rationale for this report has to do within several areas of ambiguity and given those ambiguities what would be ideal would be clinical utility studies. Clinical utility studies are studies designed to measure the direct impact on health outcomes from the use of a test or a particular testing strategy.

I'll go really quickly through the background information. The controversy, of course, centers around age-related hypogonadism, and to make that diagnosis it's necessary not only to demonstrate low serum testosterone levels but also the presence of symptoms and signs that are characteristic of hypogonadism. The prevalence of age-related hypogonadism ranges from about 2-6%. This is based on large population studies in unselected individuals who are over the age of 40, and if you compare those numbers with the numbers at the top of the slide, you can see that the prevalence of abnormally-low testosterone is quite a bit higher. So, low levels of serum testosterone do not necessarily result in symptoms. As has been stated, the test results are compared with reference ranges for healthy young men in their 20s and that's what defines normal. The typical cutoff values for low versus normal are given there at the bottom of the slide. This is a little bit analogous, I think, to the way bone mineral density is assessed. That also is in comparison with young, healthy adults.

As I said, a diagnosis of hypogonadism relies not only on test results but also on the presence of characteristic signs and symptoms. These lists were put together by the Endocrine Society and they appear in the 2010 guidelines on testosterone therapy. There are two buckets. The more specific or classic symptoms are listed on the left-hand side, and less specific symptoms are on the right-hand side. These aren't evidence based lists, but they do reflect a consensus process and the clinical experience of the guideline panelists.

So, given the discrepancy between the prevalence of low testosterone and the prevalence of symptoms that would allow a diagnosis of hypogonadism, it's reasonable to ask whether there's any systematically collected evidence showing an association between low levels and those symptoms. We did find two population studies showing a statistically-significant association between symptoms of sexual dysfunction and low levels of testosterone. In the larger of those two studies, odds ratios ranging from 1.64 to 2.24 were calculated and I'll be returning to that study later on.

Other observational studies did not present any conclusive evidence regarding a statistical association between serum levels of testosterone and less specific signs and symptoms, such as overall health status, physical performance or psychological symptoms. To put all of that into some clinical context, I've listed on the right hand side of the slide relevant recommendations from the Endocrine Society. Their guidelines advise clinicians to test individuals for low testosterone if they have some of these more specific symptoms and that would include symptoms of sexual dysfunction. The recommendation is to consider testing if men present with the less specific symptoms. The Endocrine Society characterizes its recommendations regarding testing as being weak recommendations based on very low quality evidence.

Another thing to think about with regard to the importance of serum testosterone is whether it can serve as a predictor or marker for poor health outcomes. So, in our background search, we found evidence suggesting a link between low levels of testosterone and a variety of health conditions, quite a number of chronic health conditions. The nature of this evidence ranged from simple prevalence data to meta-analyses that calculated pooled risk estimates. The Endocrine Society guidelines are consistent with that evidence. The guidelines recommend that testing be performed in men who have certain conditions even if they don't display the characteristic symptoms of hypogonadism. That would include pathology or radiation to the Sellar region where the pituitary is located, the use of certain medications that deplete testosterone levels, HIV-related weight loss, and signs of osteoporosis. For other chronic diseases, the Society recommends testing if there are also characteristic symptoms present. So, those conditions would be diabetes, end-stage renal disease, and moderate-to-severe COPD.

The preferred treatment for low testosterone, if fertility is not required, is pharmaceutical treatment. Best practice is to first address reversible conditions and if that does not take care of the symptoms or complaints, then testosterone therapy might be offered. The conditions, or the indications rather that are considered appropriate for offering testosterone therapy are to improve sexual function, to promote well-being, to correct the effects of HIV treatment, glucocorticoids and opioids and also to improve secondary sex characteristics. That item isn't listed on this slide, but it should. So, these are the indications that are considered appropriate by the professional groups. In our background search, we looked at meta-analyses and systematic reviews of the efficacy of

treatment and the areas where there seemed to be the most clearly positive evidence were for treating symptoms of sexual dysfunction, especially in men who also had low testosterone levels and for the improvement of diabetes related outcomes depending on which outcome measure you were looking at. There are safety concerns with the use of testosterone.

David McCulloch: Are you going to give us evidence on that?

Teresa Rogstad: I am. Yes, I am.

David McCulloch: I look forward to it.

Teresa Rogstad: Alright. I will also be giving evidence on these safety issues later in the presentation. The risk that's chiefly of concern, at least in the last year or so, has been cardiovascular risk, and as I said, the FDA reassessed its labeling because of these concerns.

We've already mentioned, or Dr. Matsumoto has already mentioned some of the technical issues involved with testing for low . . . testing serum levels of testosterone. There is quite a bit of intra-individual variation, variation across labs because they use different reference populations and don't necessarily control for comorbidities, and then variation within a lab, according to the commercial assay that's used. The precision of these tests is considered to be poor right around the lower limit of the reference ranges. So, there are some best practices that help compensate for those difficulties. One is to measure early in the day when levels are the highest. The other is to make sure the clinician has at least two measurements taken on different days before drawing a conclusion that levels are low. The quality control programs that are administered by the CDC and the College of American Pathologists are voluntary. They are not required for laboratory accreditation.

Some other considerations include clinical validity and monitoring. Clinical validity refers to the ability of a test to discriminate between individuals who do and do not have the condition of interest or to make valid and accurate predictions. In other words, a test has clinical validity if it enables good clinical decision making. So, the problem we have here is that normal is defined in terms of reference ranges for young individuals. We have no definitive age-specific cutoff points that serve as an indicator that an individual is at a health risk. So, for instance, a 60-year-old man with abnormally low levels of testosterone, we don't know how low those levels need to go before there's a concern about poor health outcomes. There is no definitive schedule for monitoring testosterone levels, either in treated or untreated men, but there is a general consensus that during therapy testing needs to be conducted periodically to assess the need for adjustments in dose.

The PICO statement for this report specific that we look at adult men and the intervention was described as the measurement of circulating testosterone.

The comparison of interest was the investigation and clinical management of symptoms or health problems without the use of testosterone testing.

So, the key questions that flowed from that PICO statement were: 1. Is there evidence that testosterone testing improves outcomes, and then some subpoints to that question. 2. What are the potential harms of testosterone testing? 3. What are the cost implications?

We would have accepted for key questions one and two any study that compared outcomes between a group that underwent testing and another group that did not undergo testing. For identifying optimal monitoring intervals, we were looking for longitudinal studies that tested different intervals in order to identify the optimal interval, and we would have accepted any study with cost implications or cost-effectiveness data, but we found no eligible studies. So, there was no direct evidence to answer these questions.

So, what we did mid-course in the project was to conduct what we called a post-hoc analysis. We looked back at the evidence that had been reviewed for the background for the report and we tried to identify subpopulations where testing appeared to have the greatest potential for clinical utility and the way we decided that was two-fold: 1.) We were looking for systematic reviews or large observational studies that demonstrated a statistically-significant association between serum testosterone and symptoms or health conditions or outcomes related to a particular disorder. That was important to establish some kind of clinical validity to the test. 2.) The second criterion was whether or not testosterone replacement therapy had been shown to be effective in addressing outcomes specific to that subpopulation. So, at the time of the draft report the two subpopulations that seemed most promising were men with type 2 diabetes or metabolic syndrome and men with sexual dysfunction. After the draft report was published, a second systematic review of testosterone therapy in men with diabetes was published and we brought that into the final version of the report.

So, I will be going through this evidence that is summarized on this slide in detail, but before I move on, since the methods here were kind of unusual, I thought I would pause and see if anyone wants to ask a question. OK.

Chris Standaert: I have a question.

Teresa Rogstad: Sure.

Chris Standaert: So, in your PICO, the way I'm reading this, it says in your initial search, you were trying to find people who were tested and then treated and compare them to studies where they . . . studies where they compared the people who were treated but not tested, right?

Teresa Rogstad: Right, or treated or untreated according to clinical decisions that didn't take into account test results.

- Chris Standaert: OK. It's just a little confusing to me, because we're looking at a diagnostic test, and you're looking at outcomes from treatment that result from that test, but the test may or may not be used to dictate treatment and we're not talking about sensitivity, specificity, all the things we think about in diagnostic testing which is obviously problematic. It's just a little odd to me that that's what you went looking for, because that's, that would seem to be . . . testing does the . . . does the testing influence treatment in a positive way, assuming that there's treatment for low testosterone, which is slightly different than should you do the test, you know what I mean? Does that make sense?
- Craig Blackmore: I think, is kind of like looking at breast cancer screening, for example. You either treat, I'm sorry, you either screen or don't screen and then you see what happens to the people in which you got those two . . . in those two arms. So, in this case, the arms would be we either test for testosterone or we don't. People are going to get some treatment. In the testing arm, it's going to be based in part on the treatment and in the non-testing arm, it's going to be based on whatever else and the idea is to pull the test out of the equation and, you know, seldom do we really have that sort of information though for any diagnostic test we would like to. So, it's, you know, that's sort of the reference standard for, does a test improve outcome? Well, you look and see. If you don't have that, you can look at sensitivity and specificity and try to infer benefit based on the test characteristics.
- Marie Brown: It seems similar to Vitamin D.
- Craig Blackmore: But you went for the (inaudible).
- Marie Brown: What we did (inaudible).
- Craig Blackmore: Well, it's similar to Vitamin D.
- Marie Brown . . . Vitamin D testing that we (inaudible).
- Craig Blackmore: But in this case we've got a whole other set of issues because we've also got, you know, a treatment for something that may not even need treatment.
- Teresa Rogstad: That's right. That's a general approach to assessing the clinical utility of any kind of diagnostic or prognostic test. You take a group of individuals who were tested and then treated according to those test results and you compare them with a group of people that were treated or not treated according to other factors.
- Craig Blackmore: But, seldom does that evidence exist.
- Teresa Rogstad: Exactly. It does sometimes exist. In the osteoporosis topic that we looked at in November, there were a handful of studies that compared groups that were

screened with other groups that didn't undergo bone mineral density testing until they had a fracture, for instance.

Chris Standaert: Yeah, because I'm not really thinking about this as a screening test, either. People are . . .

Teresa Rogstad: No. It's not. It's . . .

Chris Standaert . . . yeah. So, we're not looking at that way.

Marie Brown: Although medical exam, the V70 coding that we use in primary care was the third most common diagnosis given for why they did testosterone testing. So, it was a routine medical exam.

Chris Standaert: People are using it potentially as a screening test.

Marie Brown: Uh-huh.

Chris Standaert: But we're not really discussing that here. We're not addressing that.

Teresa Rogstad: Shall I move on? Oh, I should have covered this before I paused, I guess. After selecting those two subpopulations, we conducted a new literature search to see if newly published studies would alter the conclusions suggested by the systematic reviews and population studies that we had included in the background, and we reviewed the findings from those studies and did not believe that they would suggest a change in conclusions. Of course, after the draft report was posted, there was this additional systematic review of replacement therapy in men with diabetes and that did cause us to qualify our conclusions somewhat.

So, here is where I'll present data on those two subpopulations. The first one was men with type 2 diabetes or metabolic syndrome. There were two meta-analyses that looked at the relationship between testosterone levels and metabolic syndrome. Both of them demonstrated a significant association. One of those reviews calculated a pooled relative risk of 0.38, and what that means is that men with higher testosterone levels were 62% less likely to have metabolic syndrome and then a third meta-analysis demonstrated significant differences in testosterone levels between men with and without diabetes. The difference was especially great in younger men versus older and in men with higher body mass index.

Craig Blackmore: So, if I might interrupt. These are associations and from this we can't infer the direction.

Teresa Rogstad: That is, that is correct, and I should have made that point earlier. It can go either way. It's really unknown whether improving testosterone levels would improve these comorbidities or the other way around.

So, that's one piece of the picture for this subpopulation. Regarding treatment, efficacy, two systematic reviews have been published. The earlier one came to fairly positive conclusions. The other one calculated pooled estimates that favored testosterone therapy, but they were statistically nonsignificant. The two reviews are not entirely comparable because they looked at somewhat different outcome measures, and they had somewhat different study selection criteria. The baseline testosterone levels in the study participants were mostly low or in the low normal range. So, these individuals not only had diabetes, but they typically met the criteria for hypogonadism and at least in terms of low testosterone and in some of the studies the participants were required to exhibit sexual dysfunction as well. The results of both reviews should be taken with a big grain of salt because the studies did not control for confounding due to changes in antidiabetic medication during the study. So, given this lack of clarity about the effectiveness of treatment in this subpopulation, we didn't feel we could draw any kind of inference or state any implications for the effectiveness of testing. The next two slides give you some detail on those two systematic reviews of testosterone therapy. We can come back to these if that would be helpful in the discussion.

So, the other subpopulation that we looked at was men with sexual dysfunction. Two population studies demonstrated a statistical association. The larger one calculated odds ratios. Those odds ratios that you see there on the slide reflect the odds of the simultaneous presence of three specific symptoms comparing men with lower versus higher serum levels of testosterone and the reason there is more than one odds ratio is that the authors did calculations based on two different cutoff values for normal and also two different assumptions regarding whether total testosterone or total testosterone plus free testosterone had to be abnormally low.

Regarding treatment efficacy, a meta-analysis of a large number of RCTs computed large effect sizes showing that testosterone therapy does improve sexual symptoms. There were different calculations for different symptoms. The effect sizes were especially large in men who had baseline levels of testosterone that were low and also higher in men who had type 2 diabetes, as well as sexual dysfunction. The systematic review found no evidence that testosterone therapy was superior to or effective as an add-on treatment to conventional medication for erectile dysfunction.

So, given this set of evidence, we stated in the report that one could make a positive but a weak inference of the clinical utility of testing. This is based on indirect evidence and the quality of the studies that were included, we judged to be low to moderate based on assessment by the systematic review authors.

Key question 1B had to do with the minimal interval to assess a change in status. Again, there was no direct evidence. We did find one very small study that followed elderly men for five years and found that testosterone levels declined, but the symptoms that are often used to diagnose hypogonadism did not change much. The Endocrine Society recommends checking levels at three

to six months following the initiation of therapy. This is important to assure that normal values are being reached but also, and perhaps more importantly, to assure that serum levels don't go above the normal range and unnecessarily expose individuals to the adverse effects of treatment.

The harms of testing relate mainly to the potential harms of consequent treatment. The latest systematic review of the impact on prostate outcomes is still not conclusive. The relative risk suggests an elevated risk of about 40%, but as you can see from the confidence interval, that is a statistically-nonsignificant estimate. There is a clear elevation and risk of erythrocytosis. The only studies that looked at obstructive sleep apnea were small case series, and the findings were inconsistent.

For cardiovascular events, both the evidence that was actually included in the report and additional evidence, which I'll go through in subsequent slides, does not show a clear overall effect. It definitely raises the alarm and suggests the need for concern, but we don't know exactly which subpopulations are at risk. One study has suggested that treatment with testosterone replacement products reduces mortality, but to our knowledge, those findings have not been corroborated by other studies.

So, this slide gives some detail on the systematic review that we did include in the report that looked at cardiovascular risk. The pooled estimates suggest no effect at all, but the confidence intervals are quite wide and they include the possibility of substantial benefit as well as the possibility of substantial harm. Meta-aggression, according to . . . looking at subgroups according to age, frailty, baseline levels below a certain cutoff point and diabetes did not demonstrate any differential risk.

So, the systematic review that Dr. Hammond called to your attention was this Xu review. The reason that it didn't make it into the report was our pattern was to concentrate on the most recent comprehensive systematic reviews, but it is worth realizing that the two came to very different conclusions. The Xu review calculated a significant odds ratio of 1.54, and they found that risk was even greater in the subset of studies that had pharmaceutical funding. The two reviews searched different databases, and they had different search timeframes. So, they resulted in only a partially overlapping set of studies and it is difficult to tease out when you look at the Funnel plots, why exactly they came to such different estimates. It is important to realize that in both of the reviews, the only study that showed a statistically significant elevated risk for cardiovascular events was this Baseria study and according to the authors of the Corona review, the dose used in that Baseria study was a supraphysiological dose. Another thing that was a little bit unusual about that study is that they only enrolled elderly men with mobility problems. So, the average age in that study was about ten years greater than the age across other studies.

- Alvin Matsumoto: But I would counter that they isolated the study to people without significant medical comorbidities. So, they might have had mobility limitations, but they didn't have a lot of comorbidities.
- Teresa Rogstad: OK. Thank you.
- Craig Blackmore: So, I guess while we're . . . while we're on this slide, I'm very, well we were on that slide. This concept of pharma funding versus no pharma funding, which the Xu study drilled out, can you comment on . . . there's some differences in which of the trials were included in the two meta-analyses that you listed here. What is the relationship of pharma funding to the inclusion or non-inclusion of those RCTs. I'm thinking specifically the five RCTs not in the Xu review and the two RCTs not in the Corona. If there's a . . .
- Teresa Rogstad: I think I did look at that, but my notes are back at the table. So, maybe if we could . . .
- Craig Blackmore: Maybe at some point.
- Teresa Rogstad: . . . return to that, yeah. Sure.
- Craig Blackmore: Thank you.
- Teresa Rogstad: OK. RCTs, of course, never tell the whole story on adverse effects. So, these two population studies are important. We did include these in the report and these were the studies that initially prompted the FDA concern. They looked at different populations, different outcomes and had different followup intervals. The Vigan study showed a significant hazard ratio of 1.29 after adjusting for coronary artery disease. The Finkle study showed an elevated risk of myocardial infarction within just 90 days but only in men who were over the age of 65 or had a prior history of heart disease.
- This is some detail on that one study that suggested reduced mortality due to testosterone therapy. So, as I said before, the FDA has come back and announced its decision regarding labeling. I forgot to mention at the beginning of the presentation that there's a binder at the end of the . . . either end of the U-shaped table which some of you have discovered. It has hard copies of some of the key references. So, you might want to pass those around. Also, there are links in the reference list to abstracts and free access articles. But coming back to that FDA announcement, they are now requiring that labeling state the possibility of cardiovascular risk and make it clearer which indications have FDA approval. To further muddy the waters on safety issues, I learned this week that two papers were presented at the American College of Cardiology Scientific Sessions just this month that showed no impact on cardiovascular risks. I haven't looked at those studies. I've just read reports of their findings. One was a large observational study. The other was a meta-analysis. So, the evidence is a bit murky but definitely cause for concern. We found no direct evidence regarding costs or cost-effectiveness.

So, to wrap up, I am going to try to pull together the indirect evidence that we included in the background, not just the evidence that we looked at in detail but other evidence as well and put that side to side with guideline recommendations and payer policies where they are available.

These organizations did not have any relevant policies. So, all we have to go by are the FDA approval and policies from AETNA.

The next several slides were taken from table 10 in the report and the table in the report has more detail. What I've tried to do is organize things by groupings of indications. So, for primary hypogonadism, which refers to pathology at the testicular level, we didn't find any specific guideline recommendations or any evidence either but this is definitely an FDA approved indication and is not an area of controversy.

Secondary hypogonadism covers a wide range of conditions. According to the Endocrine Society, there are some conditions that should prompt testing even in the absence of characteristic symptoms of hypogonadism. Those would include pathology or radiation to the sellar region, certain medications, HIV related weight loss and osteoporosis. In general, this would be considered an FDA approved indication because the approval applies to secondary hypogonadism, but the FDA language doesn't call out these specific conditions like osteoporosis and HIV related weight loss. We did find some evidence relative to these indications, but it was incomplete, and especially weak with respect to the efficacy of testosterone therapy.

So, for other chronic conditions, the Endocrine Society suggests testing if characteristic signs and symptoms are also present. Those include diabetes, end-stage renal disease, and moderate to severe COPD, and the American Urological Association supports testing if there is evidence of infertility. Again, this might fall under the general FDA approval of secondary hypogonadism, but these specific conditions are not called out in the FDA language. I've already gone through the evidence for subpopulations with metabolic syndrome and type 2 diabetes. For kidney disease and COPD, we found very sparse evidence and non-cited in the sources that we used regarding infertility but that, again, is probably not a real controversial indication.

Sexual dysfunction . . . symptoms of sexual dysfunction alone might serve as the reason for testing and this would be supported by the Endocrine Society because those are considered symptoms that are relatively specific to hypogonadism. I've reviewed that evidence already, as well. And then for other symptoms, according to guideline recommendations, it might be appropriate to test depending on how specific those symptoms are. We did not find much evidence for anything other than sexual symptoms, and the Endocrine Society recommends against testing based on age alone. Also, acute or subacute illness, or an episode of decompensation during a chronic illness are considered contraindications to testing.

So, in conclusion, the only definitive statement that we felt our assessment allowed us to make is that there is no direct empirical evidence that testing for low testosterone in any subpopulation leads to better health outcomes. It's important to remember that the Endocrine Society characterizes the evidence behind its recommendations as low or very low. The concerns regarding analytic validity suggests that there are probably problems with clinical utility, and some caveats need to be stated for the two subpopulations that seemed to be the most promising for testing testosterone levels. The latest systematic review of therapy for improvement of type 2 diabetes outcomes showed uncertain benefit, and the Endocrine Society points out that the purpose of testing and treating in men who have diabetes is not to treat the diabetes but to treat the symptomatic hypogonadism. Regarding the other subpopulation of interest, we didn't find anything helpful in the literature regarding the clinical relevance of the gains that have been demonstrated in sexual function with the use of testosterone therapy, and there was insufficient evidence to conclude that testosterone products meaningfully enhance the effectiveness of conventional erectile dysfunction medications.

There are large evidence gaps. I won't take time to go through those, and then some limitations to the way this report was conducted that also need to be kept in mind. Thank you.

- Craig Blackmore: So, questions from the committee?
- Kevin Walsh: I have a question for the clinical expert. Can we pull up on table 4 in the study on page 39, please? In the study, in the report.
- Teresa Rogstad: You're talking about from the evidence report?
- Kevin Walsh: The evidence report. Dr. Matsumoto, do you have a copy of the evidence report?
- Alvin Matsumoto: Not with me.
- Kevin Walsh: So, this is, table 4 is looking at the prevalence of symptomatic androgen deficiency in general population studies.
- Alvin Matsumoto: Right.
- Kevin Walsh: One study is done in Europe. One is done in Massachusetts. I'm interested in your comment on why the prevalence of hypogonadism is 40 times higher in Massachusetts in men 40-49 than it is in Europe.
- Alvin Matsumoto: Because the European male aging study is a very large inter-country . . . multi-country study used as their criteria for symptomatic hypogonadism sexual symptoms only. Whereas the Massachusetts male aging study, in one study that doesn't sound like it's in here, the BACH study, the Boston Area Community

Health Study, are population studies in Boston that used multiple symptoms, not only sexual symptoms but physical symptoms, osteoporosis, a variety of other symptoms. So, it's the definition that made the difference. I would point out, however, that the reason the European male aging study used that definition is that they actually did, prior to the prevalence estimate, they actually did a study where they tried to determine at least statistically what symptoms seemed to cluster with low testosterone levels. A cluster analysis that actually, in my personal opinion, was done very well. I'm not a statistician, but it showed that the sexual symptoms clustered more strongly with low testosterone. So, they used as their definition that particular cluster of sexual symptoms, low libido, erection problems, particular spontaneous erection problems and decreased sexual activity. So, that's the difference. So, it's a matter of definition. Does that? You're still looking at it.

Kevin Walsh: I understand your comment. I don't agree with it, but I understand it.

Alvin Matsumoto: What do you mean you don't agree?

Kevin Walsh: Well, all the, so the, it looks like Boston included lethargy, sleep disturbance, depressed mood, low physiologic performance and osteoporosis.

Alvin Matsumoto: Right.

Kevin Walsh: So, there's 40 times more of that in Massachusetts than in Europe?

Alvin Matsumoto: Oh, absolutely. They didn't . . . the European male aging study didn't consider any of those at all. They defined it differently.

Kevin Walsh: I understand your point.

Alvin Matsumoto: There's a lot of low energy around. There's a lot of lethargy around.

Chris Standaert: That's Red Sox fans.

Kevin Walsh: The second question I have is, why the endocrinology field is comfortable making recommendations for testing but doesn't require that the testing be based on age-specific reference ranges.

Alvin Matsumoto: Because, as I suggested, there aren't very many of those around that are valid. You say that they're available, but go to your hospital lab and see whether or not they have any age-specific reference.

Kevin Walsh: Well, where does the pressure come from for them to generate?

Alvin Matsumoto: It comes from us. It comes from the Endocrine Society. I'm on . . . I should probably disclose that I am actually the co-chair of the partnership for accurate testing of hormones, the PATH organization that the Endocrine Society with the CDC initiated this reference . . . age-adjusted reference range project because

there was no age-adjusted reference range that people could use that was validated against the reference standard that was thought to be the gold standard. There are all different types of age-adjusted reference ranges. I would ask you to go to commercial labs and see how different they are and what populations were used. Yeah, we should insist on that. It, it's, it's fine to insist on it. It's another thing to actually have it implemented and actually validated in a scientific way that would be useful for everyone to use. So, I totally agree. It should be age-adjusted reference ranges. I just think you're going to be in the same situation if you use an age-adjusted reference range that's not valid.

David McCulloch: I applaud the work you and the Endocrine Society are doing in trying to get to that point. I think . . . I'm guessing what Kevin may be wondering then is, in the absence of that, why does the Endocrine Society feel free to issue these great proclamations and recommendations in the absence of good evidence or good data.

Craig Blackmore: I think, I mean, I don't want us to get too off topic, and the Endocrine Society is trying to do good work, I'm sure, but . . .

David McCulloch: With respect, Craig, I mean, a lot of the Hayes Report is simply spouting recommendations from unknown evidence-based specialty driven society and there is no good evidence.

Craig Blackmore: And Hayes has acknowledged that, and they are doing that because that's all they could find and we're stuck dealing with it, which none of us are probably too happy about, but . . .

David McCulloch: Right, so, I'm . . .

Craig Blackmore . . . and the reality is, if we could, we would fix a lot of these problems here today, but we can't. All we can do is decide one of three things, and I think probably what we're going to decide, and I won't even say probably. I will say one possible option for us to decide is cover with conditions so that we can allow coverage for primary hypogonadism and other things where there might be some agreement and then we're going to have to define where the boundaries of that are. Should we go down the conditions route? And I think it's going to be hard, and I think it's going to be based on very incomplete knowledge and, you know, there it is.

Alvin Matsumoto: One thing you should recognize is that the Endocrine Society, I think, is the only one of the guidelines that actually says that it's low quality evidence, and it is evidence based because we are in this situation where we don't have a lot of outcomes data. We don't have a lot of evidence, OK? This is not like hypertension and diabetes. We don't have a lot of studies to fall back on, but in the absence of those studies, I think it was a necessity for a scientific body, if you want to call it that, that specialty society to at least help some clinicians at least deal with this, and the one thing they did in the aging area was

acknowledge that even within the panel there were differences in whether or not individuals should even be tested, and then that acknowledgement is in print, and I think that goes a long way to actually being transparent about where we are in this particular area. And I think that's the kind of stuff that needs to be done, and you have already covered what this is, and you know, what the state of knowledge is, and I think we have to live with it, but as a clinician, do you just not do anything then, or you know? That's the whole point.

Craig Blackmore: So, other questions?

Joann Elmore: I want to start by thanking, I guess it was the staff that put together a binder of the primary literature, and well thank you, because that's something that we, as a committee, have asked for. Going forward, I would also ask that when we have slides that say two studies, please give us the first author and the year so that we can look up the primary literature. In addition, some of this review talked about retrospective cohort studies without mention of the quality and the limitations of the data. I think when you are reviewing guidelines, it's important to know the year that they were issued, and a final comment is that there was mention of repeat testing with the statement that I'd like to ask for clarification because the statement was that repeat testing is important to evaluate for possible adverse effect of treatment from high levels of testosterone. In other words, I heard you say that you need to get repeat testing to make certain the testosterone level isn't going high, but it's my understanding that the few publications on the topic do not study that. There is no evidence and that these risks of potential cardiac or cardiovascular disease are associated with initiation of testosterone treatment, not with a direct correlation and association with the high level that would be identified by repeat testing. So, can I please ask for clarification on the one sentence you made in your talk?

Teresa Rogstad: Sure. I believe it was one of the guidelines that we looked at pointed out that testosterone . . .

Joann Elmore: That's a guideline. That's not evidence, so.

Teresa Rogstad: I know. I'm just, I'm explaining the rationale that since testosterone replacement therapy hasn't been proven effective at above normal levels, there's no good reason to let levels creep up to that level, and then there's an applied assumption that adverse events might be increased. Also, we read that the FDA approval decision assumed that levels would not go above a certain threshold because of safety concerns. So, I'm saying that we found evidence that there was concern, not evidence proving any particular testing strategy.

Alvin Matsumoto: So, I'll just comment. This is Dr. Matsumoto. There are two issues. You don't want the levels to go too high and the issue there, primarily, is erythrocytosis, and there is evidence in comparing injectables that reach a higher level of average testosterone level versus transdermal preparations that have more

physiologic or slightly low testosterone levels that the risk of actually having significant . . .

Joann Elmore: But then you would check erythrocytes on treatment. You wouldn't test the testosterone level.

Alvin Matsumoto: That . . . but if the erythrocytes go up, then you want to know what the reason is. It's not only testosterone level. It could be hypoxic, you know, COPD patients, obstructive sleep apnea. It's part of the workup of that. So, that's the issue with the high testosterone levels. High erythrocytes are thought to be a cardiovascular risk. I'll let you know, and that could be argued, certainly. So, that's something that's . . . that's the reason for the high. More problematic, I think, is the low value. Transdermal preparations are not very effective, in general and, you know, this is something that has been known for some time from the clinicians that have used these things is that, in fact, some people don't even absorb very much of it. So, when you have lack of clinical response, you don't know whether it's due to the fact that they're not taking it, number one, which is also a very good possibility. The levels are too low or they don't get up to normal, or, you know, it's just something else that's going on. So, that has actually prompted individuals to say with transdermal preparations, you need to check it and titrate the dosage, which is also possible, to a level that would achieve normal ranges. That being said, I'll tell you as well, that . . . I'm not sure if this is published yet. There is a publication coming out, and there have been some publications that aren't as well done, that suggest that, in fact, even if you measure testosterone levels on treatment on transdermal formulations, the variability in the level itself from the in the same individual from time to time can vary. So, from my standpoint, that's something that maybe is not as needed because the variability is such that the level that you get may actually not tell you how to titrate the dosage. So, but again, if you want to speak with evidence, I'm not sure that's published, that particular piece of evidence is published yet but most clinicians will check it only in transdermal formulations. If you give an injectable that gets into the system, it's less important to do it with an injectable.

Craig Blackmore: Other questions? OK. I think it's just about 10:00. I think we should take a little break, and then we'll have to come back and see how we can create order out of all this. So, let's resume at 10:15.

Alright, we have a quorum. So, I'm going to call the meeting back to session. So, we've heard all of the formal presentations, and now it's the committee's time to have a discussion and render a decision. So, the way we found useful to start off is to have one or more committee members sort of summarize where they think we are and then we use that as a path to move forward. Joann do you want to summarize where we are and get us started in all this?

Joann Elmore: I'll only get us started with the first part, which is, a summary of the evidence as some of us heard it related to testing which was our committee's task. It shows us that there are changes with age and there seems to be a lot of evidence in

that regard. That the testosterone level is noted to change with age, and we also heard that laboratories do not report results with this additional information. So, I don't know whether our committee will end up cover, cover with condition, but one of the thought some of us had is, why we don't make it a part of any coverage that a laboratory has to provide data on age appropriate norms for testosterone testing.

Richard Phillips: The problem with that is, who's going to monitor it? I mean, you know? It costs money to monitor those things.

Craig Blackmore: So, I want to just put that aside for a moment, because it doesn't get us . . . we should talk about that, and that's something we should consider, but it doesn't actually get us to the key of the issue which is do we cover and if so, in whom? So, I mean . . .

Joann Elmore: Well, I guess that was my question is, why cover it if it's not appropriately reported. So, I was wondering whether we could add to the coverage if it's going to be done, we'd like to . . .

Craig Blackmore: Potentially we can. Again, I want to table that until we figure out if we're going to cover it and in whom, that can be an added piece, but it's still, we have to get at the gist of this, which is cover, no cover, or cover with conditions, and I don't think you're saying we should go for unlimited coverage, as long as there's age matched data. So, so again, I want to get more input on who and then we can talk as we get into more detail about other issues. So, do you want to . . .

Chris Standaert: Yeah. I think we have several dilemmas here. We have a relatively inaccurate biologically variable, unreliable test done in multiple ways, which makes it difficult to wrap your head around it, and we have, you know, people who clearly have primary hypogonadism, right, and is a biological condition and its fundamental lack of hormone, and it's been around for a millennia, and people are treated for that, and those levels have to be followed over the course of their lifetime, I assume, if they're being treated for that, because that's their medical problem, and they exist, and the testing was probably developed for that, essentially for finding out they have no testosterone production and then they monitor them in some way. Then, we have this newer phenomenon of low-T, which has very vague symptoms, very questionable biological validity, not much of a way to clearly identify it, and people are using inaccurate tests to validate it, and frankly, I don't even know if they even need or want or use the test anyway to validate treatment, and we can't . . . we're not talking about treatment we're talking about testing. So, it gets tricky for us. That, and so I, to say never test testosterone seems sort of odd, because there are people where you really have to do that, but then this other side of it is where it gets . . .

David McCulloch: Can I ask you to comment on this. I mean, given all the issues that you brought up very well, the inaccuracy of testing, reliability, reproducibility, my guess is in your clinical practice if you suspect somebody might be hypogonadal, you'd then also do the LH and FSH to see. Why don't we require that? I mean, you

can't make a diagnosis of hypogonadism, based on an inaccurate test with all the issues without also confirming that the person has high LH and FSH?

Alvin Matsumoto: Well, I do LH and FSH.

David McCulloch: Right.

Alvin Matsumoto: But the vast majority of folks don't have primary hypogonadism or have secondary hypogonadism. They'll have a hypothalamic pituitary problem and that's where you run into the problem of using that as the sole diagnostic test. It's a good . . . it's an essential test. The LH and FSH are essential for the differential diagnosis of hypogonadism. I would argue that getting back to the testing of testosterone what I would like to see is a requirement for good testing to be done with good quality control estimates.

David McCulloch: Correct.

Alvin Matsumoto: That would go a long way to get rid of some of the testing that's done with inaccurate assays in terms of, you know, the validity of the test itself, I think, is important. I don't know whether you have any authority to actually do that but maybe requiring at least an accuracy based College of American Pathology accuracy-based quality control to be an accepted test to do. So, that's number one, OK, in terms of what you would try to regulate. That would be . . . I would think that would be the first step. The second step, though, and I alluded to this before, is that one of the risks of restricting the number of tests is that this is . . . this is one thing that will lead to treatment is that a lot of people are testing once, finding a testosterone level that's low and let's say it's even a good assay. Even with a mass spec assay, and they're treated. This happens a lot to tell you the truth with primary care and nurse practitioners that really look at the test and say, OK, it's low and then we have to go and treat without confirming it. I would argue, you know, the old, I'm old school on this is that, are you going to treat somebody with a single, you know, on the basis of a single test for anything?

David McCulloch: No.

Alvin Matsumoto: You know, and you're going to repeat it. You're going to repeat it at least once and sometimes maybe over the course of time to see which way it's going, right? So, again, clinically what I'm afraid will happen if you restrict the number, now we're talking not about the quality but the number of tests that are done to confirm a diagnosis of hypogonadism is that you'll have more treatment . . . in appropriate treatment.

Joann Elmore: The evidence suggested that.

Alvin Matsumoto: Well, no. You'll have more inappropriate treatment . . . well, I think that was, I thought that was the recommendation somewhere that I read, but at any rate, that's an aside. So, I feel pretty strongly about that, and then the issue of the

age adjusted reference range, rather than trying to, you know, restrict it to people that have . . . or assays . . . or labs that have reference ranges like that, first of all, they're probably not very good anyway, most of them. What I'm afraid will happen if you do that is that people will go to commercial labs or to reference laboratories like Quest or LabCorp or any of the ones that you can send out values to, and then what you're talking about is a radical increase in cost, OK? So, part of the issue here underlying some of this is cost, right, and if you start sending things out a lot that is number one a hassle, it's a cost . . . and if you're covering the cost of the test, it's going to increase the cost. So, there you have to consider, as well, and local labs are the ones that maybe don't have the age-adjusted reference range right now. **2:25:10**

Craig Blackmore: OK. So, just, I'm going to table the issue of reference ranges and test credentialing and quality assurance, and when it gets back to the issue before us, which is in whom should we cover the use of testosterone testing and I am welcome from the committee some starting points on how we might address that question. I'm hearing that we're not going to be able to go with a non-coverage decision. At least, I've heard that. Maybe that's not the full group's opinion, but that there are some people who have either primary or secondary causes of hypogonadism that are recognizable and severe in whom testing might be appropriate, but there is also a broad group in whom there is maybe diagnosis of an entity, which is not well clinically defined and that there is not evidence on treatment. So, I guess, I think I'm hearing that a noncoverage decision is not the direction we're headed, which means we're either in a cover without restrictions or a cover with restrictions, and I need somebody to help me move forward on what restrictions look like beyond the characteristics of the test itself.

Kevin Walsh: Well, I think you, I think you delineated it nicely. I think there's kind of two subpopulations. One is the population in whom you're worried about primary or organic secondary, and then the second larger group is the low-T, I watched it on TV group. So, I think that we should discuss them in that way.

Craig Blackmore: And the challenge for us, the core challenge for us is defining the difference between those groups. So, that's where I want us to go and then we can circle back to how labs are credentialed and how the test is reported, but we need to address that. It's not going to be easy, but that's what's before us.

Kevin Walsh: The one point I would like to introduce to be considered is the notion that this is a multifactorial entity and that it's irresponsible not to require evaluation of all the other possible causes and to rely on free-T as the only test that's required to make this diagnosis is, in my mind, ludicrous.

Chris Standaert: We're not talking . . . unfortunately, we're not talking about how to diagnose primary or secondary hypogonadism.

Kevin Walsh: We're talking about what conditions . . .

- Chris Standaert: We're talking about what . . .
- Kevin Walsh: . . . under what conditions to cover the test.
- Chris Standaert: . . . when you can draw a test, right, so . . .
- Kevin Walsh: And my proposal is that you would have to do this as part of a panel of things because sexual dysfunction, if that's what we're talking about, doesn't exist in isolation of just low testosterone very much of the percent of the time in primary care.
- Chris Standaert: So, I guess, I'm running into some issues with this because, you know, our, we're supposed to use our data, right, and when . . .
- Craig Blackmore: We're supposed to use the best available evidence.
- Chris Standaert: . . . right, that has to be evidence our vendor looked at and talked about and gave us in review. We can't just pull it out of, I know this, right? I wish we could but we can't. We're supposed to use what they looked at. So, they looked at a couple particular conditions, the diabetes and the sexual dysfunction thing, which is quite fuzzy, I would agree with you. But these other, you know, the other evidence we have for where to do this is really on guidelines other people wrote of sort of, you can do it in these circumstances, and that's really what we have. So, I don't (inaudible). We don't have studies looking at other things that go with the workup, other things that affect treatment. We don't have any of that. We have no information on different assays and different things, and whether we should be testing free testosterone or total testosterone. We don't have any data on any of that that was given to us. So, how we can go there, I don't know. That wasn't looked at, but I think we're in this situation of the data we have is from these guidelines and people who talk about, especially the Endocrine Society, various causes of primary and secondary hypogonadism that are medically recognized, and then the rest of it becomes more fuzzy, but our data isn't overly full to even draw from, I don't think.
- Craig Blackmore: So, should we start sketching out some potential conditions at this point or do we have more questions that we can get our team to attempt to answer?
- Richard Phillips: A question and observation. It seems to me that this probably was driven because of the, you know, the extensive workups being done out in the, in the hinterland for sexual dysfunction in elderly people. You know, we're seeing much more testosterone testing, and that's probably what we want to go after is, maybe do we want to put some controls on it. Maybe, or maybe not, but then you know, when we get into the specifics of testing, like, if you want to, do we really want to regulate testing for, say people who come in with erythrocytosis? I mean, but I don't know we have the evidence for that, you know? I guess my point being that we could get quite prescriptive and quite restrictive, and I think it might be inappropriate, and I'm . . . I really am having problems getting a hand on what we really want to do, you know, and I think it's

almost impossible for me, at this point, to come up with a solution other than maybe starting where they, you know, like with what Steve presented, you know? Like some of the conditions, you know? At least I saw that as a good starting point, but even at that, I take issue with some of the stuff that was put up there, so.

Craig Blackmore: So, I think this is frustrating, right? It's frustrating for all of us. We would like to have some evidence. We would like to have tests that have some reasonable properties so that we can believe it. We would like to have more than society guidelines. We would like this issue not to be before the committee because practice in the community is such that there isn't a problem, but I think the numbers we have seen suggest that there is a problem and it's getting worse and so we're forced to deal with it, and we have now access to what evidence exists and we have to deal with it, and there it is. So, why don't I ask if you could put up a blank sheet of paper on the screen there, and we'll take a start at this.

Josh Morse: So, while they're doing that, I'll, this is Josh. I'll just take a moment to introduce Rachel Burke. Rachel is working today with us. She is from our policy group at the Health Care Authority and she's just assisting today with our process. We still have a vacancy in the position that Margaret Dennis left. Thank you, Rachel.

Craig Blackmore: So, I'm going to suggest, as a starting point, I'm looking through the slides to figure out what we might be able to start with.

Marie Brown: The agency . . .

Joann Elmore: Men, male . . .

Marie Brown: . . . medical directors.

Joann Elmore: . . . male patients.

Craig Blackmore: Males. Well, our charge is males.

Chris Standaert: Males.

Joann Elmore: Yes.

Chris Standaert: That's all we can talk about.

Joann Elmore: So that's . . .

Chris Standaert: Older males is all we can talk about.

Joann Elmore: Well, was it older men or just men?

Craig Blackmore: Adult men. OK. So, we're not going to discuss anything except adult men.

Joann Elmore: So, we need to write that there.

Craig Blackmore: No. It's part of the . . .

Joann Elmore: Oh, OK.

Craig Blackmore: . . . it's part of the scoping of the decision. We don't have to go there. So . . .

Marie Brown: Or, objective physical exam or laboratory imaging, evidence of pituitary or primary gonadal dysfunction.

Craig Blackmore: Alright, so . . .

Marie Brown: Primary.

Craig Blackmore: . . . where, where . . .

Marie Brown: That's on page 11 of the medical directors.

Joann Elmore: So, what we're going to do is go back and forth between the presentation and what you're drafting. Just type something for us so we can see it, I think.

Marie Brown: Have a Word document to get things started.

Joann Elmore: Suspected primary hypogonadism.

Chris Standaert: Yeah.

Joann Elmore: That's one of the conditions. That's the easy one. It's the . . . that's the easy one. So, in adult males with suspected primary hypogonadism. That is one of the cover with conditions.

Craig Blackmore: OK.

Joann Elmore: It's the next cover with condition that we all need help.

Craig Blackmore: We're getting started. We're making progress.

Chris Standaert: Yeah. You were trying to get away with adult men and stop there. You were going for that one.

Kevin Walsh: So, would you would include in the . . .

Chris Standaert: Everybody has to pick one.

Joann Elmore: Well, it took me a while we were just doing men, you know, when I was reading this over. That's why I wanted to start.

- Craig Blackmore: The question scope is for adult men only.
- Seth Schwartz: In the, and we talked about the suspected primary hypogonadism. Does that include the situation of, like, radiation to the pituitary, or things of that nature, because it seems like that's another group where you have a . . . if they have that and they have some symptoms, then that would be a circumstance where it seems reasonable to do.
- Craig Blackmore: Is that considered primary hypogonadism?
- Joann Elmore: That's secondary.
- Seth Schwartz: So, that would be secondary. So, when we talk about secondary, I think there's sort of these two categories of secondary. There is one in people where you have a reasonable reason to think they would have it, not just on symptoms but based on symptoms and something in their history that would suggest it's likely. So, again, a pituitary tumor, radiation to the pituitary . . .
- Craig Blackmore: Yeah.
- Seth Schwartz: . . . testicular problem, you know, whether it's due to cancer or something, some other reason to have acquired it.
- Chris Standaert: Right.
- Craig Blackmore: There's a list somewhere of organic causes of secondary.
- Seth Schwartz: Yeah, maybe that's the terminology, symptoms and organic . . . an organic indication for . . . or organic cause of secondary hypogonadism, and then there's this third category, which is secondary hypogonadism suspected based on symptoms alone.
- Craig Blackmore: Well, there's always going to be symptoms, but it might be . . . well, maybe not always.
- Seth Schwartz: No, because what I'm saying is there's symptoms and an organic cause, right? So, you've got symptoms and you have a pituitary tumor, then that person probably should be tested.
- Craig Blackmore: Yeah, but it . . .
- Seth Schwartz: Or it's reasonable.
- Craig Blackmore: . . . it's symptoms that cause you to think there's an organic cause, right?

- Seth Schwartz: But that's, no, that's a different story. In other words, if they have symptoms, and you think they have a pituitary tumor, you shouldn't test their testosterone. You should look for a pituitary tumor.
- Craig Blackmore: Pituitary tumor.
- Seth Schwartz: So, it's if they have a pituitary tumor, and they have symptoms, and you're concerned that they may have . . . be symptomatic because of the low testosterone and you're going to treat not only the pituitary, but you may also treat the low testosterone, which seems reasonable to do.
- Kevin Walsh: So, the second point there should read organic cause and symptoms.
- Craig Blackmore: Can you use a bigger font, please?
- Seth Schwartz: Well, I would think so.
- Kevin Walsh: You're saying the organic, the organic causes precede the . . .
- Seth Schwartz: Yeah, that's what I'm thinking. I mean, I guess the question is, do you necessarily need to test testosterone in every man with a pituitary tumor, and I don't think that you need to. I mean, you would only do it if you had some reason to do it, which would be symptoms. So, it would be organic cause and symptoms.
- Joann Elmore: Do we need to define the organic cause?
- Seth Schwartz: Well, we can do that. I'm just starting out with easy things. Men . . .
- Joann Elmore: The first one is primary hypogonadism.
- Seth Schwartz: Right.
- Joann Elmore: The second one is a suspected secondary hypogonadism, in which you have an organic cause and symptoms.
- Seth Schwartz: And symptoms, right.
- Joann Elmore: And then the third . . .
- Seth Schwartz: And the third one . . .
- Joann Elmore: . . . you're going to tell me.
- Seth Schwartz: . . . is this category of symptoms . . .
- Joann Elmore: OK. So, let's clean up the second one.

- Seth Schwartz: OK.
- Joann Elmore: Do we need to define the organic cause, like, explain, you know . . .
- Seth Schwartz: Maybe, can we just give a few examples?
- Joann Elmore: Pituitary or suprasellar tumor or (inaudible).
- Seth Schwartz: Either, yeah.
- Craig Blackmore: So, pituitary problems. If I look at the Endocrine Society guideline, they list sellar region pathology. They list medications. So, I guess it would be medications that can cause secondary hypogonadism.
- Alvin Matsumoto: Well, the biggest medication is going to be opioids.
- Chris Standaert: Opiates.
- Alvin Matsumoto: Long-acting opioids, and then second biggest one would be glucocorticoids, prednisone, or chronic prednisone. Those all cause secondary hypogonadism.
- Chris Standaert: Opiates would be the biggest one.
- Alvin Matsumoto: And then the third, more diffuse, could or could not be anything that acts on the central nervous system, particularly psychotropic drugs, but they usually do it with increasing prolactin, but there are lots of other things that could do it also.
- Craig Blackmore: OK.
- Seth Schwartz: So, I don't know how specific we need to get. If we simply say medications that are suspected to cause hypogonadism.
- Craig Blackmore: I'm happy with that, because these things can change.
- Seth Schwartz: I mean, leave that up to the clinicians to sort out.
- Craig Blackmore: OK, and then there's HIV, weight loss in the guidelines. So, HIV, what's the mechanism for HIV?
- Chris Standaert: HIV with weight loss.
- Alvin Matsumoto: It's wasting. It's nutritional deficiency. In fact, that is a very common cause.
- Chris Standaert: Yeah.
- Alvin Matsumoto: Of secondary hypogonadism.

- Chris Standaert: HIV with wasting, either from the disease or the drugs, I assume. HIV with wasting.
- Craig Blackmore: I prefer weight loss to wasting, but . . .
- Chris Standaert: Weight loss.
- Craig Blackmore: And then the other one that these guys have identified is osteoporosis and presumably we would have documentation of osteoporosis.
- Chris Standaert: Well, that one's sort of tricky, because the cause of the hypogonadism isn't the osteoporosis. The osteoporosis is a marker for the hypogonadism, I assume.
- Joann Elmore: Right, or it's associated.
- Craig Blackmore: But it's a marker for . . .
- Chris Standaert: Right.
- Alvin Matsumoto: It's a contributor of bone loss.
- Craig Blackmore: Yeah, but if the, if they have osteoporosis because they are hypo, their testosterone is too low, I could see justifying treating the testosterone in that context.
- Chris Standaert: No. I can see that, too. I'm just saying it's the organic cause where osteoporosis is not the cause of the hypogonadism. It's a marker of the hypogonadism. It's an effect.
- Seth Schwartz: I think I would be more inclusive rather than restrictive in this category, because we should leave it up to clinicians. If there's . . . these are circumstances where it's reasonable to do in my mind. I think what we're . . . what we're reacting against, I think why we're here is because of this whole low-T phenomenon, and that's not an osteoporotic man. That is an otherwise healthy guy who has decreased libido or whatever else, you know, or is fatigued, you know, and I think that's the . . . I think that's where it gets hard, which is number one, is that even a real condition or is that just getting older. Then, number two is, if it is a real condition, are we able to stratify the symptoms that would be realistic to test for versus those that are simply things that people have as they get older.
- Joann Elmore: OK. So, for these last four bullets, they need to be sub-bullets under suspected secondary hypogonadism, OK? Under organic cause and symptoms, or actually is it the last three?
- Kevin Walsh: No, it should say, it should say suspected secondary hypogonadism with organic causes and symptoms.

- Joann Elmore: With organic cause and symptoms. Well, I mean, is, with osteoporosis are we saying they have to have osteoporosis and symptoms before they get the T?
- Chris Standaert: So, you're using osteoporosis as a marker for an endocrinologic disorder.
- Joann Elmore: Right.
- Chris Standaert: So, just having osteoporosis alone . . .
- Joann Elmore: Which is, according to these guys . . .
- Chris Standaert: . . . you would, you might . . .
- Joann Elmore: . . . some of them think . . .
- Chris Standaert: . . . well go draw the testosterone in the . . .
- Joann Elmore: . . . even though it, even though . . .
- Chris Standaert: . . . midst of an (inaudible).
- Joann Elmore: . . . we did not report adequate evidence on that, but yes. In other words, for the medications it has to be . . . they have to be on medications that could be suspected and have symptoms, or for the organic, you know, sellar abnormalities and pituitary abnormalities. They have to have symptoms and that.
- Craig Blackmore: Well, I'm not sure that's true, I mean . . .
- Chris Standaert: I'm not sure that's true.
- Craig Blackmore: . . . osteoporosis is asymptomatic. HIV with weight loss, I mean, is that a symptom?
- Joann Elmore: Uh-huh.
- Chris Standaert: Yeah.
- Craig Blackmore: It's a . . .
- Seth Schwartz: So, I guess the question would be, are you testing testosterone in everybody . . . do you test testosterone in every male with osteoporosis. It's that . . .
- Craig Blackmore: I think you're giving these guys an option.
- Alvin Matsumoto: I think you should be doing.
- Seth Schwartz: OK. I mean, that's . . .

- Alvin Matsumoto: I mean, to tell you the truth, I, I agree somewhat with the organic cause plus symptoms, but most people that are seeing lots of pituitary patients, if they've got a mass in their pituitary gland, they're going to measure testosterone as part of their workup. Part of the problem is that the non-specificity of somebody that has pituitary insufficiency, it could be secondary hypothyroidism. It could be secondary hypogonadism. It could be ACTH deficiency. It could be a lot of things. So, if you're going to really restrict somebody with a known mass in their pituitary or infiltrative disease to somebody that has symptoms, you might be restricting it too much.
- Seth Schwartz: Yeah, I don't think we need to be restrictive here.
- Joann Elmore: But what about the organic . . . making the organic cause with symptoms the first sub-bullet, because we need the pituitary and suprasellar tumor things and symptoms. So, do you want to make the organic cause and symptoms the first sub-bullet and explain . . .
- Chris Standaert: You could just get rid . . .
- Joann Elmore: . . . what you mean there?
- Chris Standaert: . . . of the word symptoms. So, if you're looking for some organic reason for having suspected . . .
- Joann Elmore: Yeah.
- Chris Standaert: . . . secondary hypogonadism. That's what you're looking for.
- Craig Blackmore: Symptomatic or not.
- Chris Standaert: Symptomatic or not. So, get rid of the word symptoms.
- Marie Brown: So back (inaudible).
- Chris Standaert: This is tricky. So, are we going to try and make a definitive list of this because we get into, you know, the FDA approvals for treatment, orchitis due to mumps? I mean, we're going to get pretty far down the line here, and I don't, I don't think we can get a totally inclusive list. So, we need a term, like, suspected hypogonadism, secondary hypogonadism from an organic cause and leave it at that, e.g., and then put some examples.
- Joann Elmore: Yeah, yeah.
- Chris Standaert: And don't put . . . just say if you think there's some medical reason why this person has hypogonadism, you're not after this to treat low-T. You're after this to find their medical cause, you can go do this . . .

- Joann Elmore: E.g. pituitary tumor . . .
- Chris Standaert: . . . whatever it may be.
- Joann Elmore: . . . or suprasellar tumor.
- Chris Standaert: Organic cause goes after, is part of the suspected hypogonadism with organic cause.
- Joann Elmore: With organic cause.
- Chris Standaert: Yeah. The words organic cause go after the word hypogonadism, and all these are examples of those things. Put organic cause in there. So, everything below it will be . . .
- Craig Blackmore: OK. So, let's think while they get caught up.
- Joann Elmore: OK, and then suspected secondary needs to be a big, not a sub-bullet but a bullet.
- Richard Phillips: How does the testing for something like erythrocytosis come in here? You know, maybe there's other causes I'm not even thinking of, and I'm trying not to be . . . I'm trying to figure out how this all fits together.
- Chris Standaert: That would be under. So, if you have erythrocytosis, you might suspect there is hypogonadism. So, a secondary . . . so you might draw it if that's what you're thinking. This is secondary hypogonadism as a cause for your erythrocytosis. So, that's why we're trying not to be total . . . I don't like . . .
- Alvin Matsumoto: It's not a cause of erythrocytosis.
- Chris Standaert: . . . totally inclusive with this.
- Marie Brown: I can't hear you.
- Alvin Matsumoto: Hypogonadism is not a cause of erythrocytosis.
- Chris Standaert: It's the testosterone.
- Alvin Matsumoto: It's the testosterone treatment that would potentially cause that.
- Kevin Walsh: So, this is, right. It doesn't have to be on the list, erythrocytosis. We're talking about testing initially.
- Marie Brown: OK.
- Richard Phillips: I don't disagree with you.

- Craig Blackmore: OK. So, I'm on page 17 of the Hayes Report. We sort of went through those and then on page 18 of the Hayes Report, and this is coming largely from the guidelines from the Endocrine Society. They also list conditions in which characteristic signs or symptoms might prompt testing. So, this list, the guideline considers testing appropriate even without symptoms, and I think we talked about that, and we're on that same page, and then in the guideline, and again, it's a guideline but, you know, I'm not hearing that we have any evidence to come up with any better way to approach this. So, that's why I'm starting with the guidelines, just as everybody else has done. They talk about type 2 diabetes, end stage renal disease, and COPD, as well as infertility, as cases in which people basically with those disease who have characteristic signs and symptoms might undergo testing. So, I would propose we follow that because I think the areas we believe might be inappropriate aren't really in the individuals who have these conditions. That's my opinion, and I'm getting shakes of heads, so.
- Marie Brown: Infertility would be a priority.
- Chris Standaert: No. That doesn't go there.
- David McCulloch: I don't get it Craig. There's . . . if you've . . . whether you've got diabetes or not, you would test if you think it's primary or secondary hypogonadism. I can't think of any situation you would test somebody with diabetes just because they've got diabetes.
- Craig Blackmore: No. They're saying diabetes with characteristic signs and symptoms. So, diabetes with . . .
- David McCulloch: Characteristic signs and symptoms of?
- Alvin Matsumoto: Androgen deficiency.
- Craig Blackmore: Androgen deficiency.
- David McCulloch: Primary or secondary.
- Craig Blackmore: So, so the challenge is this, I think. The challenge is, if we say test everybody who has, you know, symptoms like lethargy and decreased libido then we're basically saying you can test anyone.
- Group: Right.
- Craig Blackmore: So, however, we also recognize that those can be indications of androgen deficiency, and when we have populations in whom androgen deficiency is thought to be more prevalent, it might be appropriate, maybe, to deploy testing for more vague symptoms in that group. Now, that's . . .
- Seth Schwartz: When are we going to talk about safety?

- Joann Elmore: Yeah, really.
- Marie Brown: We will in a minute.
- Seth Schwartz: Because we're so far on thin ice that . . .
- Craig Blackmore: You tell me.
- Kevin Walsh: . . . it's cracking underneath my feet here. I mean, so the notion is, if you have diabetes you might have androgen deficiency, but the question is, well are you going to treat that androgen deficiency in a diabetic because they have it? That's when the safety issue comes in, because I don't feel that it's at all conclusive that there's no cardiovascular use to using testosterone. So, you already know that diabetics are at increased risk for cardiovascular disease because of their diabetes. So, I don't . . . I can't go along with testing diabetics even with symptoms, personally.
- Seth Schwartz: So, I'm challenged a little bit by this, because, you know, while the safety concerns aren't, you know, completely 100% convincing, I agree with Kevin. I'm pretty suspicious that treatment has some risks, but that's also not entirely what we're talking about, you know? Because if you have a patient in whom you really suspect this disease, it doesn't seem unreasonable to find out if they have it or not and then as a clinician have the discussion about, you know, yeah. Now we know you have this but treatment may be fraught with problems, and you may elect not to treat that patient, but if you never knew they had it in the first place, you can't even have that discussion. So, I'm not sure where we fall at on that one. What I'm still thinking about this categorization, I think we're good so far, and I would sort of envision a secondary category, which we may decide to include or totally exclude, but it would be the suspected secondary clinical hypogonadism without organic cause, and then we can decide if we want to try and classify those conditions or not, or if we're just going to throw that out completely, but I think we're pretty good with where we are so far. It's this next one where it gets (inaudible).
- Chris Standaert: So, I guess . . . so, would you say . . . this is now symptomatic patients, right? So, now we have people who we're not chasing a diagnosis. Our primary goal isn't chasing a diagnosis of hypogonadism and some pituitary axis problem. Now, we're after people who come in who are symptomatic. They may have diabetes. They may just have sexual dysfunction. They may have something else, but these aren't people where you would do the workup because of the nature of their disease. Those people you would, right? Whether they're symptomatic or not, they have HIV with weight loss, you may go look. If they're osteoporotic, you're going to go look. If they have a pituitary tumor, you're going to go look.
- Seth Schwartz: I guess the question is . . .

- Chris Standaert: But the other category seems to be people who are just symptomatic.
- Seth Schwartz: So is . . . but, I guess the question is, is symptomatic from low testosterone, is that not secondary hypogonadism?
- Chris Standaert: But saying without organic . . . so, is diabetes an organic cause of hypogonadism. I mean, that's what (inaudible).
- Seth Schwartz: Well, this is important. I mean, we're . . .
- Chris Standaert: Right, so . . .
- Seth Schwartz: . . . I mean, I'm not convinced at all about that.
- Chris Standaert: . . . no. Neither am I.
- Seth Schwartz: We don't know what those (inaudible).
- Chris Standaert: (inaudible) All I'm saying is that in the, in the guidelines, where they talk about it, they are talking about secondary hypogonadism, but they're talking about signs and symptoms, and then we get into people where . . . I guess, without. . .
- Seth Schwartz: I guess the . . .
- Chris Standaert: . . . organic cause throws me, because I don't know how to know whether end-stage renal disease would be considered an organic cause of hypogonadism.
- Seth Schwartz: Well, I guess the point here is that suspected secondary hypogonadism is because of the signs and symptoms, right?
- Chris Standaert: OK, well I guess due to symptoms alone, I guess you could say, and then put the conditions under which symptoms alone with one of these medical conditions would make you go look?
- Alvin Matsumoto: Can I interject?
- Chris Standaert: Something like that?
- Alvin Matsumoto: I think one way of thinking about this that makes sense to me, it's not totally accepted, but I think, I like the term organic, because I've used that before, and you define that as something that's structural, congenital, or infiltrative, something that actually damages or you're born without some part of the hypothalamic, pituitary axis, OK? So, I like organic. I've used the term functional hypogonadism for the others because what happens with a lot of these causes is that there is something, like a medication, that suppresses the hypothalamic pituitary axis but doesn't actually cause damage to it. So, if you take away . . . if you give a long acting opiate, LH/FSH, testosterone, go down. If you take it away and you wait for a while, it comes back again. So, there was

really no structural or organic issue there. With renal failure, you get this for a multitude of reasons, nutritional, illness, cortisol, a variety of reasons, but they're all functional reasons for suppressing the gonadotropin axis. If you get a renal transplant and you correct the renal function, in fact, testosterone levels will come up so that there was no permanent damage associated with the illness. Same with glucocorticoids for all of those. So, if you classify these things into functional causes versus organic causes, organic causes you've already kind of done. The functional causes become more difficult. You hit the nail on the head basically is that if you allow, like, type 2 diabetes or obesity or anything that, you know, is commonly found to have, in these conditions, low testosterone, but you require that they have symptomatic symptoms, as well as a low testosterone, most people will have symptoms because of their reasons, right? I mean, so they'll have comorbid reasons to actually have symptoms. So, you're going to allow a lot of people in. I feel for you, because this is what you basically deal with every day if you see a lot of people with hypogonadism, but then you don't want to ignore those small percentages that actually do have hypogonadism that have symptoms that are related to low testosterone. So, I can't help you with that, but I think it's a matter of severity, but you can't actually put that in a document. My own personal practice would be to gauge this with a symptom complex, not just one or two symptoms but maybe a whole set of symptoms and the severity of the symptoms to actually guide me to say this is likely related to low testosterone, but you know, again, you have to be evidence based. It's not empiric at this point.

Seth Schwartz: What I'm struggling with is, I like that classification, yet I don't feel like we have the evidence to make that determination, and then the secondary issues is, I'm trying to . . . I'm still trying to figure out what our concern is, why are we here, and I'm not . . . I don't really think we're here because there are people who have medical conditions or other things that are associated with low testosterone levels that may be causing their symptoms. I don't think those are the people we're worried about. It's the . . . I'm still thinking it's the TV diagnosis of low-T, and so . . .

Chris Standaert: Otherwise healthy men who are . . .

Seth Schwartz: Right.

Chris Standaert: . . . getting tested.

Seth Schwartz: Right. So, we may be over-testing in diabetics or people who have . . . who are obese or whatever. We may be over-testing in those patients, but it doesn't feel like that's the runaway problem that we're concerned about. So, I don't think we need to be restrictive about that stuff. So, I think coming up with some definition that allows for that but says you've got a 50-year-old guy who's more tired than he used to be, that guy shouldn't get a test. So, again, I'm not exactly sure how you make a classification, but I just am thinking about it and that's, that's the divergence that I think, I, I'd like to see us classify somehow.

- Chris Standaert: So, is there, could you say something like symptoms alone in the absence of a concurrent medical condition that would be expected to cause secondary hypogonadism is not covered, I mean, could you say something like that, or does that kind . . . I don't know the right word, but does that kind of language work. So, rather than trying to find . . . at some point, rather than try to say everything that should be in, we say everything below this is out. We just draw . . . so if you don't meet one of these things where you really have . . . somebody knows you have some medical problem or some medication or something that is going to, is known to cause true hypogonadism, which isn't what we're worried about. You just say you can do that, but if really you're just doing this in people who are symptomatic without any known medical problems that would be suspected of being causative of secondary hypogonadism, you shouldn't do that, something like that?
- Craig Blackmore: Flipping that around would be coverage for individuals who have symptoms of hypogonadism and a diagnosed medical condition known to be associated with hypogonadism. Now, I don't know what can of worms that opens up. People could say everything's associated with hypogonadism, and if that's just an open door, I mean, I think that's what you're getting at. What that would look like, I don't know. I mean, I don't know if that would be, I mean, you know, I think the, I think the, I think the committee is all in the same place of trying to restrict one group, one component of the testing that we see, and we're just trying to figure out how to put that into words, and it's not easy. Thoughts?
- David McCulloch: I would keep the first three bullets, remove bullets four and five, and leave the basically the ones we struggled over with the five sub-bullets and then just below that say symptoms alone in the absence of any organic cause is not covered.
- Craig Blackmore: So, I'm sorry. I missed that. Keep the first three and then the fifth, symptoms only.
- Marie Brown: Well, the fourth, though, helps us with that negative case.
- Chris Standaert: We're saying that's not covered.
- Kevin Walsh: Can I ask the agency chiefs. A negative case means you have to, aren't you, then, required to look and see if everything else has been ruled out? I mean, how, how do you enforce a negative case?
- Steve Hammond: Well, it could be helpful, I think, to state what is not covered. I mean, implementing this is going to be a challenge, but having the decision could be helpful in . . .
- Kevin Walsh: So, the statement symptoms alone in the absence of any organic cause is not covered is a helpful statement?
- Joann Elmore: Well, it might be educational for the clinicians.

- Steve Hammond: Yes, that could be helpful.
- Kevin Walsh: OK.
- Chris Standaert: Because I don't . . . we're not going to be able to get a conclusive list of what should be in. So, at some point, we just have to say, this category is out, because we just can't come up with every single medical thing.
- Kevin Walsh: So, we're saying takeaway bullet point four, the one that says suspected secondary hypogonadism with symptoms alone, take that out. Leave in the next one, and then do we leave in the one after that, as well?
- Chris Standaert: That sort of repeats the second bullet, the bullet point right above, the suspected secondary hypogonadism (inaudible).
- Seth Schwartz: I think the fourth one might be more restrictive than we want to be and I could be wrong about that, but I mean, that's pretty restrictive. I see that as being pretty restrictive.
- Craig Blackmore: See, I worry the opposite. I worry that organic has a meaning to us in this room, but it doesn't have a standard meaning, and, you know, I think you could come up with things and say they're organic causes.
- Marie Brown: Or the structural, infiltrative.
- Alvin Matsumoto: Yeah, yeah. I, I think you can run in . . . I agree that the fourth one is, is going to be . . . is restrictive. So, you have a person who's on a methadone maintenance program that's taking chronic methadone that is . . . well, you could argue that, you know, well at any rate, that has low testosterone levels in the castrate range, which is very common, OK? They . . . it suppresses the axis, and you wouldn't consider that an organic cause, because if you could ever get the person off of methadone, they would be . . .
- Chris Standaert: So, if we change the word organic to any medical condition or medical treatment known to be associated with secondary hypogonadism is not covered.
- Craig Blackmore: I mean, it's already . . . medication's already there.
- Michelle Simon: Yeah, it's covered above.
- Seth Schwartz: It's the medical condition, I think.
- Chris Standaert: Medical condition instead of organic cause.
- Craig Blackmore: Yeah, that . . .

- Chris Standaert: It would seem to me you'd see, like, yeah. The total cynical side of me . . . the pain and Vicodin clinics that are so badly run combined with the testosterone clinics and then you have everybody on it, but yeah. This is . . .
- Craig Blackmore: So, it'd be . . .
- Chris Standaert: . . . the other side of the world.
- Craig Blackmore: . . . medical condition associated with hypogonadism.
- Seth Schwartz: The symptoms alone is pretty vague. Maybe we want to say something more about that?
- Kevin Walsh: Make a proposal.
- Seth Schwartz: You know, I guess there's two types of symptoms that we're looking at. There's sexual dysfunction symptoms and then there's I don't feel good symptoms. I don't feel as good as I did when I was 20 symptoms. So, I mean, realistically that's what we're talking about, and I don't know how you, you know, how you classify that, but, or at least say symptoms suggestive of secondary hypogonadism.
- Craig Blackmore: So, how about the four words from the final bullet there, we move those up, say symptoms of secondary hypogonadism in the absence of any medical condition associated with hypogonadism is not covered. I like it. That's restrictive in the sense that somebody might really . . . really might . . . well, I don't know.
- Marie Brown: Try that.
- Seth Schwartz: Symptoms of secondary hypogonadism.
- Marie Brown: Type it in.
- Seth Schwartz: Perfect.
- Craig Blackmore: And then you can get rid of the final bullet. So, the risk here is, somebody could have really severe symptoms and maybe have a problem, really have secondary, maybe, you know, really have very low pituitary or testosterone, and we wouldn't allow testing unless they were a diabetic, and I don't know, I'm just . . . I don't know what you guys think about that.
- Chris Standaert: But what would, I mean, what would prompt somebody to come in where the only differentiator between well and not well would be a low testosterone with that? Well, like, so they didn't know what they had. They came in. They're totally fatigued, they're wasted or whatever. They've got a whole bunch of things, lots of things are going to be off, I assume. It's not just testosterone. If the whole pituitary is out, you're going to find all sorts of things are off.

- Joann Elmore: Mm-hmm.
- Craig Blackmore: But we're saying you can't test that person for low testosterone.
- Seth Schwartz: No, but if you work them up and they have a low, and they have low TSH, they've got a low pituitary function or something like that, then you could, because then . . .
- Chris Standaert: Right, because then . . .
- Seth Schwartz: . . . they have a medical condition. Then, they fit that category. They're saying it's not, it shouldn't be your first test is essentially what you're saying.
- Craig Blackmore: I found something else, right.
- Seth Schwartz: That could cause low testosterone.
- Chris Standaert: I mean, it's not . . . I don't know if we define . . . would sexual dysfunction alone be a medical condition? Would someone define it as such? That's up to them, I guess, the state.
- Joann Elmore: Well, we'll try.
- Chris Standaert: Better for people to try.
- Craig Blackmore: Right. So, that's, then the . . . is this really restrictive, I guess, is the question, or will somebody say, oh, low libido is a medical condition associated with hypogonadism.
- Chris Standaert: Right.
- Craig Blackmore: I don't know.
- Alvin Matsumoto: I'm not sure you need secondary there. The symptoms of primary and secondary hypogonadism in terms of androgen deficiency are the same.
- Craig Blackmore: Alright. So, is, is this sufficiently restrictive for the committee's needs?
- Kevin Walsh: I, I, I think this is a . . . this doesn't close the door at all for me.
- Chris Standaert: Because they're just going to say fatigue, loss of libido, whatever.
- Craig Blackmore: It's a medical condition.
- Chris Standaert: Whatever medical conditions.
- Kevin Walsh: They've all got CD-9 codes. They've all got CD-9 codes.

- Craig Blackmore: Alright, Kevin. How are we going to fix it?
- Kevin Walsh: Well, you were concerned that we . . . that there were these microscopically small subsections of patients that we were going to exclude from having a free-T or a testosterone if we didn't make this broad enough, and I say, somebody gets lost in the wash here, and we either close the door or we leave it open, and if we close the door some people are going to get excluded, but we've not succeeded in coming up with an approach that includes every possible reasonable cause that we would want to cover, but restricts the wide open use of it because I don't feel good. So, I feel in our . . . I guess you could take the perspective that your responsibility is to the individual patient or your responsibility is to the population, and I would advocate a population approach.
- Craig Blackmore: So, what is the counter-proposal?
- Marie Brown: Eliminate that last bullet.
- Kevin Walsh: We don't cover it. Symptoms of secondary hypogonadism are not covered.
- Craig Blackmore: OK. So, can you take that bullet point and make it a different color for us, please, and then we can.
- Seth Schwartz: And one more question. Was . . . I think we heard reference to a cluster analysis looking at different symptom complexes and their stratifying risk of actually having this condition. Was that part of the Hayes Report, or was that just an independent paper that was . . . you mentioned for us, do you know?
- Alvin Matsumoto: European male aging study. It is . . .
- Steve Hammond: It's page 38.
- Seth Schwartz: Can we look at that in terms of, I mean, if we're . . .
- Alvin Matsumoto: Yeah. I'm not sure that's going to help, because they're going to be . . . it's going to be nonspecific. You're going to . . .
- Seth Schwartz: OK.
- Alvin Matsumoto: . . . have sexual symptoms in people that don't, you know, have hypogonadism.
- Joann Elmore: Right.
- Alvin Matsumoto: Just because it clusters doesn't mean that it's in the diagnosis.
- Joann Elmore: Yeah. It's still low sensitivity and specificity. It doesn't show us if the . . .
- Alvin Matsumoto: Yeah, it doesn't help.

- Joann Elmore: . . . treatment helps these people.
- Alvin Matsumoto: It doesn't help. You know, it is going to . . . the interesting . . . population approach is a very interesting approach, because that's . . . when I review athletes that want to try to get testosterone treatment, the U.S. Anti-Doping Agency and the World Anti-Doping Agency take a very restrictive view of the diagnosis, and they only restrict to organic . . . the first three bullet points, individuals with organic hypogonadism, because there are ways, if you over-train or under-eat, to actually lower your testosterone so that when you get tested you are . . . you look like you're hypogonadal, OK? So, that was the rationale. So, the restrictive version of this is . . . I don't actually support in clinical practice. I do support it in terms of restricting athletes that might actually abuse the process, but again, it just raised the point, in my mind just now, is that, you know, we have a lot of abuse going on here, you know, in the community, and maybe it's very analogous, and if you'd take this restriction, maybe it will help, but unfortunately, it will also be harmful to some segment of the population.
- Marie Brown: Can you think of a patient situation where if we didn't have the red bullet you would truly be limited?
- Alvin Matsumoto: Yeah. There are people that have symptoms that don't have a recognized condition because they didn't get a T-test, and then you didn't work them up. So, it's a double-edged sword is that, you know, the low-T might actually, actually lead to a diagnosis that would be a medical condition.
- Richard Phillips: Yeah, it's sort of a recursive part of the diagnosis.
- Alvin Matsumoto: Yeah. So, restricting tests, I think, my personal opinion, and this is a personal opinion, and it's not evidence based, I guess, if you want to call it that, is that the testing part of it is the least of the problem. It's the treatment part that is the problem, and I keep saying this. You look at the cost of the test versus the cost of the treatment.
- David McCulloch: Yeah, we get that.
- Chris Standaert: Yeah, I don't think we disagree with you.
- Alvin Matsumoto: So, that's why I'm saying, being restrictive on the testing part is not where you're going to keep the low-T clinics . . .
- Craig Blackmore: The charge of this committee is to deal with the testing.
- Alvin Matsumoto: I realize that, but OK, so then be not restrictive and then work on the, I guess it's not your committee, but . . .
- Joann Elmore: Our task today is the testing.

- Chris Standaert: Yeah, that's all we get.
- Joann Elmore: Let's get back to our conditions.
- Alvin Matsumoto: Well, then I, well then I, you know, I, I don't have a vote but, I, I guess I'm saying the, the testing should be less restrictive then, because you're not going to be able to, you're not going to be able to restrict this, I don't think.
- Craig Blackmore: So, David.
- David McCulloch: I would just say another approach would be to leave the first three black bullets, as is, and just say, you know, in the absence of that they have to, you have to ask on a case-by-case basis. That way . . .
- Joann Elmore: I don't think we even need to say that. I think it . . .
- Craig Blackmore: Mm . . .
- Joann Elmore: . . . isn't it known that they have to ask for . . .
- Seth Schwartz: We're getting a face from the agencies.
- Steve Hammond: Well, if I can comment.
- Craig Blackmore: Please.
- Steve Hammond: Yeah, I, I mean, I struggled with the same question you're struggling with and I thought it might be better to take the more positive approach that it's covered when there are clinical findings that are well correlated with HPT axis pathology. Trying to take a more positive rather than a negative approach, because I, I share Dr. Matsumoto's concern that if you could not test strictly based on symptoms, somebody who had significant sexual dysfunction might not get tested, and that's the, sometimes, the first clue that you've got serious pituitary pathology going on. So, in any case, I, I share your struggle but there . . . I think there is a different tack, which is to try to take the . . . you have to have some other clinical findings other than nonspecific symptoms that are well correlated with the classic hypogonadism syndromes, so.
- Kevin Walsh: So, but how does, how does including sexual dysfunction as a covered symptom . . .
- Steve Hammond: Well, there could be different . . .
- Kevin Walsh: . . . prevent, prevent everybody who's watched the low-T commercial from coming in. How does it do that?
- Steve Hammond: You could accept that, that it was over-inclusive. It still, in studies, sexual dysfunction is not often volunteered as a symptom that leads to this diagnosis

of late onset hypogonadism. So, you could accept that there might be some over-inclusion and still evaluate that or you can try to define, more precisely, what is sexual dysfunction, such as in the European male aging study, which, but there would be different . . . that would be a possibility.

Craig Blackmore: So, what you're saying is . . .

Steve Hammond: And that was things like no spontaneous erection, what, for the past month.

Craig Blackmore: So, if somebody comes into the low-T clinic and they say we can't test you unless you say you haven't had sufficient erections over the last month, you know, isn't that true so that I can get the test and, you know, suddenly every, every guy who walks in has got . . .

Steve Hammond: So, there's not going to be . . .

Craig Blackmore: . . . decreased sexual function.

Steve Hammond: . . . a 100% effective screen, but I think this can help in setting a signal. I agree, we need to also look at criteria for covering the prescriptions. That would be the responsibility of the state P&T Committee, but I think it has potential value in coming up with a decision that . . .

Craig Blackmore: So, what's on the table, or one consideration that the committee has mentioned, is having a defined list of criteria, as we see here, when testing would be covered, and then allowing for additional . . . for testing in additional individuals who are able to convince the agency medical directors that they have more than a little bit of fatigue and they're not 20 anymore. So, our question to you is, would you be able to operationalize if we had, as a fourth bullet point, not the red one, something along the lines of testing purely for symptoms or testing for symptoms in the absence of the above is only allowed following agency approval.

Group: Yep, mm-hmm, yes.

Craig Blackmore: So, how would that resonate with the agencies?

Charissa Fotinos: This is Charissa Fotinos from the Health Care Authority. The only way that we could do that would be to have this test require prior authorization, which would be untenable in a lot of ways. I think our challenge . . . one could hope that by putting these out there and having people pause and think, that assumes that they read them, they would be a little bit more thoughtful in their ordering of tests. That said, it would be a challenge to do anything without PA before the test was ordered. So, at least from the Health Care Authority perspective. Lisa, would you add anything? Yeah, this would be a challenge.

Seth Schwartz: Can I just make one comment? You know, we're looking at these symptoms differentiated. So, we look at those two different studies. If there's . . . when

you include sexual dysfunction symptoms, you basically decrease the pool of people who would qualify for the test to about 30%.

Kevin Walsh: 40 times.

Seth Schwartz: 40 times. So, even that alone would drastically decrease the number of people who qualify for the test. Now again, I'm not saying that's right. I'm just saying, if we're thinking about, you know, when we think about kind of the low-T syndrome, or whatever it is, you know, there's . . . it seems like . . . it's more convincing, at least, that low testosterone is a cause of, of the syndrome if they have sexual dysfunction. If they don't it's a much, much vaguer circumstance. So, while, you know, and that's, that's a distinction we can make, you know? Sexual dysfunction symptoms. We don't have to classify it any more than that versus, you know, the other symptoms. I'm not saying it's right. I'm just saying, in terms of thinking of ways of being reasonable, yet, not just leaving it open to everybody. We know people can say, yes, I haven't had an erection in two months, fine, but I mean, at least they have to say that. At least that. . . that may be a different group of patients than the ones saying, ah, I'm just feeling a little tired. I'm feeling, you know, because those are the ones we don't want. This is a waste of time. We don't believe that this is really a cause in, in the patients who don't have anything, but maybe we can at least differentiate it slightly based on that alone.

Steve Hammond: Can we add a comment on the implementation side?

Craig Blackmore: Yeah.

Steve Hammond: There is a process called expedited prior authorization, which is not a formal review, individual case review, but lists criteria, and that is not as effective in eliminating inappropriate testing, but it does have some effect, because it's a published criterion under which a service is covered. Do you want to add to that?

Charissa Fotinos: Yeah. The idea is that for common things you would not require approval, things that are clearly supported by the evidence you would not require prior authorization, but if the condition you were ordering it for fell out of that standard list of we don't go ahead and order it at will, then you would require an authorization and what that means is that the provider ordering it is, is on their honor. It's a little bit easier to implement from a, from a drug perspective. I don't know that we do this right now for any lab tests. I don't think we do. Again, I think it would be a challenge for the same reason you said. You can just say the right word and you can order it.

Kevin Walsh: So, I'm going to make another . . . a different proposal.

Craig Blackmore: OK.

- Kevin Walsh: My proposal is that we say that we cover symptoms of sexual dysfunction and list the three things that are in the European Study.
- Alvin Matsumoto: I think the key symptom is loss of spontaneous erections not just erectile dysfunction and loss of libido. So, that's very good. I think I could go along with that.
- Teresa Rogstad: I just wanted to say on that point, there is a table in the Wu study that specifies that these types of questions they ask about sexual dysfunction and the tools they use to (inaudible).
- Craig Blackmore: Less frequent thoughts about sex. That's not exactly an objective . . .
- Teresa Rogstad: Well, no, the . . . it was defined as less than or equal to one time in the past month.
- Chris Standaert: I wonder a couple of other things here. So, this is a \$25 test, and I think for a normal doctor in their office, as soon as you start putting any of these things on there, you're going to make them think about it. They're not going to draw it all the time. They're not just going to do it routinely because they know they've got to go through this hassle. Whatever you do for these clinics that are selling testosterone, we can't stop them. We cannot create a . . . the control has to be paying for the drug, right? They'll find a way around whatever we say because they'll create something.
- Kevin Walsh: We've said that about ten times.
- Chris Standaert: Right. So, we can't regulate that group by doing this.
- Kevin Walsh: We all know that.
- Chris Standaert: So, we can make primary care doctors think and say, do we have a reason to do this, and how the, you know . . . I have no idea how the . . . how these people do this, because they're going to try and, I guess, cross-correlate billing codes with the testing code and they're going to have to put in sort of one of these . . . they're going to have to come up with this list that we're not coming up with. They're going to have to create a list of codes that match, because we don't . . . we're not doing that, but it's tricky, and I don't . . . that's where I don't . . . and then you start getting into sort of really describing symptoms of sexual dysfunction and all. It . . . they're going to have to pull that from medical records and an ICD-9 code for this sort of stuff. There's no tracking thing. It's getting very tricky to do all this and that's . . . most doctors . . . again, when you get to who you're trying to get at, which is a primary care . . . we're not going to regulate the industry doing this. We have to regulate the drug, not the test. If we're just trying to help primary care doctors or other people, primary care providers with where is this appropriate to do and appropriate to do, we sort of have it, and we say, you have to be thinking there's some other reason for this.

- You shouldn't just do this because they're tired, and we're getting at that part of the population.
- Marie Brown: In that red bullet.
- Chris Standaert: With the first points, including the red one.
- Marie Brown: Yeah.
- Chris Standaert: So, I don't know that we . . . I, I don't know how much we get for going deeper.
- David McCulloch: So, Craig, can you help us with . . . in the agency's recommendation, page 11, slide 22, they do also ask or suggest that we talk about, and if you're going to do this test at all, I mean, once you get past whatever wording of what's appropriate, it needs to be fasting. You could argue it needs to be repeated at least once, and it needs . . .
- Craig Blackmore: Yeah.
- David McCulloch: . . . to be done in a reputable lab. I mean, are we going to get to that.
- Craig Blackmore: I think we can get to that. I just, I want to try to, that I think will be easier than this and . . .
- David McCulloch: It, it may help us in terms of . . .
- Craig Blackmore: It, it may help. It may absolutely help.
- David McCulloch: . . . getting to, yep.
- Craig Blackmore: But I . . . but we still have to get past this. So, one, one thing I've heard is, if we take that red bullet and we change it instead of saying symptoms of secondary hypogonadism but saying symptoms of sexual dysfunction, which there seemed to be some semi-objective criteria around, at least as part of the European male aging study. That that might be a little more restrictive but yet still appropriate.
- David McCulloch: As a covered condition or uncovered condition?
- Craig Blackmore: Symptoms, well right, so that's all wrong isn't it? So, it would be symptoms of sexual dysfunction with a medical condition associated with hypogonadism is covered. Does that?
- Chris Standaert: But how is that different than just above. You think they have a medical condition causing the hypogonadism. How is that different from that? Whether it be . . . whatever it is.
- Craig Blackmore: So, so then we're . . . then we're saying even if you don't have a pituitary mass, if you have real sexual dysfunction defined by these things . . .

- Chris Standaert: You can do it.
- Craig Blackmore: . . . you can do it, I guess. So, the medical . . . the medical condition.
- Chris Standaert: Right.
- Craig Blackmore: I, you know, again, I'm trying to capture all the proposals and then . . .
- Alvin Matsumoto: The one thing you need to put in there is symptoms or signs because there are some people that are pretty hypogonadal on physical exam that don't have symptoms. Klinefelter's patients . . . syndrome patients, sometimes will have normal sexual function but have testes that are pea-sized and things like that. So, and have low testosterone. So, you need to include signs as well.
- Chris Standaert: (inaudible) already in there.
- Alvin Matsumoto: No, no, no, but I mean it's, OK.
- Craig Blackmore: It gets very complicated.
- Chris Standaert: This is where the parsing it gets really difficult, because we just, we're not going to be able to get everything. It's impossible. We just can't do it. So, somewhere you have to take a broad brushstroke and say yes or no.
- Craig Blackmore: So, one proposal is to stop after the word osteoporosis. The second proposal is to include men who have sort of severe symptoms or really symptoms of sexual dysfunction but not include the broad categories of, sort of, fatigue, and I don't feel like I did when I was 20. Does that resonate? So, it would be after the word osteoporosis. The next one would be symptoms or signs of sexual dysfunction. Not . . . so getting rid of the with secondary hypogonadism piece, keeping the criteria, getting rid of secondary hypogonadism. You make that a different color.
- Teresa Rogstad: You might want to make a little bit clearer that the criteria from the European male aging study (inaudible) symptoms.
- Craig Blackmore: I don't see green as visible, but, well, let's just leave it for . . . just leave it for now, please, and I want to get the committee to kind of reflect on that. Does that help? So, I need input from the committee on adding the purple bullet to . . .
- Seth Schwartz: Take away the red one.
- Craig Blackmore: Sorry?
- Seth Schwartz: Adding the purple one to the top three?

- Craig Blackmore: Adding the purple one and removing the red with the final black. So, it's the purple instead of the red and . . . where the final black bullet.
- Kevin Walsh: I think that's as good as we're going to get.
- Michelle Simon: So, are the . . . the signs aren't of sexual dysfunction, though. The signs are physical signs, aren't they, that we're looking for?
- Craig Blackmore: They are signs of hypogonadism.
- Michelle Simon: Right.
- Chris Standaert: So, gynecomastia.
- Craig Blackmore: Signs of, alright. So, it's going to be signs of hypogonadism or symptoms of sexual dysfunction.
- Marie Brown: Mm-hmm.
- Craig Blackmore: Is that . . .
- Michelle Simon: And then the criteria fits with the symptoms, too.
- Craig Blackmore: . . . and then the sexual dysfunction criteria are the European male aging study.
- Chris Standaert: What happens with, like, a category on the endocrine side you had of sort of renal disease, end-stage renal disease, and other sorts of things where they link them. They're symptomatic. They have end-stage renal disease. Do they fall into our organic cause, because they don't . . . they don't list them as quite them. They list them as . . .
- Craig Blackmore: (inaudible) fall in if they have sexual dysfunction.
- Teresa Rogstad: Those conditions were supposed to be paired with symptoms (inaudible). Not specifically sexual symptoms, but . . .
- Chris Standaert: Right, but . . .
- Teresa Rogstad: . . . classic. (inaudible)
- Chris Standaert: . . . right. So, the guideline talks about symptoms in general, not specific sexual dysfunction.
- Teresa Rogstad: Well . . .
- Chris Standaert: But it's included in the symptoms. It's included but not the only symptom.

- Teresa Rogstad: Right, but, I believe that recommendation meant symptoms that are relatively specific to hypogonadism, or signs.
- Chris Standaert: Right.
- Teresa Rogstad: Not the, I'm tired, or the (inaudible).
- Richard Phillips: We would remove the red, right?
- Craig Blackmore: So, I need, I need feedback from the committee on the purple. Is this getting to a place of comfort or not?
- Richard Phillips: I like the purple. I don't like the red. I think . . . I think we should get rid of that. I think secondary hypogonadism might be only diagnosable by getting a testosterone level, so it becomes a recursive thing, and it . . .
- Craig Blackmore: Well, it . . .
- Richard Phillips: . . . doesn't make any sense to me.
- Craig Blackmore: . . . signs of, or, secondary. So, push return about five times for me, please. Thank you. So, now you can't even see the red. It's hidden. Scroll to the top, please. Thank you. It went away. So, I need committee member feedback here, because I'm going to move on one way or the other.
- Marie Brown: It's a first step because all the low-T clinics will then suggest to men that they report symptoms of sexual dysfunction, which . . .
- Seth Schwartz: We can't deal with disingenuous people. I mean . . .
- Marie Brown: Right, right, right. So, but this is a start and it helps well-intending primary care providers.
- Craig Blackmore: And they are objective criteria. I mean, they are defined criteria, although I'm not sure less frequent thoughts about sex is terribly restrictive, but . . .
- Seth Schwartz: Less restrictive than what, less thoughts than what is the question?
- Craig Blackmore: OK . . .
- Alvin Matsumoto: Can I ask something?
- Craig Blackmore: Yes.
- Alvin Matsumoto: I'm not sure we need that bullet primary hypogonadism. I think it's now covered by the last bullet, and I don't know how we're defining primary hypogonadism without signs of hypogonadism or symptoms. I don't think it's helpful, and I think it's potentially problematic if it's not defined.

- Craig Blackmore: OK, I, any, any objection to getting rid of that?
- Seth Schwartz: So, then do we get rid of the term secondary and just, I mean, in other words, if you're getting rid of that, to say secondary without primary doesn't make a lot of sense. So, we're just saying suspected hypogonadism with organic cause?
- Chris Standaert: In somebody with primary hypogonadism who's on testosterone. I mean, they have, they have the disease. You diagnosed them with the disease, and they're on testosterone. They don't have signs or symptoms. They have the disease and you're not going to test them?
- Craig Blackmore: So, that gets at the whole question of repeat testing, which we haven't discussed.
- Chris Standaert: Yeah, we just talked about testing. When would you do this test in general? I would think if you had somebody who has a known diagnosis absent testes, you're going to draw their testosterone (inaudible).
- Craig Blackmore: OK. So, we . . .
- Chris Standaert: Even if they're . . . even if they seem (inaudible).
- Craig Blackmore: Do we wish . . .
- Chris Standaert: . . . so I don't know if I'd take that out.
- Craig Blackmore: . . . do we wish to restrict repeat testing. It's come up a few times, or do we wish to not try to place any restrictions on repeat testing. OK. So, then we could add a bullet point that says documented hypotestosterone or something as a criterion for testing.
- Marie Brown: Wouldn't primary hypogonadism be better than documented (inaudible).
- Chris Standaert: I guess . . . I think I would leave it too. I think you're just getting to the . . . we're trying to help doctors know when to do it or not do it. I guess I don't know . . . that seems the primary reason for testing it.
- Craig Blackmore: Yeah.
- Chris Standaert: So, I would leave the word in. I don't think I would take the word out and put primary hypogonadism. That seems the most obvious reason to do it.
- Marie Brown: Right.
- Michelle Simon: I think if we . . . if we're concerned about safety, at least one of these studies showed that some of the folks were getting an awful lot of testosterone. That

may have been one of the safety issues. So, if you're not testing at all, you won't know that if they're on testosterone.

Alvin Matsumoto: So, you could put suspected primary hypogonadism, as well, because there are some people that would come in with a history of mumps and small testes on exam. They haven't had a testosterone level.

Chris Standaert: Isn't that sec- . . . is that secondary hypogonadism or primary?

Alvin Matsumoto: No, it's primary.

Marie Brown: No, it's primary.

Chris Standaert: It's not secondary to mumps? It's not counted as (inaudible).

Alvin Matsumoto: No. Primary means there's a problem in the testes. Secondary means there's a problem in the pituitary or the hypothalamus.

Chris Standaert: Oh, got you.

Craig Blackmore: Suspected, yeah. That's fine.

Chris Standaert: Suspected or known primary hypogonadism. Or known (inaudible).

David McCulloch: The problem with that, I mean, suspected primary hypogonadism is the low-T clinic. You think you're just tired, but I think you may have primary hypogonadism. We need to test you.

Chris Standaert: Right.

David McCulloch: Ask your doctor.

Chris Standaert: And that's going to be the code they click on their box.

Joann Elmore: Do we need to add congenital abnormalities, destructive orchitis, trauma, I mean, do we need to specify?

Alvin Matsumoto: Well, you could say organic cause.

Craig Blackmore: Does organic have a meaning for . . .

Joann Elmore: I think it does. I think we need to specify . . .

Craig Blackmore: . . . billing codes.

Joann Elmore: . . . if we go there.

Alvin Matsumoto: Well, if you want to specify all the organic causes, that's fine.

- Craig Blackmore: I don't want to specify all the . . .
- Alvin Matsumoto: Or you could specify the . . .
- Craig Blackmore: . . . organic causes.
- Alvin Matsumoto: . . . fact that it has to be a, you know, structural destructive, you know, all of that as a general thing.
- Joann Elmore: So, congenital or destructive?
- Craig Blackmore: Destructive?
- Alvin Matsumoto: I don't think you (inaudible).
- Marie Brown: Organic has four subcategories that you can . . .
- Alvin Matsumoto: But, yeah.
- Marie Brown: Which is easier than all the conditions.
- Richard Phillips: Does primary hypogonadism occur very often in men over age 50?
- Alvin Matsumoto: It's much less frequent than secondary. Secondary is much more common.
- Craig Blackmore: So, when . . . when they talk about low-T, that's, it's theoretically a primary or a secondary?
- Alvin Matsumoto: No, second . . . it's usually a low, a low normal or normal testosterone in the presence of a normal LH and FSH . . . normal gonadotropin level. So, it would be classified as secondary hypogonadism. That's what most people are being diagnosed at low-T clinics. It's not a primary.
- Craig Blackmore: So, if we say suspected primary, then that . . .
- David McCulloch: But if the LH and FSH are normal, it's not secondary either. That's just BS.
- Alvin Matsumoto: That's correct. Well, no, it could be normal. That's what I'm saying, but the argument is made there that the T is low for his age or his particular . . .
- David McCulloch: When, in fact, it's usually telling you that's not true. The pituitary is quite happy with that testosterone.
- Alvin Matsumoto: Yeah, but the same thing could happen if you really did have a pituitary problem. It would be low normal, inappropriately normal for the level of testosterone, and that's what people are saying. I'm not justifying this. I'm just saying . . .

- Seth Schwartz: I don't think . . . I think we're too far in the weeds here because as has been said 50 times, we're not going to control the use of testosterone by limiting this. So, I think we're good where we are now.
- Craig Blackmore: With suspected primary hypogonadism?
- Chris Standaert: Can you put suspected or known?
- Joann Elmore: Yeah, suspected or known.
- Chris Standaert: Suspected or known primary hypogonadism.
- Craig Blackmore: OK. I'm going to move . . .
- Marie Brown: Just, well why do we even need if suspected or known? What about just primary?
- Chris Standaert: That's where we started.
- Marie Brown: Yeah.
- Chris Standaert: That's what we had.
- Marie Brown: I know.
- Craig Blackmore: Because then . . .
- Seth Schwartz: That seems fine.
- Craig Blackmore: . . . what if, what if you don't . . . what if you don't know they have it, but you, I don't know.
- Charissa Fotinos: Mr. Chair?
- Craig Blackmore: Yes.
- Charissa Fotinos: This reminded, brought to my attention that we have just included surgical coverage and medical coverage treatment for people who were transitioning, transgender persons, and so maybe our clinical expert could help us in figuring out a way to phrase that. We don't want to limit testing in people who are transitioning when it's appropriate. Not quite sure how we'd say that, but we don't want to get in the way of that.
- Joann Elmore: That's why we wanted to add that final bullet point.

- Seth Schwartz: Could that be an exclusion criteria? You know, when someone's talking exclusion . . .
- Craig Blackmore: Well, you know . . .
- Seth Schwartz: . . . I mean, we need to talk about exclusions. I think that's, you know, that's not what we're talking about.
- Chris Standaert: I mean, that's what that last, yeah. I mean that last . . .
- Seth Schwartz: I mean that's a . . . that's going to be a small subpopulation.
- Marie Brown: Very small.
- Charissa Fotinos: It's very tiny, but it's also (inaudible).
- Craig Blackmore: Yeah, you don't want to do anything inappropriate for a small group.
- Seth Schwartz: No, but don't . . . when we make our recommendations, don't we also talk about exclusion criterion to whom this doesn't apply? We don't have that?
- Chris Standaert: It's adult . . . it's adult males.
- Marie Brown: Well, I mean, we could add it, though.
- Alvin Matsumoto: Yeah, you could add it as for management of transgender treatment.
- Charissa Fotinos: Yeah, this does not apply to management of transgender, yeah. That would, that would be fine. If you're OK . . . if that's acceptable that would, that would help us.
- Craig Blackmore: OK.
- Charissa Fotinos: Thank you.
- Craig Blackmore: OK. I want to move on . . . I want to move on to this other issue of labs.
- Joann Elmore: Can I make one more clarification, though, we talk about symptoms of sexual dysfunction, but the paper requires three positive responses to the sexual, not just any vague one symptom. Wasn't it . . .
- Craig Blackmore: So, that's . . .
- Joann Elmore: . . . wasn't it you had to have all three. So, I . . .
- Kevin Walsh: But it says criteria. We could just put in all three.

- Joann Elmore: Yeah. I just want to make certain that when you type this up that it is not just any vague symptom. It is, they have to have all three of these.
- Craig Blackmore: So, it's all three (inaudible).
- Joann Elmore: All three.
- Craig Blackmore: So, that is restrictive.
- Joann Elmore: Mm-hmm.
- Christine Masters: All three symptoms of sexual . . .
- Joann Elmore: In the Wu, et al.
- Richard Phillips: All three criteria from the (inaudible).
- Marie Brown: Under, in the params, all three criteria from the . . .
- Joann Elmore: Or, all three . . .
- Marie Brown: Three symptoms.
- Joann Elmore: . . . three sexual symptoms.
- Christine Masters: (inaudible)
- Craig Blackmore: OK. Let's leave it like that for now and any other comments from the committee? OK. So, now, uh, on the line after European male aging and above the line that says this does not apply, there has been discussion of how we might talk about the testing itself, and I think we have to be a little careful with this, because our job is not to credential labs, and we're not experts on calibrating tests, but I think we can maybe say a few things that are within our scope that might be useful here. Does somebody want to start us off on what that might look like? Joann?
- Joann Elmore: Well, I'm actually starting to think we should step back, because the labs are not ready to do this, but I would want our committee to make a request that the medical director send a letter out to every single lab in our state saying that within two years, if you have not developed a method for quality assessment, assurance, and age appropriate standards, in two years we're going to review this and we will not fund potentially.
- Craig Blackmore: Yeah. So, we're not in the business of credentialing labs, so . . .
- Joann Elmore: Right, we (inaudible).

- Craig Blackmore: . . . we're not going to have them send letters telling labs how to be credentialed.
- Joann Elmore: Well, but in two years, we would . . .
- Craig Blackmore: We will still not be in charge with credentialing labs. Our job is to determine coverage.
- Joann Elmore: Right.
- Craig Blackmore: And not to develop quality standards, but if there's a way that . . . making sure the testing is done appropriately, we can keep . . . phrase that within our charge, then we can do it.
- Joann Elmore: Is there any way to ask for reporting of information on age standardized results?
- Craig Blackmore: Well, I'm not sure that information exists, and could we ask for that? Can we say testing is covered, I mean, we, we could, I think, say testing is only covered in labs that are accredited or qualified based on some criteria set by whatever the agency medical directors use, and they could rely on some other third party like, you know, society guideline or whatever, and we could say it has to be an accredited lab, but we can't define what the accreditation criteria are, because that's not our deal.
- Chris Standaert: And even then, I mean, if we go on the data we got, we don't, we don't talk about labs. We don't talk about lab types. We don't talk about accredited or non-accredited.
- Marie Brown: That's true.
- Chris Standaert: I have no idea what that means. We don't talk about . . . the only things we ever even remotely saw is that it should be done in the morning between 8:00 and 10:00. How good that data is, I don't know, and then if you have one low result, you should certainly repeat that before you initiate any test, any treatment, but again, we're not talking about . . .
- Kevin Walsh: I would be happy if we could include those two caveats.
- Craig Blackmore: Which are?
- Chris Standaert: So, that it . . .
- Kevin Walsh: Test . . . testing twice before you make a diagnosis, and testing before . . .
- Craig Blackmore: We can't . . . we can't say that. We can say we're going to pay for it or not, but we can't say you have to do it twice to treat.
- Chris Standaert: What I was talking about . . .

- Craig Blackmore: Our job is to figure out who's allowed to get a test, not how the information from the test is used. That's not within our prerogative.
- Richard Phillips: In other words, somebody could start treatment without even testing.
- Chris Standaert: Yeah, we don't . . .
- Richard Phillips: We can't do anything about it.
- Craig Blackmore: We don't have any control over that. We just have control over what test gets paid for.
- Michelle Simon: But we could cover a morning test, fasting test, between 8:00 and 10:00.
- Craig Blackmore: We, we could say that. We could say it's only covered if it's a fasting test between 8:00 and 10:00 in the morning.
- Marie Brown: I'm not sure that's going to help though.
- Craig Blackmore: I don't know if it's going to help, and I don't know if we have evidence to drive it.
- Joann Elmore: Does it say fasting or just 8:00 to 10:00?
- Alvin Matsumoto: It doesn't have to . . .
- Kevin Walsh: It doesn't have to be fasting?
- Craig Blackmore: I don't . . . I don't . . .
- Chris Standaert: And does that apply . . .
- Alvin Matsumoto: There's two studies on fasting versus non-fasting. Food or glucose load lowers total testosterone level.
- Joann Elmore: OK. So, they want it (inaudible).
- Alvin Matsumoto: But, there's only two studies, very small studies.
- Marie Brown: Yeah.
- Alvin Matsumoto: I, I think you have to pick your battle.
- Marie Brown: Right.
- Alvin Matsumoto: I think the most . . . the most . . . the biggest reason for biological variability is day-to-day variability. So, the testing twice is much more important than in fact

even doing it in the morning or doing it fasting or fed, you know? It's really . . . the driver of the variability is the fact that it bounces around a lot, and so you do need to have two tests in order to make the (inaudible).

Chris Standaert: Right.

Craig Blackmore: I believe that, but I can't (inaudible).

Chris Standaert: Right. We can't . . .

Alvin Matsumoto: No, I realize that, but you can't . . .

Chris Standaert: say that.

Alvin Matsumoto: . . . what I'm saying is that, don't put something in there on fasting because I think the data are slim.

Craig Blackmore: Not worth it.

Chris Standaert: Right. Even the morning . . .

Alvin Matsumoto: It's not . . .

Chris Standaert: . . . what do you . . .

Alvin Matsumoto: . . . not worth fighting . . .

Chris Standaert: . . . people work at night.

Alvin Matsumoto: . . . that battle.

Chris Standaert: People who don't live, I mean, it's just, you know.

Teresa Rogstad: And the society is taking that on. So, maybe this is a little premature for us to do and just let the society take on the testing issues.

Craig Blackmore: Thoughts? David? David and Joann, do you guys have any more comments to share with the group or not?

David McCulloch: I'm just depressed.

Chris Standaert: He's just depressed.

David McCulloch: (inaudible) rational evidence-based changes. I mean, so, I'm, I'm hearing that we can't require two test and requiring it 8:00 to 10:00 doesn't make a lot of difference either.

Joann Elmore: Well, is that true or not true?

- Alvin Matsumoto: No. It makes a difference. I'm just saying it's relative to the biological variability day-to-day (inaudible).
- Joann Elmore: We get that, but we cannot vote that we require two tests. We can only vote about . . .
- Craig Blackmore: Can't vote for it.
- Joann Elmore: . . . a single, you know . . .
- Craig Blackmore: I, I . . .
- Joann Elmore: . . . whatever they are testing. So, should we add a requirement . . .
- Alvin Matsumoto: Preferably in the morning.
- Joann Elmore: . . . that it should be in the morning?
- Alvin Matsumoto: That is the preferably is the . . . is the . . . you know, if you're in clinic in the afternoon and you have to have a patient come back in the morning, I personally don't think that's a big deal, but a lot of practitioners feel that that's onerous.
- Chris Standaert: And what do you . . . so is that test done on people who work nights, right? So, they're flipped. Their, their . . .
- Alvin Matsumoto: Well . . .
- Chris Standaert: . . . morning is, they sleep all day . . .
- Alvin Matsumoto: No, no. This is based on the fact that there is a diurnal variation in testosterone.
- Chris Standaert: Right. Does it have to do with sleep patterns? Does it have to do with daylight? No, that's what . . . I'm saying stay out of the weeds. You're saying stop it. I'm . . .
- Alvin Matsumoto: It has to do . . .
- Chris Standaert: . . . saying stay out of the weeds.
- Kevin Walsh: We can't cover everything.
- Alvin Matsumoto: . . . yeah, you can't, yeah.
- Chris Standaert: I'm not saying that, but I'm just saying, we're going into territory where . . .
- Joann Elmore: He's trying to limit it . . .

- Chris Standaert: . . . we don't have the data.
- Joann Elmore: . . . to just morning.
- Alvin Matsumoto: Yeah. Yeah. Yeah.
- Chris Standaert: We just don't have it.
- Marie Brown: Stay out of the weeds.
- Craig Blackmore: I don't, I mean, it sounds good, but, you know, somebody who has a clear issue comes in, in the afternoon, you know, saying you have HIV and you have . . . you've been losing all this weight, and I'm really worried about you, but come back tomorrow, you know, when you're not looking for some . . . somebody on the edge of the normal curve. You're looking for, you know, somebody who's, who's way down. I don't know that that would be appropriate.
- Seth Schwartz: Those sound like the criteria for treatment.
- Craig Blackmore: Well, I think the problem is, we want to address the criteria for treatment, but that's out of our scope.
- David McCulloch: Yes, we do.
- Chris Standaert: Yes, we do.
- Craig Blackmore: OK.
- Kevin Walsh: Then, then let's . . . I would say scratch this bullet altogether.
- Craig Blackmore: Yeah.
- Joann Elmore: Yep.
- Marie Brown: Yeah.
- Chris Standaert: That's where I was going. I wasn't try to (inaudible) cover people who were nocturnal individuals.
- Craig Blackmore: Alright, anymore thoughts? Have we done the best we can here?
- Alvin Matsumoto: Can I suggest that that last point really is . . . should be cast as a condition of coverage and just say . . . take out the this does not apply and just say for management of transgender treatment and add that as another condition of coverage.

- Craig Blackmore: Alright, and then I'll have you erase everything below the management of transgender treatment bullet, and then if you could please save, and then again, I want to ask the committee members if they have any further thoughts on this.
- Richard Phillips: I have a question in terms of our . . . the purpose here. Is, is there going to be a separate pharmacology assessment of the treatment, the use of it? It seems to me we're not really accomplishing anything by what we've done here.
- Craig Blackmore: No. Now, we're accomplishing a lot.
- Richard Phillips: We are?
- Craig Blackmore: We're not accomplishing everything we want to accomplish, but this is . . .
- Richard Phillips: I mean, I'm not talking about . . .
- Craig Blackmore: . . . productive process.
- Richard Phillips: . . . I'm talking about substantive.
- Craig Blackmore: We're . . . well, what we're accomplishing is substantive.
- Alvin Matsumoto: I think it's likely that treatment will be referred to the state P&T committee.
- Richard Phillips: Oh, good.
- Joann Elmore: You just accomplished something.
- Alvin Matsumoto: So, is coverage for monitoring of therapy going to be eliminated, then, is that correct?
- Craig Blackmore: No.
- Joann Elmore: Well, hopefully if they're on therapy they have some of these signs or symptoms that we've delineated.
- Alvin Matsumoto: Well, hopefully if they're on adequate therapy they won't have them anymore.
- Joann Elmore: I think we've had a history of it.
- Alvin Matsumoto: But, OK. So, that's covered in this. It would be covered?
- Joann Elmore: One would hope. I would not want to cover just because they're on testosterone, because who knows why they got on the testosterone.
- Seth Schwartz: But that goes to Michelle's point, which is that one of our biggest safety concerns is over-treatment and if you're saying, well, we're worried that you

- may be over-treated but we're not going to let you test for it, that . . . that doesn't seem right.
- Craig Blackmore: Yeah, I didn't see a lot of . . .
- Joann Elmore: I didn't say that. I just said that hopefully they have had one of these before they got on the testosterone in the beginning.
- Seth Schwartz: But maybe they . . . maybe they did and they don't have it anymore because they're on treatment.
- Marie Brown: Symptom free.
- Seth Schwartz: So, I mean, again . . .
- Kevin Walsh: Their insurance doesn't pay for the . . . for the testosterone in the first place. So, if they can afford to buy the testosterone, they can afford to pay for the test.
- Craig Blackmore: OK, but I mean, there's . . . there's . . . we should be clear on this, because somebody who has a pituitary tumor. Well, no, that's not a good example. Somebody who has, you know, true hypogonadism and then gets treatment, do we want to allow a repeat test.
- Joann Elmore: I didn't see a review of evidence. I don't think there was evidence on it.
- Craig Blackmore: Right. I didn't see evidence. I didn't hear concern from the agency directors, but I could see interpretation of what we have here as not allowing that, and so if you're treated to the point where you become asymptomatic, you would not be . . . you would not fit these criteria.
- Chris Standaert: Well, if you have, if you have known or secondary hypogonadism . . . if you have a diagnosis you should be covered, right? So, if you have a secondary or primary hypogonadism, you should be covered.
- Seth Schwartz: Established diagnosis of secondary hypogonadism.
- Chris Standaert: Yeah. We said known primary. So, we could say known or suspected secondary hypogonadism.
- Marie Brown: Right.
- Chris Standaert: We could use the same language.
- Joann Elmore: It's the same language, and then it's covered.
- Chris Standaert: And then anybody who has a reason for being on testosterone covered. If he doesn't have a reason, it's not covered, because he probably shouldn't be on it in the first place.

- David McCulloch: Well, you need to specify, yeah.
- Michelle Simon: Suspected or known secondary . . .
- David McCulloch: Monitor . . . monitoring for people on testosterone treatment for sensible reasons.
- Kevin Walsh: But we didn't say you only get a single test. It says we'll pay for the test. So, we've covered that by definition. We didn't restrict it to one test.
- Joann Elmore: Right.
- Kevin Walsh: So, we don't have to come up with caveats.
- Joann Elmore: Well, adding the known was important, because it could be known suprasellar tumor, they're on treatment, so now it's not just suspected. It's known. Now, they can do the monitoring. So, that was helpful.
- Craig Blackmore: Alright. Well, so how about signs of or known hypogonadism? Nah, that's nobody there.
- Seth Schwartz: I mean, I guess the underlying question is, does anyone object to monitoring, I mean, to using this test for monitoring? Are we worried that that's . . . that the test is being . . . I think, particularly getting to the earlier concern, if we're concerned about treatment, we're really not concerned about . . . I mean, the ultimate concern is that people are being over-treated for this condition. If they're already treated, we're not going to impact it. The only thing we're going to do is, if we . . . if we monitor them for treatment, we might stop them being treated or decrease their treatment or decrease the risks of treatment by monitoring. So, I'm trying to . . . and, while there's not a lot of vagueness, I could see how someone could say it's not clearly covered, that it's OK to monitor. So, if we don't object to monitoring, I don't see why we don't just explicitly state that. It seems like that's actually a real potential quality improvement that we're offering here.
- Craig Blackmore: OK. So, let's add above maybe management of transgender treatment, monitoring of testosterone therapy.
- David McCulloch: No matter why we started in the first place.
- Joann Elmore: No. I would want to say for appropriate . . .
- Craig Blackmore: Oh, come on. I mean . . .
- David McCulloch: I think we're . . .
- Craig Blackmore: I'm not saying that.

Kevin Walsh: It's a drop in the bucket.

Joann Elmore: OK.

David McCulloch: I don't like it.

Charissa Fotinos: This is Charissa Fotinos. May I ask for an amendment that would help in the implementation of this and that is, between the first two bullets, adult males and suspected and then or so that it . . . it doesn't imply that it's all of those but . . . so adult males and . . .

Craig Blackmore: Yeah. So, we can remove the word adult . . . the words adult males because . . .

Charissa Fotinos: OK.

Craig Blackmore: . . . we are only . . . the scope of the decision only applies to adult males. So, we don't have to have that on there.

Marie Brown: Great. So, we could just put or.

Craig Blackmore: It's not in the title. OK. I'm sorry. Maybe it's not.

Joann Elmore: It's two words. Can we just . . .

Craig Blackmore: OK.

Joann Elmore: We need to add the or . . .

Chris Standaert: Adult males . . .

Joann Elmore: . . . with suspected or . . .

Chris Standaert: . . . with any of the following.

Joann Elmore: . . . known primary hypogonadism or . . .

Craig Blackmore: Yes. OK. So, what Chris just said.

Chris Standaert: Adult males with any of the following.

Craig Blackmore: Colon.

Charissa Fotinos: That's fine, too, yes, just something that helps.

Craig Blackmore: Yeah, that's great.

Chris Standaert: And do we have to . . .

Richard Phillips: Is a transgender a male?

Charissa Fotinos: Uh, that would be an or.

Craig Blackmore: No, we can't say that either, because now we're saying females don't get covered.

Seth Schwartz: I think we just have it the way it was . . .

Chris Standaert: So, do . . .

Seth Schwartz: . . . before, which is, does not apply to (inaudible).

Chris Standaert: . . . so we, we could put . . . this is what we could do. We could (inaudible) this decision does not apply to females, transgender individuals, or males under age 18, because we didn't address them and just say that. So, get rid of the management of transgender, because you're right. It makes no sense in males, so.

Marie Brown: That works. And persons . . .

Craig Blackmore: Persons.

Marie Brown: . . . persons undergoing?

Kevin Walsh: Persons undergoing, yeah.

Chris Standaert: Transgender individuals.

Marie Brown: Transgender persons.

Chris Standaert: And transgender persons, yeah. Whatever the . . .

Michelle Simon: I think it's an or.

Charissa Fotinos: Thank you.

Michelle Simon: I think that's an or transgender, right?

Craig Blackmore: Alright. So, any other comments.

Richard Phillips: That's a good evidence-based decision.

Craig Blackmore: There you go. Dr. Matsumoto is going to think we're all crazy but, this is what we have to go through in an attempt to make sure that the words that we put on the paper actually reflect what the committee's intentions are.

- Alvin Matsumoto: Is this reviewed every once in a while?
- Craig Blackmore: It is reviewed. There is . . . part of the process, there is the opportunity for re-review when new evidence becomes available.
- Alvin Matsumoto: Well, I'll just tell you, within this year, there will be a randomized control trial of older individuals above the age of 65 that have signs and symptoms.
- Craig Blackmore: OK, and if that . . . again, there's a formal way that there's consideration for re-review and we're . . .
- Alvin Matsumoto: I'm not sure it's going to help you.
- Craig Blackmore: We'll see. So, what are we doing? Why did we add the word or?
- Chris Standaert: We added the word or so that any of the following.
- Craig Blackmore: OK. Can you save that for us, please? No, get rid of the adult males with any of the following.
- Seth Schwartz: The, the bullet for pituitary should probably say more than just pituitary.
- Chris Standaert: Disorder?
- Michelle Simon: Macroadenoma or something.
- Craig Blackmore: Mass.
- Marie Brown: Disorders?
- Michelle Simon: Or dysfunction.
- Chris Standaert: Pituitary dysfunction, disorder?
- Craig Blackmore: OK. Can you get rid of adult males with any of the following from the top, please?
- Richard Phillips: Now, that, for example up there, the organic causes e.g., I mean, those are just 5 examples. That's not all inclusive at all.
- Craig Blackmore: Correct.
- Richard Phillips: Because we did not put in, you know, radiation therapy and stuff like that, so.
- Craig Blackmore: And then yes. OK. Any other comments? Alright. Well, I think we should proceed. Shall we proceed? We will turn to our decision tool, which is green, I think. No, it isn't green. Where is it? It's in front of the green. OK. So, to the back, just before the final tab in the binder is the decision tool that we use,

which is the HTCC coverage and reimbursement determination analytic tool, and this is a document that summarizes the decision making process that the committee has been going through. It recognizes that we're making a decision based on the best available evidence, even though there may be uncertainty that still exists, and this document also delineates the outcomes that the committee felt were important, and this has been . . . this table has been prepopulated by staff with various outcomes. So, we should look at this and determine if there are other outcomes for safety, efficacy, effectiveness, or special populations or costs that the committee felt were important in decision making and we should put them in here, and so I guess one thing that we were cognizant of was the reliability of the test, which definitely factored into our discussion and were there other outcomes that we were concerned about? Maybe not.

Chris Standaert: I think the outcomes of concern arise from the treatment not the test. So, the safety issues are the treatment.

Craig Blackmore: Yeah, yeah. Treatment-related harms, over-treatment, the test itself was fairly innocuous. OK. Then, we have a listing of CNS coverage decisions, which there are none, and we have some guidelines from professional societies, some of which we've definitely included, and we saw on the slides in the presentation what other insurers do, at least . . .

Josh Morse: Craig?

Craig Blackmore: Yes?

Josh Morse: You did consider, under special populations, we did not include transgender, but you did?

Craig Blackmore: That was another special population, yes, and so that brings us to the first voting question, and so these will be the tan cards, and the first voting question is, is there sufficient evidence under some or all situations that the technology is effective, safe, and cost effective. So, first on effectiveness, and you should vote yes if you believe there is evidence that testing, under any circumstance on any population, is effective in terms of outcome.

Joann Elmore: Any?

Craig Blackmore: In any.

Joann Elmore: Any. Wait, less, more in any.

Craig Blackmore: Is there . . . so the question is, is there sufficient evidence under some or all situations? So, under some would apply here. If you think there is at least one situation where the testing . . . where there's evidence the testing improves outcome, you should vote more.

Michelle Simon: OK.

David McCulloch: As opposed to not testing at all.

Craig Blackmore: As opposed to not testing.

Josh Morse: Seven more, two unproven.

Joann Elmore: We didn't actually get to see any data, but it kind of makes common sense.

Craig Blackmore: And then safety, and again, this is a little tricky, but is . . . safety.

David McCulloch: This is only about not the downstream effect.

Craig Blackmore: Not the downstream effects.

David McCulloch: Is it actually unsafe to stick a needle in somebody's arm and put it to luck, no.

Craig Blackmore: But then you have to go to the comparison, and the comparison is to not doing the test, and so, how, you know, is it more, is it less safe? Is it safer, so, equivalent or unproven?

Josh Morse: Seven unproven, one more, one equivalent.

Craig Blackmore: OK, and then cost-effective.

Josh Morse: Nine unproven.

Craig Blackmore: Further discussion based on the preliminary vote? OK, then we will move forward to the pink cards, and they . . . this is the binding vote now, and you have three choices, and the first choice is that the testosterone testing will not be covered under any situations for any patients. The second choice is that it will be covered without condition for all patients, and the third choice is that it will be covered only under certain conditions, and the conditions are those before you, which I assume we've saved recently. So, those are your choices, so.

David McCulloch: Can we not have a fourth card, covered reluctantly because we don't (inaudible) no? Maybe not. OK.

Chris Standaert: Cover reluctantly. What a great card.

Josh Morse: Nine cover with conditions.

Chris Standaert: Cover with reservations.

Joann Elmore: Disappointment with the other ones.

- Kevin Walsh: Grudgingly cover.
- Craig Blackmore: What would we do if the evidence didn't disappoint us once? Where would we be? Alright, so is this determination consistent with identified Medicare decisions, and there is no Medicare decisions, with expert guidelines, and it . . . there's a lot of similarity to the expert guidelines, though we interpret the evidence and maybe didn't agree exactly. Let's see, and then the next step is at the next public meeting we will review the draft findings and decision and come to a final decision, and there's an opportunity for public comments, particularly if there's evidence that was overlooked in the process, and the other question we'll be asking when we finalize next week is, does what's on the document actually reflect what we had intended in our discussion, and that completes testosterone testing. Next on the agenda is boxed lunches, which we can grab and then do you want to just tell us where we are on tympanostomy?
- Josh Morse: So, at this point we can give you an update on where we are with various projects, and we should have the key questions for the tympanostomy tubes review, which is currently in a public comment phase. We have the draft key questions. If you can review those during lunch, or if you have any feedback on that, now is a good opportunity.
- Craig Blackmore: So, can we put those on the screen?
- Josh Morse: Yes.
- Craig Blackmore: OK, so I'm going to ask the committee members to grab their lunches real quick, and then we'll spend about 15 minutes trying to fine tune the key questions for the next one, and then we'll get out of here by 12:30. So grab a lunch and come back. We are not adjourned.
- Alright, I'm going to ask the committee members to start looking at these draft key questions. They are not . . . I don't think they're in our folders.
- Josh Morse: They've just been handed out.
- Craig Blackmore: They've just been handed out.
- Josh Morse: So, you have them.
- Craig Blackmore: So, contemplate while you're nibbling and see if we can, if there's anything here we can do to avoid downstream problems.
- So, I guess just looking at this, one thing that I'm wondering about and maybe Seth, maybe you can help, but when we talk about recurrent or persistent acute otitis media, does that have a definition and would the number of recurrences and the number and frequency of recurrences, you know, is there . . . is there some granularity around recurrent that makes a difference?

- Seth Schwartz: Yeah, there are some criteria for that. So, for the recurrent acute, typically the current acute is classified as three episodes in the last six months or four in the last year with one occurring in the last six months. So, the criteria are pretty well established for that. Those tend to be entrance criteria for (inaudible) studies and ways to define.
- Craig Blackmore: OK.
- Seth Schwartz: I guess I would have two comments. One is, the age 16 years and younger is a little challenging, because if you look at the vast majority of the studies, patients . . . they include patients 12 and younger, as opposed to 16 and younger, and that adolescent population is a little bit less clear whether they function the same as 12 and under do.
- Craig Blackmore: So, in the . . . when we get to the subcategories, we would want to specifically call out 12 and under, and then is there also . . .
- Seth Schwartz: There's just not going to be any data on that 16 age . . .
- Craig Blackmore: . . . (inaudible) data on the older.
- Seth Schwartz: . . . age group, and then one other thing I would say with question number three talking about special considerations, I think underlying hearing loss is not included. So there's, because the . . . there's two issues. There's the hearing loss associated with the effusion . . . with the infection, and then there are just children who have underlying sensorineural hearing losses who are differentially effected by episodes of acute otitis media or chronic otitis media.
- Josh Morse: So add . . .
- Seth Schwartz: Underlying sensorineural hearing loss.
- Josh Morse: I didn't get the middle word, underlying . . .
- Seth Schwartz: Sensorineural.
- Josh Morse: Sensorineural.
- Seth Schwartz: The terminology that typically gets used is at-risk populations, and it's actually pretty broadly defined. It also tends to include kids that have speech delay.
- Richard Phillips: One thing it . . .
- Kevin Walsh: Isn't it . . .
- Richard Phillips: . . . is there likely to be a difference in outcomes for kids between 12 and 16 and those below 12?

- Seth Schwartz: The challenge is that it's a different disease in adults versus in children.
- Richard Phillips: Yeah.
- Seth Schwartz: And where that transition happens is not clear. So, most kids under 12 are thought of as kids that fall under the same risk factors and the same impact on function versus adults have different risk factors and different impacts on function, and that in between group, it's not that it doesn't apply to them, it's just that it's unclear which . . .
- Richard Phillips: Which way it goes.
- Seth Schwartz: . . . category they fall into. So, they're classically excluded from studies.
- Richard Phillips: So, your . . . your recommendation would be that we do it less than 12 then.
- Seth Schwartz: I mean, we can . . . I don't . . . I think it makes more sense. If you're talking about otitis media in children, it's generally considered 12 and under. If you're thinking about . . . because I think the adolescent populations are different than the child population.
- Richard Phillips: Yeah.
- Seth Schwartz: But, it depends on what the studies did. I mean, they may . . . they may be able to find some evidence on those in between children, but I think it's going to . . . it muddies the waters a little bit. So, the recent guideline that came out from the American Academy of Otolaryngology was applied to children 12 and under.
- Richard Phillips: Got you.
- Seth Schwartz: Plus it's, you know, the other incidence . . . questions about the incidence of disease. So, it is a highly prevalent condition in children. It's not that common in adolescents or adults. So, it's sort of a different disease process with different concern, and I'm sure the cost and impact concerns are really related to children, not really adolescents and adults.
- Josh Morse: OK, any other questions or thoughts on this? I can take these . . . I'll take the question of age back and inquire about how we arrived at 16 on this draft.
- Joann Elmore: And I'd like to give you later names of two individuals to email this to who can give you very helpful feedback, ENT physicians who do research and understand population issues.
- Josh Morse: OK. We have, OK, thank you. We've engaged one expert, so far.
- Seth Schwartz: Who was the expert? Was that (inaudible)?
- Josh Morse: I'm not going to remember her name. I think she's a colleague of yours.

- Seth Schwartz: Was it Kathy (inaudible) from Childrens or was it?
- Josh Morse: She's from VM.
- Seth Schwartz: She's from VM?
- Josh Morse: Yep. I think. Maybe I'm confusing . . . nope. I'm confusing the rhinosinusitis topic.
- Seth Schwartz: Oh, OK.
- Josh Morse: So, yes. I will . . . I will engage somebody.
- Richard Phillips: So, is it fair to say that you look at this disease as ages 0 to 12, that 12 to 18, and then adult, or is that?
- Seth Schwartz: I don't think that's entirely fair. I think . . . I think . . . I would say loosely five and under is different than the sort of 5 to 12 is different than the adolescent is different than adult. So, but where exactly those cutoffs happen is sort of individualized a little bit, but it's different . . . it's clearly a different disease in young children versus older children versus adults.
- Richard Phillips: OK.
- Kevin Walsh: And aren't the . . . aren't the overwhelming majority of the surgeries done in young children?
- Seth Schwartz: Far, far, and away.
- Kevin Walsh: Right.
- Chris Standaert: So, age should be one of those. We have a differential population of age. That should be one they should pay attention to particularly, because it may be different in the 3-year-olds versus the 10-year-olds.
- Seth Schwartz: And there is a little bit of data on that. They're called out as subpopulations in some of our randomized trials. It's also different in terms of treatment. So, children under 12, if they get . . . if they are going to have tympanostomy tubes, usually it's done in the operating room. However, if it's an adult, you do it in the clinic in 15 minutes. So, it's a very different resource allocation, you know, resource heavy allocation. Risks are very different.
- Chris Standaert: So tympanostomy tube is one thing or are there multiple ways of doing them, like, different procedures? Should they be looking at that, or are they going to fall under one (inaudible).

- Seth Schwartz: There's no data. So, I mean, there's . . . so, one of the questions that we looked at where the guideline was, what type of tubes do you use, does that make a difference, and the answer is, you can't call it out. There's just not, not adequate data to look at that differentiation. How you do the procedure is fairly standardized. So, it's not worth looking at. Whether you include adenoidectomy and things like that, that's a big question and we can decide. I mean, I think there's some stuff in here about, you know, alternatives, but in terms of how you actually use tympanostomy tubes, it's not of interest.
- Craig Blackmore: Any other questions, comments, or thoughts? Alright. We are adjourned.
- Josh Morse: Oh, whoa.
- Craig Blackmore: No, we're not. Sorry. No, we're not.
- Josh Morse: Updates.
- Craig Blackmore: Do an updates, please.
- Josh Morse: Christine, can you push the slides button? So, I'll just go over where we are with these various reports. So, the next meeting topics are the imaging for rhinosinusitis and the bariatric surgery. We have those final reports. They're not published yet. They will be published by April 10<sup>th</sup>. The draft reports should be online if you haven't seen those already, and then what we just talked about, the draft key questions for tympanostomy tubes we looked at. There is a public comment period on that now through the 25<sup>th</sup>, so five more days, and then lumbar fusion, the re-review. We are just kicking that off. We don't have a draft yet of the . . . of that framework. So, and as you . . . I think we talked about this in January. The topic selection for this cycle is concluded. We just ended the comment period on the final selected topics. So, this is the new, or the next list. I'll start from the bottom. Two subjects identified for re-review are cardiac stents, which was originally done in 2009 and spinal injections, which was done four years ago now. Then, the new topics identified you can see here are the ECMO topic, bronchial thermoplasty, a device called Novocure, or Optune.
- Kevin Walsh: What is that?
- Josh Morse: That is a treatment for glioblastoma.
- Chris Standaert: It's a little . . . it sends some sort of electrical wave through the brain through a headset you put on and carry around a little (inaudible) box with you and treats you for . . . it's treatment for glioblastoma.
- Richard Phillips: Will the same vendors be doing the re-reviews in general, or?

- Josh Morse: I'm thinking. I'm not sure because we haven't worked on assigning those yet. So, I was trying to remember who did the original cardiac stents. It's possible. It depends on what vendors we have when we get there.
- Richard Phillips: I was mostly curious whether or not they would have the benefit of their prior study on which to do it. That's where I was going.
- Josh Morse: Yes, yes.
- Richard Phillips: It's not a question if they're (inaudible).
- Josh Morse: Right. So, I think so far the re-reviews that we've had done have been aligned original vendor did the followup for the two that we've done, Spectrum and Hayes did re-reviews. The lumbar fusion re-review is not the case. We don't have that original vendor anymore so it'll be a different vendor. These two, I believe, were done by Spectrum, but we're not at the assigning point.
- Richard Phillips: I think (inaudible).
- Josh Morse: Right. I think they both were, so . . .
- Chris Standaert: Spinal injection wasn't done by Spectrum.
- Josh Morse: Right. So, it's possible. The other topics, the new topics, pharmacogenetics, which we have not initiated . . . we haven't initiated work on any of these topics yet, platelet rich plasma injections, negative pressure wound therapy for home use, and fecal microbiotic installation. So, this is information you've seen before. This is the scope of the rhinosinusitis report, which again, we're in the phase where we're about to publish the final report on this. This is the timeline so it's the main meeting. Bariatric surgery, you've seen this before also. This is the context, and this is also in the phase where we'll be publishing the final report here in a couple weeks.
- Craig Blackmore: So, is that, I mean, we, we did pediatrics a while ago. This is just adult . . . oh, it says there, sorry.
- Josh Morse: No, that's OK. I went through it quickly. So, this will be all inclusive this time.
- Craig Blackmore: So, it'll be a partial re-review and a partial new review.
- Josh Morse: Yes. This will supercede the original.
- Craig Blackmore: OK.
- Josh Morse: And we just talked about the key questions for tympanostomy tubes, and this is the timeline for that. So, we're scheduled . . . we have this one scheduled for November. So, we're . . . it feels like we're early on this, but November, I guess, is . . . it's the next . . . next open meeting for . . . following May, so, we started

that one, and like I said lumbar fusion re-review is . . . we're planning to do that month, as well. There it is, and there's the timeline. So, I'm hoping that with the way we have our plan going that we'll have the draft key questions for lumbar fusion for the re-review in its scope for your May meeting, which should cross-over with the public comment period. You can talk about that at the end of that meeting, and that's . . . those are the updates we have on the reviews in process.

Craig Blackmore: Any questions or comments?

David McCulloch: Just the one, I mean, Joanne has mentioned it a few times, and it may be . . . it's going to take time for, I mean, we've requested, I mean, I thought that was a dreadful evidence review, not just because there wasn't very much evidence, but what evidence there was I don't care if she's still here, it was terrible. The meta-analysis had five studies, and there's no data, unless we plow into it. As much as possible, we want to get to the data presented from individual studies. It wouldn't take that much more time and effort for them to summarize some of the key (inaudible). From this study showed this. This study showed that.

Kevin Walsh: Or even give us, just give us the links. Like, I have to go . . . you have to go back and, like, start doing a literature search.

Joann Elmore: She didn't even say (inaudible) analysis. We had to figure that out.

Kevin Walsh: Yeah, I mean.

Chris Standaert: That was, yet again, another reliance on systematic reviews and we reviewed systematic reviews and you sort of go, what are you talking about? There's no, yeah, I found that (inaudible) problematic (inaudible).

Craig Blackmore: Systematic reviews that conflict with other systematic reviews.

Chris Standaert: But it's just . . .

Joann Elmore: Show us the primary data.

Chris Standaert: But reviewing systematic reviews, it's like playing telephone. You just . . . you lose so much that it's . . . we've complained about this for years.

David McCulloch: Right.

Chris Standaert: But that, what they started on . . .

Craig Blackmore: Right, so . . .

Chris Standaert: . . . just a totally wrong track than where they wanted to go.

Kevin Walsh: Well, they started off . . .

- Chris Standaert: It yielded nothing.
- Kevin Walsh: . . . yeah.
- Chris Standaert: That wasn't going to yield anything, but you should have known that wasn't going to yield anything. They should have thought, then said, oh, well then we'll just go look at these two conditions and ran into . . . leaving it very difficult for us to draw up anything based on the evidence they gave us. I found that challenging myself.
- Marie Brown: I know you've given them that feedback. What's been their response?
- Josh Morse: So, we, the . . . on this particular report, we had the original evidence search led to limited information, and so there was the evolution to look at the . . . you asked them to look at the evidence for treatment, and they looked at the high level evidence, and they primarily looked at efficacy to start with and then moved more towards the safety question, but those really weren't on the target of the question that we were asking. So, it was a, I would say, glancing blow (inaudible) where it was and not an in-depth dive on what's the efficacy of treatment.
- Richard Phillips: In the lumbar fusion, are you going to be addressing artificial disks and joint replacement as an alternative or are you just going to . . .
- Josh Morse: Oh, no. I can say pretty confidently that that . . . the lumbar fusion question does not include the alternative. It is not a comparative effectiveness review of lumbar fusion and . . .
- Chris Standaert: Total disk replacement.
- Josh Morse: . . . and artificial disk replacement for the lumbar spine.
- Richard Phillips: Right, well just, the question is, you know, we're always having a comparator. So, we're basically saying versus no . . . it's . . . the comparator is still going to be no fusion whatsoever.
- Josh Morse: Actually, I don't know, but we're not evaluating . . . the question won't be should this be covered or that be covered or when should each, either one be covered, but it could be a comparator. So, I'm un . . . I'm uncertain about that.
- Richard Phillips: Well, that's part of where I'm getting at is, you know, I don't know where it sits in the . . . but, you know, there's a lot of things that have changed in the last seven, what seven years since we did it last, and I would wonder . . . I know we had had that in the discussion at the time. We did discuss it briefly. I don't know to what degree, but my memory's not that good, but I would . . . I do know it was raised. We had a . . . we had a separate review of joints, as you know, too, lumbar, but anyway.

Josh Morse: Right. You'll have that . . . like I said, the plan is to have a draft of that you can see what that looks like in I guess a month and a half.

Richard Phillips: Great.

Craig Blackmore: Anything else?

Josh Morse: Not from the program.

Craig Blackmore: Alright. Thank you all. We are adjourned. See you next time.