National Government Services, Inc.
LCD Open Meeting: J6 and JK
Moderator: Carolyn Cunningham, M.D.
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12:00 p.m. CT

Coordinator: Welcome and thank you for standing by. At this time, all participants are in a listen-only mode. During the Q&A session, if you'd like to ask a question, you may press Star 1 on your phone. Today's call is being recorded. If you have any objections, you may disconnect at this time. I'd now like to turn the call over to Dr. Carolyn Cunningham. You may begin.

Dr. Carolyn Cunningham: Thank you. Good afternoon, everyone. I'd like to welcome you to the National Government Services J6/JK open meeting. All of our colleagues are here, and as well as our MPU staff, Dr. Awodele, Dr. Boren, Dr. Duerden, Dr. Haug and Dr. McKinney.

We have three LCDs that are going to be presented. First is transvenous phrenic nerve stimulation on the treatment of central sleep apnea. And the second is biomarker testing. And the third is platelet rich plasma.

For transvenous phrenic nerve stimulation, we have a current LCD, and this is a draft revision that was brought by a reconsideration request. There was more literature submitted previously to give us additional data. However, we have a non-coverage policy at this time because there's currently no clinical trials that show improvement in patient morbidity and mortality outcomes directed at central sleep apnea with self-improved randomized trials (made in comparison) to standard therapy for central sleep apnea. And I should have said initially, I have to apologize for my voice. I have a cold that won't go away. I think we have several presenters on this call, and Dr. Germany is our first one. Dr. Germany?

Dr. Robin Germany: Thank you very much. Can you hear me?

Dr. Carolyn Cunningham: Yes.

Dr. Robin Germany: Thank you very much to the committee for allowing me to present today. My name is Robin Germany. I'm the Chief Medical Officer at (Respicardia), and I would like to address this local coverage decision. I am an employee of the company that manufactures and sells the phrenic nerve stimulation therapy device. Next slide.

I would first like to state that there's significant additional published data that continues to support the safe and effective use of the transvenous phrenic nerve stimulation, which should result in expanded coverage. There are sustained long-term outcomes trial and safety demonstrated, with three years data published and five-year data that's been presented and is in the mission currently.

In all, there are 17 additional peer review publications on transvenous phrenic nerve stimulation and CSA that are new in the literature since your last review. And also, the remedē System has been granted a traditional pass-through payment by CMS against clear and stringent criteria, including affirmative recognition that TPNS provides substantial clinical improvement over the existing therapies for central sleep apnea.

TPNS implant has been covered on a case by case basis in most of the other Medicare jurisdictions. And in fact, eight of the top 10 commercial payers are covering this procedure. And two of them have affirmative coverage policies on TPNS. Six others have continued to approve multiple procedures on a case by case basis. Next slide.

So, we would like to address several of the concerns which NGS has brought up during the coverage policy review. Next slide. The first concern was that there are no clinical trials that show improved patient outcomes directed at CSA. So, first and foremost, transvenous phrenic nerve stimulation is a sleep therapy, and its supporting data is on improving sleep and quality of life.

And in fact, in sleep medicine, the standard outcomes recognized by the American Academy of Sleep Medicine, and using clinical trials, were established as the AHI and the oxygen desaturation index. And this was reinforced recently and published this last year by an FDA panel of sleep experts.

AHI and ODI both had very statistically significant and clinically meaningful improvement, demonstrated in the remedē System randomized clinical trial. And these are the same outcomes that have been used by Medicare as a basis for coverage of other sleep apnea treatments, including CPAP, ASV and hypoglossal nerve stimulation.

And not only has TPNS been shown to reduce AHI and ODI, but it is the only CSA treatment to demonstrate significant improvements and arousals sleep quality as measured by the percent of time at REM sleep and quality of life in randomized clinical trials. Next slide.

And as you can see here, the study met its primary and all of its secondary endpoints shown here by very significant improvements in the AHI and the ODI, as well as improvements in quality of life metrics of the patient global assessment and the Epworth Sleepiness Scale. Next slide.

And long-term now, there's been data published out to three years, and then on the right, data that's been presented nationally at five-year showing continued and sustained improvement of these metrics over time. Next slide.

The next concern is that AHI continued to be reduced from baseline, but also continued to be elevated. Residual elevated AHI is a challenge for all therapies in sleep medicine, including CPAP, due to the mixed etiology of many of these patients.

And in fact, the 2016 ASM practice parameter for CSA treatment just stated that CPAP continues to have a residual mean of AHI of 15 in all CPAP studies, despite CPAP treatment. Notably, TPNS not only had no - did not have a cutoff for AHI, and in fact, enrolled patients in the clinical trial with as many as 98 events per hour, so that we didn't keep the therapy from patients with the most severe disease. And this is in contrast perhaps to the hypoglossal nerve stimulator, which cut off patients above an AHI of 50. And in fact, in the clinical trial, 39% of patients had an AHI of at least 50 events per hour. Next slide.

The second concern that was raised that there were no head-to-head trials compared to CPAP or other therapies for CSA. Well, while the practice parameter states that there are some therapies that can be used for CSA, all of the clinical trials to date have used an untreated control.

This included both CPAP, ASP studies, as well as our study, but importantly, the ongoing NIH-funded oxygen trial locked HS, and the ASB trial advent HS, both of which are using untreated controls, demonstrating this is the appropriate comparison therapy. And in fact, the hypoglossal nerve stimulator, which is covered by NGS, was also completed without any comparison therapy or an entry to control. Next slide.

In addition, there is a concern that there were, and I'll read here, no measures of cardiovascular outcomes, left ventricular ejection fraction, six-minute hall walk test, except in the Zhang study, which only included six patients. And then on the update that although subjective measures of outcome were reported, an objective outcome, the six-minute hall walk test only improved at six months in the pilot group.

And I would call out here that there has been significant additional cardiovascular data available in the literature. As you can see on the right side, there's three studies, Costanzo, (Fudan), and (unintelligible) that have been published. These publications include data on left ventricular ejection fraction, hospitalization, as well as the core sleep and quality of life metrics in the heart failure cohort.

Now, we firmly believe that the appropriate end points for this therapy are sleep metrics. However, we do take onus that this data has been published now. And in fact, both the Costanzo and (Fudan) articles were cited that do not seem to be reflected in the data analysis of the LCD. Next slide.

Here, you can see the significant numbers of data points in these trials here, including ejection fraction volume changes, six-minute hall walk tests as well. Next slide.

Another concern was that CSA might be simply a marker of disease severity and no need of treatment is needed beyond that for the underlying condition. The first, only 40% of patients in the clinical trial had heart failure. This was a concern that was raised in an editorial back in 2012. There was no clinical data to support this assumption.

And in fact, multiple review articles have taken a contrary view, which were not cited in the literature that you presented in the local coverage decision. Long-Term cohort studies and physiologic studies continue to show the harmful effects of intermittent hypoxia and central sleep apnea on patients. Next slide.

And in addition to that, there's a very clear unmet need for patients that don't have heart failure. In the remedē System pivotal trial, 40 - almost 40% of patients did not have heart failure. And in fact, many did not have any cardiovascular disease.

So looking for cardiovascular outcomes in that patient population would not be a valid marker for those patients. There are very few treatment options for these patients. And without offering the remedē System to these patients, they may very well go untreated with significant impact on their lives. Next slide.

So I would say that you did point out with the hypoglossal nerve stimulation as well, that there was a clear need for alternative therapies. Central sleep apnea really has much fewer alternative therapies than obstructive sleep apnea. And there's a clear need for new treatment options.

As I - as a closing here, clinical evidence is sufficient to demonstrate that TPNS is reasonable and necessary for the treatment of central sleep apnea. Treating sleep disorder breathing is important, and current treatment options are insufficient to adequately treat this patient population.

In light of this, we ask you to revise the proposed limited coverage decision, to provide support for TPNS, or retire the policy and allow for case-by-case review for medical necessity, consistent with the other MACs and commercial payers United States. Thank you very much.

Dr. Carolyn Cunningham: Thank you, Dr. Germany. Does anyone have questions for Dr. Germany?

Coordinator: The phone lines are now open for questions. If you would like to ask a question over the phone, please press Star 1 and record your name. Thank you.

Dr. Carolyn Cunningham: Okay. Thanks. Dr. Iber, hope we’re not mispronouncing your name. Are you available?

Coordinator: Dr. Iber, your line is open.

Dr. Carolyn Cunningham: Operator, has he signed in? We're going to go ahead..

Dr. Iber: Operator, can you hear me now?

Coordinator: Dr. Iber appears to have disconnected from the call.

Dr. Carolyn Cunningham: Okay. Well, let's see if we can't go to the next presentation and then we'll come back to him. Can we go to the next one, please? Dr. Nayak?

Dr. Hemal Nayak: Yes, I'm here. Can you hear me?

Dr. Carolyn Cunningham: Yes. Thanks.

Dr. Hemal Nayak: Okay, great. All right. I'll get started then.

Dr. Carolyn Cunningham: Please.

Dr. Hemal Nayak: Great. Wonderful. First of all, I want to thank the panel for allowing me to address them. I'm going to be talking about treating CSA with the transvenous phrenic nerve stimulation. My name is Hemal Nayak. I'm an Associate Professor of Medicine at the Pritzker School of medicine at the University of Chicago. Next slide, please.

These are my disclosures. I have received speaker honoraria from Respicardia, which is the company that manufactures the remedē phrenic nerve stimulator device. Next slide, please.

So why is a cardiologist talking to this panel about treating central sleep apnea? And that's because sleep apnea, both obstructive and central, lives within cardiology. What I mean by that is, it is a major co-morbidity in the patients that I see on a regular basis.

For example, atrial fibrillation is the most common arrhythmia that we see in the Medicare population. And it is many times triggered or worsened by co-morbidities. And therefore, it is imperative that co-morbidities such as weight loss, alcohol use, and sleep apnea, be addressed before moving to advanced treatments like catheter ablation.

In the electrophysiology space, there's growing body of literature showing that addressing all of these issues prior to ablation, not only improves outcomes and success rates for catheter ablation, but also helps our medical therapy work better.

And therefore, patients referred for ablation are routinely screened for sleep disorders. In fact, the 2018 Heart Rhythm Society consensus statement for atrial fibrillation centers of excellence states that addressing risk factors such as obesity, diabetes, hypertension, sleep apnea, and others, are a critical function for any center of excellence. Next slide, please.

Now, just like atrial fibrillation, I see a ton of patients with congestive heart failure, and similar to afib, heart failure therapies such as advanced pacing techniques like cardiac resynchronization therapy, which has been shown to improve survival, reduce morbidity and heart failure, hospitalizations, require treatment of co-morbidities to be the most effective.

In fact, the American College Of Cardiology heart failure guidelines recommend assessing for sleep apnea and treating based on the type of sleep apnea, and stresses the importance of distinguishing the type of sleep apnea that exists.

So it's not (assumed) that all patients will have obstructive sleep apnea. They will likely may have central sleep apnea. In fact, the combination of central sleep apnea and systolic dysfunction is a deadly combination. And therefore, treatments of these co-morbidities are directed for improvement in the quality of life for our patients, not necessarily heart failure directly. Next slide, please.

So, because sleep apnea plays such an important role in the patients that I see in cardiology, my colleagues and colleagues throughout the nation, are leading sort of at the forefront in trying to make this diagnosis. And so, because undiagnosed and untreated sleep apnea affects - adversely impacts the quality of life of my patients, I screen for sleep apnea by ordering a sleep study.

Now, when we send the patients for a sleep study and the results get back to us after they are reviewed by our sleep medicine colleagues, we've seen, and I've seen this personally, that patients with obstructive sleep apnea have many options for treatment, and we all know what those are.

However, patients with central sleep apnea, when they're diagnosed with this condition, have very, very few options. Often, and this has been my experience, CSA patients have been sent back to me and to other cardiologists in my practice without any therapy due to lack of options for these patients. Essentially their central sleep apnea is not being treated. Next slide, please.

Now, it appears that obstructive sleep apnea and central sleep apnea seem to be treated differently by Medicare for unclear reasons. Now, the policy review for transvenous phrenic nerve stimulation is focused on improvements in cardiovascular outcomes, even despite this not being the goal of the treatment.

Remember, the goal of sleep apnea treatment is to improve sleep quality and to reduce apnea hypopnea index. It is important to see improvements in quality of life, along with reductions in AHI. And these metrics, meaning the improvements in quality of life, reduction in AHI, are the basis for other cover therapies for sleep apnea, for example, CPAP, BIPAP, ASV, and the relatively new hypoglossal nerve stimulator. Treatment of CSA has much

fewer treatment options, but should have the same goal, reduction of AHI and improvement in quality of life. Next slide, please.

Now, you will probably see some of this data in multiple forms, but with the pivotal trial that is - that was published and some long-term follow-up that's been now published, you can see that transvenous phrenic nerve stimulation improves AHI and quality of life.

With the information presented, you can see that the median apnea hypopnea index AHI went from 42 to 17. That's the median values. We have improvement in the Epworth Sleepiness Scale, as well as an improvement in patient global assessment. Next slide.

Now, a question was raised in your limited coverage decision regarding whether CSA was a compensatory mechanism. I think Dr. Germany touched on this as well. So, this concept was developed after one positive area pressure treatment, ASV, was shown to increase mortality in patients with LV dysfunction.

Now Cheyne-Stokes respiration is a form of CSA, which occurs almost exclusively to subset of heart failure patients. It is possible that CSA and Cheyne-Stokes respirations could begin as a compensatory mechanism, similar to, for example, a tachycardia when somebody is in heart failure.

However, long-term CSA, long-term central sleep apnea, with or without Cheyne-Stokes respiration, has significant and devastating effects, which independently contribute to the poor prognosis associated with these patients. In the electrophysiology and cardiology literature, patients with CSA and Cheyne-Stokes respiration, have increased hospitalization, ventricular arrhythmias, sudden cardiac arrest, and mortality. Next slide, please.

Now, the transmitted phrenic nerve stimulator is very similar in terms of how it's implanted to standard pacemakers, defibrillators, and cardiac resynchronization therapy devices. As implanting electrophysiologists, we are experts in placing leads in small veins, and phrenic nerve stimulation is no different.

It is a fully implantable system placed by electrophysiologists generally using moderate sedation, very similar to CRT implantation. It’s generally an outpatient procedure. There are three components of post generator that sits in the pectoral region in a pocket that's created very similar to a defibrillator, and there are two leads that are placed essentially in locations that electrophysiologists feel very comfortable accessing. Next slide.

In the pivotal study, there was a 91% freedom from serious adverse events associated with the implant procedure. That's the remedē System, or the delivered therapy at 12 months. All related serious adverse events, which were quite small when it did happen, were resolved without any long-term sequelae.

There were no deaths associated with the procedure system or therapy. And there was a 97% implant success rate, even amongst new implanters. Now, you might say, well, this is a device, certainly. And a lot of these patients have - who have CSA, may have heart failure and they may have concomitant pacemakers and/or defibrillators.

Well, in fact, 42% of the patients in the pivotal study that underwent phrenic nerve stimulator implantation, had concomitant devices, either pacemakers or defibrillators. There were minimal device-device interactions, and it was deemed safe in the setting of concomitant device therapy. Next slide, please.

So let me share with you my experience with transvenous phrenic nerve stimulation, just as a step back. So I work on the South side of Chicago. I've been at the University of Chicago for about 12 years. We serve a very predominantly underserved population with a huge heart failure prevalence, primarily African-American and Latinx.

Over 65 to 70% of our population are Medicare beneficiaries, and this is an example of one of those patients. So this was a 54 year old man with diabetes, end stage renal disease on hemodialysis. Had a non-ischemic cardiomyopathy. Underwent a subcutaneous defibrillator implant in 2015 for primary prevention of sudden cardiac arrest. His ejection fraction was around 30%.

In November of 2018, an in-laboratory polysomnogram was obtained to evaluate for obstructive sleep apnea due to complaints of daytime sleepiness, fatigue, and difficulty initiating and maintaining sleep. We sent him for the polysomnogram, and the total apnea hypopnea index was 61 events per hour.

The central apnea index was 42 events per hour. This gentlemen has severe central sleep apnea. And the obstructive apnea hypopnea index was 19 events per hour. So, he was prescribed home PAP ST therapy with the following settings, backup respiratory to 16 breaths per minutes.

Despite adherence to this, the device estimated residual index was 22. The patient felt no improvements at all with this type of therapy despite an adequate adherence, which we documented. And therefore, he was referred for phrenic nerve stimulator implantation, which was performed successfully at the University of Chicago. Next slide, please.

This is an example of his polysomnogram. This is a two minute window from his overnight sleep study, demonstrating frequent central sleep apneas with Cheyne-Stokes respiration. If you take a look at the flat line where it says NPT therm and chest, this chest is not moving. Each central apnea lasted 30 seconds. This gentlemen stopped breathing multiple times for 30 seconds. Did not have any breathe, had hypoxia, in fact, a 10% oxygen desaturation. This was happening to this gentlemen. Next slide.

After implantation, we were then able to activate the device and upon follow-up, we did a six-month sleep study of polysomnogram, and his AHI markedly decreased to 12 events per hour, which is a marked reduction from his 60-plus events. There were no central sleep apnea as noted after the initiation of transvenous phrenic nerve stimulation.

More importantly, and probably most importantly, he had a tremendous improvement in his quality of life and his ability to sleep and rest. And he then translated that to an improvement in his overall exercise tolerance and exercise capacity.

Currently, I have three highly qualified Medicare beneficiaries now waiting on this implant for over a year. All three have been diagnosed with central sleep apnea. All have failed all the therapies that are potentially possible, and they're highly symptomatic. Next slide, please.

Ladies and gentlemen, I'd like to conclude that patients treated with phrenic nerve stimulation have improvement in daytime sleepiness, improvement in quality of life, similar to those seen when they get treated for obstructive sleep apnea.

Patients with obstructive sleep apnea have many, many treatment options, and we all know what those are. Patients with central sleep apnea currently lack access to the only FDA approved therapy in many cardiac patients, many vulnerable patients.

Medicare beneficiaries need access to phrenic nerve stimulation so we can effectively treat this debilitating condition. I respectfully and humbly ask that NGS reverse this policy, to allow Medicare patients to receive this type of therapy. I thank you for your attention and your time and giving me the opportunity.

Dr. Carolyn Cunningham: Thank you. Does anyone have questions?

Coordinator: And again, if you would like to ask a question over the phone, please press Star 1 and record your name. Thank you.

Dr. Carolyn Cunningham: Thank you again, Dr. Nayak.

Dr. Hemal Nayak: Thank you.

Dr. Carolyn Cunningham: Is Dr. Iber on?

Coordinator: Dr. Iber, your line is open.

Dr. Iber: Can you hear me?

Dr. Carolyn Cunningham: Yes. Please go ahead. Thank you.

Dr. Iber: Okay. So I'll be talking about perspectives from a sleep medicine provider and organizer. I see about 10,000 patients a year in our system of care.

The second slide reflects - relates to the prevalence of this condition, central sleep apnea in that general population, not our population, but sleep heart health population.

You can see it's a relatively uncommon problem. About 1% of patients meet criteria based on five events per hour. So it's not a prevalent condition, and yet subset populations, for instance, those with heart failure, patients on narcotics, as examples are - have a much higher prevalence, with prevalence rates as high as 40, 50% in some heart failure series.

So, it is a condition that does complicate heart disease and contributes to increase morbidity as previously mentioned, and mortality association with this condition. It is - next slide.

It is a different disease mechanistically. Obstructive sleep apnea is due to collapse of the airway, which is normal relaxation of the upper airway. All of us have some of that. Exaggeration due to morphological differences between people and structural differences cause obstruction of the airway.

This is a condition that has been related to outcomes and well documented in the literature mechanisms. We'll talk about on this slide, but it follows this, but it's differently diagnosed. We do separate these out, different mechanisms, obstruction of the airway on the left, with effort occurring and no flow at the top.

On the right, with central sleep apnea, there's a failure of the rhythm generator, often due to periods of hypercapnia in the case of heart failure, for instance, probably related to increased circulation time, as well as low carbon dioxide levels. These pauses do result in hypoxemia and drop in oxygen saturation, well-defined mechanism for outcomes in multiple areas. Next slide.

So the downstream areas from any cause of central sleep apnea do share some commonalities. There are arousals. Arousals are a little more frequent with obstructive sleep apnea as the breaking breath. Arousals occur during the peak inspiratory effort and central sleep apnea. Arousals and sleep disruption are important, probably under-recognized as the benefits of sleep in general, with remodeling of nearly 20% of the trillions of connections in the brain, and removal of toxic neurotoxins in the brain.

So, anything that disrupts sleep and interferes with sleep, is not just a disturbance, but has a substantial long-term impact. The effect of arousal also caused sympathetic activation decrease. Immediate effects are the cognitive effects, as well as some of the changes in sympathetic activation, increased heart rate, peripheral vascular resistance, Ren and release.

And then secondarily, depending upon the severity of the hypoxemia, this is well known cardiovascular risk long-term. Subsequent to the studies nearly 40 years ago on outcomes of providing oxygen, for instance, for hypoxemia, we have multiple studies showing in obstructive sleep apnea

and in other mechanisms, hypoxia is a generator of vascular inflammation, which causes and just really this function, cancer risk, as well as ischemic risk in the population.

So certainly in terms of lines of evidence, we have evidence that central sleep apnea mechanistically can cause these problems. And indeed in observational studies, outcome measures have shown cardiovascular risk and sleep disruption. Next slide.

So the treatments to this condition are relatively limited. CPAP was designed to open the airway. It can have an effect in some individuals with central sleep apnea, but not reliably. In fact, in some cases, the application of CPAP results in increase in central events.

The other option, adaptive servo ventilation, does require mass therapy. We're going to talk about the burdens of therapy, as this requires adherence like any mask therapy, as you well know. Compliance with mask therapies is in the range of 60 to 70% in the best of circumstances, and may not be a patient's first choice.

Additionally, there is the associated risk, particularly in patients with the reduced ejection fractions of less than 45%, of mortality risk with this intervention. So, some of the other therapies we have, certainly oxygen therapy in cases who have hypoxemia, is a reasonable first attempt at effective therapy. Often not actually effective in eliminating the arousal central sleep apnea in all patients.

We have actually less prospective data in many of these pending the study, the controlled study of oxygen in the future. We have less clinical data on long-term outcome and short-term outcomes than what the current controlled study that we have with phrenic nerve stimulation.

The guidelines that were developed by the American Academy of Sleep Medicine have been revised primarily to add the additional warning for ASV in 2016. At the time of this publication, there wasn't sufficient information to allow review of phrenic nerve stimulation.

I might mention there are, at this point - move on to the next slide, there aren't options for phrenic nerve stimulation other than implants, which are much more complex than this device. This therapy does resemble with the cannulation of the phrenic vein and a sensing lead.

This kind of therapy is well - has a long history of success and safety and general and cardiology. It has been used in hypoglossal neurostimulation in sleep apnea, similarly with the stimulation leads of the hypoglossal nerve, and a sensing lead in the chest.

And so the implantation concept has a long safety history and proven safety in the controlled trial. It also has some advantages long-term over the use of mask devices, which do have compliance and adherence problems, in

that it's an automatic device that doesn't require an interface with facial application. So, much like a cardiac pacemaker has limited burden once in place. Next slide.

Now, the results do hinge upon several studies, which are observational studies, the Costanzo study, which we'll talk about next, is one of these studies. And as a group, the studies do show a difference in one of the most measurable outcomes, the Apnea-Hypopnea Index as a reliable outcome, both in observational studies and the pivotal trial. And move on to the next slide.

I would like to point out something really important here, and that is, it has been stated several times in this discussion so far, that this therapy is aimed for correcting and improving the burden of suffering related to sleep. The measureable outcomes related to that are the - in this case, in this slide, are the reduction in arousal index.

The arousal index dropped from 46 episodes per hour to 25 episodes per hour. It is true that that's a residual arousal index, but remember, the normal arousal index, particularly in this population, is in the range of 20 to 30 per hour. These arousals are very subtle events.

It's the increase above this level that results in measurable outcomes. Impairment in cognition and vigilance are well-documented with arousal events in the range that these patients had mean value 46. So other measurable outcomes on the right, between group differences there, dropped by 23 in the central apnea index. The Apnea-Hypopnea Index drops by 25.

I might mention, there was some concern about residual disease and central events. The frequency of central events doesn't necessarily translate into hypoxic stress nor even arousal index. The frequency of arousals is much lower with a central advanced than with obstructive events.

So I think the evidence is in the next line. The arousal index drops, the architecture of sleep is improved. The line following that is the improvement in REM sleep. And then finally, the global assessment is a measure of quality of life.

Some of the outcomes we see in daytime include the Epworth Sleepiness Score, probably one of the more standard scores. And that moves from a baseline value, which is at normal of 11 - a score of 11, down to a normal value of seven, pretty much in the normative range.

So I think if you're looking at burden of suffering related to sleepiness, burden of suffering related to arousal index, or even the central - residual central events, if the target is to improve quality of life and sleep quality, which is the major target, then this has achieved that outcome. And in addition, there is an improvement in oxygen desaturation index.

So again, question, next slide, often is, are these outcomes supported long-term? And in the measures taken here that reflect the sort of classic sleep outcomes, Apnea-Hypopnea Index, arousal index, central sleep apnea index, and even a desaturation index. These are sustained over 36 months in a long-term efficacy trial. The last slide.

So conclusions here, central sleep apnea is rare in the general population. However, it's relatively common in subgroup populations, and carries a substantial burden of suffering related to sleep disruption and respiratory events, in addition to hypoxemia.

So we have few treatment options at this time that moderate and severe sleep - central sleep apnea can result in hundreds of episodes of hypoxemia. And adrenergic stimulation on nightly basis, which is a long-term burden for patients who have underlying disease in particular.

The transvenous phrenic nerve stimulation really has strong data of improvements in sleep apnea, sleep quality, hypoxia, and quality of life at this point. Even when compared to some of our long-term data in CPAP, this compares very favorably.

And for that reason, it makes sense certainly to me as a provider and a system of care, to request that NGS consider transvenous phrenic nerve pacing as one of our substantial treatment offers to patients who have debilitating disease that doesn't respond to other interventions. Thank you.

Dr. Carolyn Cunningham: Thank you. Questions for Dr. Iber?

Coordinator: And again, if you would like to ask a question, please press Star 1 and record your name.

Dr. Carolyn Cunningham: Thank you again, Dr. Iber.

Dr. Iber: Thank you.

Dr. Carolyn Cunningham: Our next presenter is Mr. Dingledine. Are you there? Hello?

Coordinator: Dr. Dingledine, if you're on, please press Star 0. We can open your line.

Dr. Carolyn Cunningham: Hello.

Mike Dingledine: Hello.

Dr. Carolyn Cunningham: Mr. Dingledine.

Mike Dingledine: Yes. Can you hear me?

Dr. Carolyn Cunningham: We can. Please go ahead.

Mike Dingledine: Hello.

Dr. Carolyn Cunningham: We can hear you. Please go ahead.

Mike Dingledine: Thank you. Hello. I'm Mike Dingledine. I'm from Coldwater, Ohio, and I've had the remedē System from Respicardia since January of 2020. When I was diagnosed with sleep apnea in early 2017, I was to the point where I didn't have the energy to function properly. And quite frankly, I was losing the desire to even try.

I was tired all the time. I struggled with sleep apnea for almost three years. And during those three years, I was being treated with the CPAP machine, but it just wasn't helping. I was still waking up six to eight to 10 times a night, and I wasn't feeling any better than I did before.

It wasn't until late 2019 that I was told that I had central sleep apnea, rather than obstructive sleep apnea. And from everything I've read about central sleep apnea, the CPAP machine is not an effective treatment for central sleep apnea.

It blows air into the body to open the airways, but it doesn't communicate with your brain. And with central sleep apnea, it's your brain not telling your body to breathe. I knew then that I needed more than a CPAP machine, and that's when I found the remedē System.

What has it done for me? The remedē System has given me, I feel, a new lease on life. I'm able to sleep through the night without constantly waking up. I'm more active. I feel better, and I have the energy and the desire to do things. I'm able to enjoy life again.

My family thinks I'm a happier person, and my wife even went so far as to tell me that I'm a more pleasant person since I got the remedē System. I'm 70 years old and I'm on Medicare. Medicare covered the cost of the remedē System for me, and I think Medicare should cover that same cost for those on Medicare, regardless of where they're located in the United States.

Senior citizens such as myself, have been paying into the Medicare system for a long time. And I think it's time we all enjoy the same benefits. I appreciate you listening and I thank you for your time.

Dr. Carolyn Cunningham: Thank you. Question for Mr. Dingledine?

Coordinator: And again, to ask a question, please press Star 1 and record your name.

Dr. Carolyn Cunningham: Thank you again.

Mike Dingledine: Thank you.

Dr. Carolyn Cunningham: You're welcome. Now, let’s go to Dr. Ahmed. You may open the line, operator.

Dr. Qanta Ahmed: I'm here. I want to ask a question.

Dr. Carolyn Cunningham: Okay. I'm sorry. You wanted to ask a question to Mr. Dingledine?

Dr. Qanta Ahmed: Yes. Thank you very much, Dr. Cunningham, Mr. Dingledine, I'm a sleep disorder specialist in New York. I would like to know, how quickly after the device was implanted did you feel better? Thank you.

Mike Dingledine: I would venture to say that it was probably two to three months into it when you've really started noticing a significant difference. I was sleeping better from day one. The first night it turned on, I never felt it, slept from 11 o'clock at night to after seven o'clock in the morning without waking up once.

But, you know, it took - it takes years to get to that point and it doesn't correct itself in a month or two, but I would say at about three month stage, I started noticing a significant improvement, and it just keeps getting better.

Dr. Qanta Ahmed: Thank you very much.

Mike Dingledine: You're welcome.

Dr. Carolyn Cunningham: Any other questions? Thank you again. Operator, has Dr. Ammed signed on?

Coordinator: Yes. Dr. Ahmed is on.

Dr. Carolyn Cunningham: Very good.

Dr. Qanta Ahmed: Thank you very much, Dr. Cunningham, and thank you also to your colleague, Virginia, for assisting me in joining the meeting. And thank you for all of my colleagues. I very much enjoyed listening to the discussion. I am an Associate Professor of Medicine here at NYU Langone.

I have practiced sleep disorders medicine for about 17 years. I've practiced medicine for 30 years. I see about, I'd say five to 6,000 patient visits a year, and read well over 1,000 sleep studies a year. It is very important to me that we're able to provide transvenous phrenic nerve stimulation for central sleep apnea patients. And I want to spend a few minutes explaining why, if you could kindly change the slides.

I don't have any financial relationships relating to this technology. I don't have any consulting fees with the makers of the technology. I have no conflicts of interest, but I'm extremely vested because I look after many patients with central sleep apnea. So that's my prime motivation. Next slide, please.

It's difficult to explain to physicians that aren't immersed in sleep disorders medicine, just how challenging it is to treat central sleep apnea. And even before that, how challenging it is to find central sleep apnea. It's often overlooked and undiagnosed by sleep specialists themselves.

It's not a favorite diagnosis of mostly sleep specialists, because it is difficult to diagnose, difficult to score on the sleep study, difficult to think about those patients as having central sleep apnea. So this is a patient population that is very overlooked.

Once it is found, most sub-specialized sleep specialists are not familiar with how to manage it or how to treat it. And essentially the CPAP device, the continuous positive airway pressure device, is almost like a hammer to treat every nail, if the patient was metaphorically a nail. And it is often unsuccessful, and or it may even exacerbate the sleep disorder.

We may as well mention now, we haven't talked really about the difficulties of wearing a breathing device with a mask in every hour of sleep, but there are significant morbidities related to that, skin infections, skin breakdown, sinusitis, even dental shifting if the mask is not fitting properly, or there's some gum disease.

So it's not completely benign to try and treat somebody with a sleep apnea breathing device. So I use that in the bulk of my patient population. As a result, doctors are not thinking about central sleep apnea. Patients do not know about central sleep apnea. Some sleep centers are not expert in scoring and finding it, and these patients are essentially invisible or unseen. We can go to the next slide.

These patients will show up in the office, like many other patients with sleep disorders. They'll have fatigue. They may have headaches, low mood, depression, dysphoria, impaired quality of life, frequent nighttime awakenings, unable to stay asleep, daytime sleepiness. And many of these symptoms are ascribed to a lot of their coexisting health conditions.

These patients may well have already diagnosed cardiac disease. They may well have already cerebral vascular disease. They may be stroke patients. They may have arrhythmias. They have a lot of complications of the sleep disordered breathing phenomenon itself, without getting a diagnosis.

So it's - unless a sleep specialist is really looking to these patients, they're easily overlooked when they come with relatively nonspecific symptomatology. We'll go to the next slide, please. Thank you.

And this is really the most important part of my remarks, and that's why we're so excited to hear from a patient who actually has the device in. In my practice, I have identified 34 potential candidates. I have screened the first three to four, and I'm requesting implantation in two patients at the moment.

I want to talk to you about those two patients without breaking any HIPAA confidentiality. One patient, the very first patient that I've identified who needs the device, actually is a physician. I've been treating him for about six years. He is in his 60s.

He came to me with a history of two cerebrovascular accidents, but also cardiac disease, hypertension, arrhythmia, permanent pacemaker, a (unintelligible). The patient is incredibly resilient, still practices a form of telemedicine, yet has very impaired sleep quality.

And I looked at him and I thought, of course you have obstructive sleep apnea and began the diagnostic process. This patient's sleep studies, he's had four sleep studies since about 2015. Initially appeared to be regular obstructive sleep apnea, but on closer scrutiny, it really was central sleep apnea.

We wanted to treat him with an oral appliance the dental sleep specialists make, and it seems to make central sleep apneas much worse. That was very unexpected. So I look back at his first study, and realized they had overlooked the central sleep apnea component to his disorder.

We then went through the usual algorithm, which is often required because of insurance related guidelines. We commenced him on CPAP, and he could not sleep through the night with that. We commenced him on auto PAP to see if that was comfortable. The apnea hypopnea index did not improve.

I was beginning to think about the adaptive servo ventilation and we - I decided, several years after I made the diagnosis, to screen his sleep once again with repeat diagnostic study about four and a half years after I first diagnosed him, and he has over 66% of events of central apnea.

So what I'm saying is, even as a seasoned sleep disorder specialist, it was very difficult to recognize the disease and the diagnosis. We then identified this patient could benefit from the transvenous phrenic nerve stimulation. He is already exhausted of wearing sleep apnea machine.

So he continues to do that and continues to be very committed, but both of us can see his central sleep apnea is not improving. And it's a worry because he has arrhythmia sufficient to warrant the device, and he has had two strokes already.

And we know from the disturbed breathing pattern from central sleep apneas, or even from obstructive sleep apneas, they cause these EEG arousals you've heard many of my colleagues speak about, that raises the circulating activity of the sympathetic nervous system.

That's the background nervous system that effectively raises circulating hormones that accelerate heart rhythm and cause irregular rhythms more commonly. On top of that, my patient practices medicine, and we want his mind and his memory and his focus to be the best it can be, for the best quality of life that he's trying to hang on to, despite disability from stroke.

Now, this patient has been seen by the implant cardiologists. We've all agreed, he's a candidate. The patient is educated, and now we hit the barrier of reimbursement. And so, that's a prime example of just one person in my major academic practice.

The other person, because now my radar is up for central sleep apnea, is a even more troubling story to me, myself. I first saw him in August 2010, and

he came as someone with snoring and moderate obstructive sleep apnea. Over the course of 11 years, I performed five polysomnographies.

All of them were through Medicare, enormous cost and effort on the patient's part and cost on the insurer. And over the course of 12 years, he's developed cardiac disease. And I was shocked to discover, he has developed central sleep apnea, with 83.3% of events coming out as central apneas, 11 years after his first diagnosis, which was clearly obstructive.

I looked back to see, could I have made a mistake? Could I have misdiagnosed him? But actually what was happening is, his cardiac condition was evolving. He developed atrial fibrillation, which was diagnosed in my office when I heard it on physical exam.

He developed a dilated cardiomyopathy. He’s developed congestive heart failure, but I do not have a practice of routinely studying people annually. And therefore, I was eventually able to find the central sleep apnea some years after his heart function has deteriorated.

This patient has an ejection fraction that makes it risky to put the adaptive servo ventilation device on. And so, the only option for him is transvenous phrenic nerve stimulation. We have measured him on CPAP three times. We've measured him on the bilevel positive airway pressure.

The patient struggles with a mask fit, has insomnia, but is too fearful to sleep without the device because he knows about the dangers of the irregular breathing in his sleep. So, these two patients are a very good example of the central sleep apnea patient.

These are the patients that are extremely diligent in seeking help, because they have so many symptoms. They also have no other place to go apart from their sleep specialists. They will do anything to try and comply with treatment, but they are not getting the outcomes that they need in terms of improvement in their cardiac function, quality of life, or sleep. So, for these two specific patients, I would be very grateful if we could consider making access to this treatment available to us in New York State.

And if we go to the next slide, which I think is Slide number 6, you can see that obstructive sleep apnea syndrome has countless numbers of treatment options available, and very widely advertised. Central sleep apnea really does not have a meaningful treatment option, except for a narrow population that may use the adaptive servo ventilation, which I am finding as a minority of my patients because of the ejection fraction problems.

So, to underline how much my patients want this is, they are meeting with me regularly, asking when can it be done? They're very anxious to do it. One of them wants to consider exploring other healthcare systems where this might become more accessible. And I don't want my patient of a decade or six years to travel to another system where there are no doctors that know them.

I want to add one other remark. If we go to the next slide, there have been - many of my earlier colleagues speaking, have provided you all of the evidence. I did not compile that for you, but the evidence for the transvenous phrenic nerve stimulation is actually at a higher index, and I think stronger than much of the evidence we use to justify even trying CPAP in the central sleep apnea patients, or trying the adaptive servo ventilation device.

I personally never recommend oxygen as a treatment option, but I have seen it used. So we have very strong evidence. We have a revolutionary device that can help patients that are invisible, deeply symptomatic. These two stories encompass almost 16 years of visits to my office, and a total of 11 sleep studies, which are extremely expensive to perform, labor intensive, several different kinds of sleep apnea devices, one oral appliance. Just imagine the cost burden just for those two patients because we did not have this technology.

And if we can go to the next slide, please. There are some remarks made by patients. They hear on the television about the device for the obstructive sleep apnea device, which Medicare has approved. I'm hoping one day, they'll be able to hear information about this device more broadly.

But this device, the phrenic nerve stimulation device, is much more needed in this patient population that frankly has many more serious illnesses that are in some part because the central sleep apnea is not there, and in some part, a cause of the central sleep apnea. It's bi-directional.

One other discovery I'd like to say, and this will be my final comment, and I'm happy to answer questions is, I'm discovering, and we listened to very eloquent colleagues earlier on, Dr. Germany, Dr. Iber. Dr. Nayak’s remarks really impacted me. The - I think he's a cardiologist EP specialist from the South side of Chicago.

I am discovering, many of our cardiologists in our society here, are well-educated in sleep disordered breathing, but actually uneducated about central sleep apnea. They're not aware as to how it causes increase in atrial fibrillation, how it can worsen the ejection fraction, and the function of the left ventricle.

And they are also confusing some of these devices. When we have - meaning, they think the inspire device might be for congestive heart failure patients, and it doesn't always work like that. So, I also want to mention, once a new technology becomes approved by Medicare, this would be an incredibly generous and enlightened set for Medicare to take.

It results, not only in increased patient access for a transformative treatment, which does not have a peer treatment, a treatment that can really change important end points, not only sleep quality, which is really the focus of my practice, but actually outcomes in terms of the function of the cardiovascular system, reduction in arrhythmias, reduction in

hospitalizations, improved time to stay away from the hospital and be in your home living a full life, but it also is an opportunity for incredible education of many specialists who are looking after these orphan patients who are completely not seen and invisible.

It is also a chance for many sleep centers that are not academic, we're in a pretty sophisticated academic sleep center, but it will be a chance for other sleep centers to learn about a new technology, and therefore identify patients that are actually overlooked.

And that is all I would like to share. I'm really grateful for the opportunity to be able to speak in this discussion and listen and learn from my colleagues. And I'm happy to answer any questions, and I'm most thankful to the patient who joined us. Thank you.

Dr. Carolyn Cunningham: Thank you, Dr. Ahmed.

Dr. Qanta Ahmed: Thank you, Dr. Cunningham.

Dr. Carolyn Cunningham: You're welcome. Thank you. Questions?

Coordinator: And again, if you would like to ask a question over the phone, please press Star 1 and record your name.

Dr. Carolyn Cunningham: Thank you again, Dr. Ahmed.

Dr. Qanta Ahmed: Thank you.

Dr. Carolyn Cunningham: Operator, is Dr. Morgenthaler with us?

Dr. Morgenthaler: Yes, I'm here. Can you hear me all right?

Dr. Carolyn Cunningham: Yes, we can. Thank you. Go ahead.

Dr. Morgenthaler: Perfect. Thank you. So thank you so much for allowing me the opportunity to talk with you all about how I feel this phrenic nerve stimulation is really able to fill a significant gap in patients who otherwise really don't have a good treatment for their central sleep apnea. If you could go to the next slide, please.

I just have my disclosures in here. I did receive some consulting fees from Respicardia to help develop the research database, and also have some consulting agreements with Withings and ER Medical. Thank you.

So this slide here, I assume you may have already seen this. I presented to this group I think some time ago, and it's just to remind us that, particularly amongst patients with heart failure, if you direct your attention towards the last three sets of bars, is really present - central sleep apnea is present in about a third of these patients, regardless of how well or poorly compensated they are.

If you go to the next slide, the next series of slides, and I'm not going to review in detail because I have been with you - with this group through them before, but it's just to point out the marked divergence between outcomes in patients who have heart failure with - versus without central sleep apnea being treated.

So here you see, you know, the two green lines are patients with heart failure who have tested, diagnosed, and treated sleep apnea, and the red, those who are not tested, not diagnosed, not treated. Next slide shows a very similar set of figures from a different study entirely, where you're really looking at, again, the divergence between patients who have central apnea problems, versus those with no breathing abnormalities. The gray line being the survival curve, those with central sleep apnea, and the blue for those who have heart failure, but not central sleep apnea.

If you go to the next slide, you'll see a similar conclusion, again, where patients with heart failure and sleep apnea just generally do more poorly. So this is really the reason that the American Academy of Sleep Medicine some years ago, decided it was time to provide some guidance on how to treat central sleep apnea.

So if you go to the next slide, you'll see a summary of those. And I just want to point out that these clinical guidelines were last updated in 2016. And at that time, this phrenic nerve stimulation therapy was really not available. And actually, there was very little published about it and they certainly - I can vouch, since I was part of this team leading the development of this guideline, they were not - no data from the phrenic nerve stimulation was not considered at all in the development of these guidelines. These need to be updated, but I don't believe that's occurred so far.

The initial guidelines actually stated that it was standard to use adaptive servo ventilation in patients who had central sleep apnea and heart failure. But a very surprising result was published at the end of 2015 in the survey HF trial that really indicated that for patients who have low ejection fraction, heart failure, that they have a worse outcome when treated with that particular version of adaptive servo ventilation.

I also want to point out before we leave this slide, that although acetazolamide and theophylline were provided as options, with very low levels of evidence, that the guideline development group actually had considerable debate about whether to provide this as an option, because the relationship between benefits and harms was very equivocal or not known. And I can tell you that the decision to include it really comes because there's very little else that we have to offer these patients. So it's a little bit of a Hail Mary with some evidence.

If you go to the next slide, what I'm highlighting here then is the particular difficulty we get into with our patients who have reduced ejection fraction heart failure and central sleep apnea. And on the right is really the real-

world experience tempered by published outcomes of the different treatment options that we have available.

CPAP, in less than a third of patients, does it actually correct their sleep abnormalities when you study them? The evidence shows that there's probably no harm. There are some indirect and uncertain benefits, things like improved ejection fraction, improved catacholamines, and the mortality benefit is unknown.

When you look at oxygen therapy, again, the evidence suggests there's no harm, benefit is indirect, mortality benefit uncertain. And the reality is that many of these patients do not actually qualify under current coverage determinations for oxygen therapy, because they're not actually hypoxic. They're often just having fluctuations in oxygen above the hypoxic threshold.

BIPAP S, although it's mentioned on guidelines, is almost never used because almost every patient gets worse who has central sleep apnea that you apply BIPAP S to. So it's a non-entity. ASV, we've already talked about. Theophylline and acetazolamide, we've already talked about. And so the - really the new kid on the block is the transvenous diaphragmatic pacing, which really I think offers potential hope for these otherwise quite miserable patients.

If you go to the next slide, I'm going to just take this opportunity to tell you, you know, you've seen, I'm sure these data that the efficacy of this device and safety of this device is not only present almost right away when you use it. And you can see that in the marked reduction in the central apnea index on the figure at the right at the six-month mark, which is shortly after activation.

But that kind of improvement persists right on through now to 36 months of published data. You can see above those, the central sleep apnea, the apnea hypopnea index and the oxygen desaturation index, that 4% desaturation index, which is a very hard outcome.

I mean, that's oximetry in response to breathing. It's not something that one can manufacture. And you can see that, you know, over time - you know, fairly quickly after initiation and over time, this is coming down such that over half the patients have event frequencies that are less than 15 per hour, which would place them in very mild circumstances for sleep apnea.

If you go to the next slide, I think more important than all of these data, are patients. And so I'm going to just briefly share a story of a few patients of mine that I have had experience with the phrenic nerve stimulating device. This patient is a Minnesota resident presented to our clinic with an abnormal overnight oximetry in the setting of heart failure.

The squiggly line, the green line on the top, is really showing their oxygen saturation across eight hours of testing during sleep. And you can see what

should be a very boring, straight line traveling across the page above 90%, what you're seeing is these repetitive, almost sick with dips and return to above baseline that you see, and is very typical for patients who have Cheyne-Stokes respiration with severe central sleep apnea.

On the next page, you can see, if you go to the next slide, please, you can see just an outline of his history. Now, he's a 70 year old. He's previously been a pillar of his rural community in Minnesota. He's the guy who, you know, starts off the 4th of July picnics. He's the guy who organizes the parades. He's the guy who organizes the Habitat for Humanity.

And unfortunately, he developed severe heart failure. He's not doing those activities anymore. He's had his coronary artery bypass grafting. He's had afib. He's got a pacer. He has multiple problems that is really taking him out. And he doesn't feel well.

If you go to the next slide, the sleep history is such that he really - you know, this is really affecting his energy levels. He reports some nights that, you know, may take up to an hour to get to sleep, and then he has to get up to go to the bathroom and he can't get back to sleep. And he is quite sleepy.

Epworth Sleepiness Scale, which under normal circumstances would be certainly less than 10 and maybe even less than eight, you know, he's above that. He's drowsy. He needs to pull over when he's driving because his wife doesn't trust him.

If you go to the next slide, this gentleman, when we first tested him in the laboratory, had an apnea hypopnea index of 53, and almost all of those were central apneas. After implantation and activation of the transvenous phrenic paced - phrenic stimulating device, you can see immediately he was reduced to half of that.

And with further adjustments as sometimes - well, so far, I've found that often there's a requirement for some additional adjustment. You know, his most recent test finds that his apnea hypopnea index is 12. He's feeling substantially improved. His sleepiness scale has come down.

If you go to the next slide, I'm just sharing with you that, you know, he is now - this last summer, he worked back for Habitat for Humanity. He's gearing up to do this again. You know, he's got his little utility belt and his hammers in it. And so, this has really helped his quality of life.

If you go to the next slide, I'm just going to share again another patient story, a carpenter from Wisconsin, who's been unemployed since cardiac events rendered him with heart failure with reduced ejection fraction. He's been sleepy for a long time in the past. He wasn't able to use CPAP, and now he has central sleep apnea.

He's got, you know, moderately severe central sleep apnea, reduced ejection fraction. And because of this intolerance of CPAP, you know, we - while we were waiting to get started with our phrenic nerve stimulating program, we tried oxygen. It didn't really help them either symptomatically or by oximetry.

We tried to temporize with acetazolamide. It was temporarily only modestly helpful, and he still remained not feeling well. After insertion of the device, over a relatively short period of time, his PROMIS 10T scores have improved from being more than one standard deviation below population normal, to actually being right in the middle of normal. And he's actually feeling very well. So, he's not going to return to work, but he is working on his little rural property in Wisconsin and is very happy with that.

If you go to the next slide, just one last patient in brief, a furniture contractor from North Dakota, very sleepy guy, also with heart failure with reduced ejection fraction and central sleep apnea. He also had difficulties tolerating CPAP. It did not work well for him.

And he was able to get a placement of a phrenic stimulator, and actually immediately began doing better. He did better enough that he unfortunately ate too many cheeseburgers and got a little heavy and developed some mild obstructive sleep apnea.

The post remedē polysomnogram showed total elimination of the central sleep apnea, but he now had a little bit of OSA, which he is now being treated with a CPAP, and he's doing quite well. So, just to give you three quick vignettes of people whose lives have been changed by this therapy, who had no alternative therapy.

If you go to the next slide, I just wanted to address two additional important questions. I had an opportunity to view the NGS observations, and there were a couple of comments that I just thought could be addressed. One of them was, someone had suggested that the sleep metrics in the randomized controlled trial were subjective. And the other comment that I just want to briefly address is concern about that residual AHI in the pivotal trial.

So if you go to the next slide, I'm just going to address these sequentially and then make myself available for questions. With regard to the outcomes in the pivotal trial, the American Academy of Sleep Medicine actually has published a paper regarding study design considerations for sleep disordered breathing.

And the AHI and the ODI four are exactly the objective endpoint recommendations. And those are exactly what was used. And they went on further to indicate that we should not use threshold values as success. That instead, we should really look to see whether various treatments or devices improve the AHI or other aspects of the patient's care.

If you go to the next slide, I think I'll probably make very short trip of it, but just to show that, you know, these signals come from patients who are sleeping. It's not that they have any influence over their breathing patterns. And I think even if any of you are not polysomnographers, you can look at these breathing patterns and very readily see that an apnea is where there's a cessation of flow and where there's more flow that's not an apnea. So these are very objective measurements. Oxygen saturation - desaturation of 4% is calculated entirely by a machine without any human assistance. So they're very hard outcomes.

If you go to the next slide, I just want to very briefly address the other issue of residual AHI, and I've already kind of alluded to that. You know, the central apneas are very effectively eliminated, if not, you know, severely reduced, if not eliminated by this device.

And what you're often left with are hypopneas. These are the little areas in blue that you're seeing in the residual graphs, both the graph on the left and the graph on the right. And these hypopneas sometimes are somewhat subclinical and threshold, but even if we assume that they're important hypopneas, you can see that, you know, the median event frequency is, you know, below 15 and almost approximating 10.

And there is debate about how important that lower threshold of having very mild sleep apnea might be. I think it would be very clear consensus of physicians though, that moving from severe sleep apnea into a very mild sleep apnea, is likely to provide benefits.

And so, I actually value the fact that we're able to get down to this low of an (indice) and considered a great success. And I think that success is mirrored in the clinical results that you saw just in these three patient vignettes. So, I think that's what I wanted the opportunity to share with you, and I'll make myself available for any questions.

Dr. Carolyn Cunningham: Thank you. Questions?

Coordinator: And again, if you would like to ask a question over the phone, please press Star 1 and record your name.

Dr. Carolyn Cunningham: Thank you again, Dr. Morgenthaler.

Dr. Morgenthaler: Thank you and the committee.

Dr. Carolyn Cunningham: Okay. Next, we want to turn our attention to biomarker testing prior to initial biopsy for prostate cancer without making a diagnosis. Craig?

Dr. Craig Haug: Dr. Cunningham, just want to - yes. Just want to first check and see if there are any other comments out there from the audience.

Dr. Carolyn Cunningham: We can. Any other questions or comments?

Coordinator: And again, if you would like to ask a - I'm showing no questions at this time.

Dr. Carolyn Cunningham: Very good. Thank you, operator.

Dr. Craig Haug: Thank you, Dr. Cunningham.

Dr. Carolyn Cunningham: Go ahead.

Dr. Marc Duerden: Yep. And thank you, operator. Welcome, everybody. The second draft LCD in the discussion today is biomarker testing prior to initial biopsy for prostate cancer diagnosis. It's an existing LCD for which we received a reconsideration request from the manufacturer Exosome Diagnostics.

Based on a level one randomized controlled trial published last year, it's listed down at the bottom of this slide, authored by Tutrone, clinical utility of the Exosome based Exo diagnosis prostate EPI test in men, presented for initial biopsy with a PSA 2 to 10, again, published 2020.

Based on this study, the below contraindications no longer apply to the EPI test, given the study patient mix and results. Excuse me. Those two are ethnicity and higher risk for prostate cancer and first degree relative with prostate cancer.

The other significant change was the one biomarker test is covered once criterion was liberalized to each biomarker is covered once. We received three requests to present comments on this policy. I think the first one is an employee of Exosome Diagnostics, Dr. Skog. Operator, can see if you can open his line?

Coordinator: Yes. Dr. Skog, your line is open.

Dr. Johan Skog: Yes. Can you hear me okay?

Dr. Craig Haug: Yes, Dr. Skog. Please proceed.

Dr. Johan Skog: Oh, well, perfect. Thank you. First of all, I would like to say, thank you for the opportunity to speak here. And I am the Chief Scientific Officer at Exosome Diagnostics biotech brand. Next slide. So the ExoDx prostate test, also known as EPI, is a urine-based liquid biopsy tests that do not require prostate massage or DRE.

And its intent is to assess the risk of high-grade prostate cancer in men 50 years of age and older, with a PSA results between 2 to 10 nanograms per milliliter, considering an initial or repeat biopsy. And that the men that have a PSA between 2 to 10 are especially challenging when determining the deficient to biopsy, since PSA performs very poorly in this gray zone, and there's a lot of subjectivity sort of on who gets a biopsy in this Tufts range.

So the ExoDx prostate test is supported by two validation studies, one in JAMA Oncology and one in European Urology in 2018, followed by a clinical utility study which is a randomized control arm study that was published in May 2020. The (SGN) guidelines do recommend consideration of additional non-invasive testing in men with PSA of over three. And the

Exosome epitaph is mentioned as a test to consider for men before a biopsy. Next slide.

So I do want to set the stage really quick though on how the test has been utilized. So the test is giving a score from zero to 100, where if you're below 15.6, you're at a very low risk for high-grade prostate cancer. And the higher the score is, the higher the chance is that you find high grade prostate cancer upon a biopsy.

So then if you have a test score of 30, you have roughly 30% chance of finding high-grade prostate cancer. And at a score of 50, it's about 50% chance. And this is really useful, especially here when you have this PSA gray zone of 2 to 10, where if a patient, if you have a group of patients with very similar age, let's say 60, and a PSA level that is very similar around five, there's no standard of care criteria that can actually differentiate these into low-risk or high-risk.

And this is where EPI comes in as a standalone sort of test that gives you new information to classify them into either a low risk or high risk. In these studies, we included basically all comers too so that the population where the test was validated, includes patients of varying ethnicities, patients with varying degrees of risk based on first degree relatives, as well as other considerations without other biomarkers. So, we really appreciate the NGS's review of the clinical evidence, and we support the revised coverage criteria to remove the limitations on ethnicity, as well as the first degree relative. Next slide.

So when you look at the validation studies published in JAMA Oncology, as well as European Urology and the clinical utility study, you can clearly see here that we have even a higher representation of African-Americans, which is a higher risk ethnicity for prostate cancer.

And in our utility study, we found that doctors that had access to the EPI test, found almost twice as many high-grade prostate cancers among African-Americans, compared to the standard of care. And so, we really think it's a useful tool in this population.

And we also found that in patients with a family history of prostate cancer, a first degree relative, actually the tests performed very well, even higher than the tests in the general population, where in this population, the negative predictive value was 93.5%. That's a sensitivity of nine to 5.8%. So this is all furthering the support of the removal of those limitations. Next slide.

So we also recommend, to remove the suspicious DRE limitation, because these patients were included in our validation studies. They were not being excluded from our validations. And when you look at the pulled analysis from all studies that we have performed so far, even if you have - so we had 155 patients who have a suspicious DRE. There's a missing word there, who obtained a suspicious DRE.

They showed no significant difference in the EPI performance in this population. And the validation studies, both the first and the second validation study, demonstrate highly similar performance, regardless if DRE or family history patients are included or excluded. So the negative predictive value and the sensitivity are basically the same. Also, the NCCN guidelines recommendation of EPI is not limited to patients without suspicious DRE. And next slide.

So we also recommend the removal of the one-time utilization for the EPI test, because in our studies, for example, we did not have an exclusion criteria for patients that have gone through the biomarker testing. And we know that NCCN guidelines and the clinical practice in general, they call for a tailored repeat testing where men are not only tested once, but they can come in for PSA testing at intervals of between one to four years, depending on PSA, age, DRE status.

And we also know that the NCCN guidelines do call for a PSA from DRE at six to 24 months interval, if high-grade PN is found. So the NCCN guidelines do not limit EPI to the patients who have not previously been tested using a biomarker, nor do they limit patients to one EPI test per lifetime. And there's, for other biomarkers here, new evidence that performance of EPI would be any different if you do the test more than one time. Next slide.

So in conclusion, we do support the proposal to be to remove the FDA coverage limitations for the ethnicity at higher risk for prostate cancer, as well as the first degree relevant, based on all the evidence that has been presented. But Exosome also recommends additional changes where we remove the DRE limitation, as well as the limitation of one-time utilization on the EPI test. And with that, I'll take any questions.

Dr. Craig Haug: Dr. Skog, thank you for these comments. I have a couple of questions for you, but let me first express my appreciation to you and your company for the multiple earnest attempts to answer my many questions on the statistical analysis of the Tutrone study. You may recall, we had some meetings and email exchanges on that. It was very helpful.

Regarding repeat testing, you mentioned studies that included patients with prior biomarker testing. Are there a published subset analysis of that group?

Dr. Johan Skog: In the validation studies that we have, there was no exclusion if they've had another biomarker test, like a 4K or MRI or any other biomarker testing prior to it. So they were all included in both of those kind of patient studies.

Dr. Craig Haug: Were those results stratified out in terms of, you know, those patients alone or their results, their outcomes?

Dr. Johan Skog: Yes. There was no significant difference in the EPI performance, whether they've had a prior biomarker test or not.

Dr. Craig Haug: We may see those various results isolated. What about in the Tutrone study?

Dr. Johan Skog: Same there. There was - that was a study where they follow the traditional standard of care. So they did all of the biomarker testing that they normally do on these patients. So some patients had an MRI, a fairly low patient - low percentage with MRIs, but they had other tests that could include a phi test or a 4Kscore or other biomarker tests. So they were all included in (unintelligible).

Dr. Craig Haug: Well, as a formal subset analysis, that's my main question. Was there a formal subset analysis of those patients?

Dr. Johan Skog: We can certainly provide that. We have looked at that selection, that there was no difference in the EPI performance based on if they've had a prior biomarker or not.

Dr. Craig Haug: Right. Yes. I think if you could provide that, and if you had something similar on the DRE patients, that would be great, because looking back, I didn't really find that there's a formal subset analyses of those groups, and the - especially in the Tutrone study that the patients that had the DRE, there was a very small percentage, around 5%. So, but anyway, I appreciate it if you could send that.

And as you probably know, the draft states that none of these assays are recommended for routine use, as they have not been prospectively tested or shown to improve long-term outcomes, for example, quality of life, need for treatment or survival. Are there any such long-term outcome studies in the pipeline for EPI?

Dr. Johan Skog: Yes. We have a - so the Tutrone study has a five-year outcome coming up in 2023, I believe.

Dr. Craig Haug: Okay. Thank you. And thank you again for your comments. Next on the agenda.

Dr. Johan Skog: I appreciate it.

Dr. Craig Haug: Thank you. Next on the agenda is Dr. Pieczonka. I hope I'm not savaging that name. Operator, can you open his line?

Coordinator: Yes. His line is now open.

Dr. Chris Pieczonka: Hello. Thank you, everybody. Thank you to NGS for allowing me to participate in this meeting. By way of introduction, my name is Dr. Chris Pieczonka. I've been a practicing urologist in Syracuse, New York with Associated Medical Professionals for almost 20 years.

I serve as the director of our advanced prostate cancer program and also have a clinical assistant professorship faculty position at Upstate University here at Syracuse. And I've been listening on the phone call here and I

second the - kind of the comments originally about supporting the removal of the ethnicity and family history. But I wanted to just sort of share my thoughts and clinical experience using this test.

I have no pertinent disclosures. I have no financial relationship with Exosome DS or the parent company. But will say that this is a test that we use a lot of, particularly in the COVID world. So I think that the way that we have approach prostate cancer screening, kind of the rug got pulled out from underneath us in the last year or so relative to patients not wanting to come into the office to be seen, both for fear of COVID, for medical reasons, whatever you might have.

And one of the reasons that I think that's important is that a lot of patients were having to make decisions now based on the assay itself, independent of really what would happen with the digital rectal exam. And so, one of the things that I wanted to give my support and credence to, would be the potential for removing the digital rectal exam limitation, as well as the family history limitations that have been proposed by my colleague a little while ago.

And I think probably one of the biggest reasons for that is that, at least in my practice, I've found that this test appears to be pretty actionable without the need for bringing the patient for digital rectal exam, particularly because of the limitations that we have with COVID and patient hesitancy for face-to-face visits.

And I think the second thing that I wanted to have a conversation about, and I see this a lot in my world, is the potential usage of this particular test on more than one occasion in the patient's lifetime. You know, what we do is we use this test upfront to help stratify whether or not more invasive testing should be performed.

And years in the past, when somebody would have some sort of elevated PSA, let's say hypothetically, often we would make a knee-jerk reaction and end up doing an invasive biopsy, which arguably could be more costly to the system. And we use this test to help stratify risk assessment upfront.

So the typical sequence of events that happens on our patients is, if somebody were to have a PSA that would fall in that sort of suspicious range between two and 10, often we'll reach for this test off the shelf to get an assessment as to whether or not further testing is necessary.

It's a pretty common occurrence that we would have that if a patient's PSA might be in the five or six range, which would be abnormal, if this test were to be within the normal range, I can go back to the patient and tell them that I'm pretty comfortable about watching this with surveillance PSA testing, rather than having to move forward with a biopsy, plus or minus doing an MRI targeted biopsy.

The reason I think that that's important is I think there's going to be a whole cohort of patients that are going to come due after having had this test sort of in 2020, let's say where I might want to use it again at some point down the road. Arguably if their PSA goes up just a little bit, you know, it would be nice for me to be able to reach back and grab this test, rather than having to go down the rabbit hole of getting an MRI, doing an invasive biopsy, exposing them to the risk of potential sepsis.

So I think that the - although the original test and study was validated on kind of a one-shot deal, I can clearly see the benefit and utility of being able to use it again if the clinical situation were to warrant on more than one time in the patient's lifetime.

I don't know if it needs to be done monthly, certainly not, but I could see a circumstance that on a yearly basis, if there was some suspicion that we would like to be able to reach for grabbing the test again and not put the patient in an unenviable situation to tell them that they would need to have a more invasive procedure done.

So those were really the - kind of the highlights of my conversation. I'd be happy to answer any questions that you might have regarding my experience. And thank you again for allowing me to participate in the presentation.

Dr. Craig Haug: Thank you, Dr. Pieczonka. It seems like you're making a slightly different argument here. You're not saying that we should eliminate necessarily contraindication of a suspicious DRE. What you're asking for is that a DRE is done at all because of the COVID situation, but that's more of an NCCN requirement, isn't it?

Dr. Chris Pieczonka: Well, I guess I'm making the point that the real world is that we're not doing digital rectal exams. So one could argue that the limitation that is done for an abnormal exam is almost usurped by the real world situation that we're faced of using a test that is independently validated on the results of the urine test, sort of independent of what the digital rectal exam would be.

So, you're right. Although that's what the NCCN guidelines indicate, I'm just sort of pointing out something that we may not have thought of, because we live in this world all the time, and we have boatloads and boatloads of people that we simply cannot be doing any type of digital rectal exam on.

So it's - again, it is mixing metaphors a little bit, but I think it's important for the purposes of consideration, that in the real world we're using, we would like to be able to use the test, independent of what the digital rectal exam would be.

If I were to have a patient would come in with a digital rectal exam would be abnormal, arguably I wouldn't put that patient to a biopsy if I had a normal test. So maybe I should sort of, you know, indicate that if I have the opportunity to see the patient, the patient had an abnormal digital rectal

exam, I would not necessarily jump for going forward with an invasive biopsy and not do some sort of additional urine based biomarker because of the potential risk that we would have of biopsy related sepsis.

Dr. Craig Haug: Got it. Thank you. Next on the agenda is Dr. Cooperberg. Operator, can you open his line please?

Coordinator: Yes. Dr. Cooperberg, your line is open.

Dr. Matthew Cooperberg: Great. Can you guys hear me?

Dr. Craig Haug: Yes, we can hear you. Go ahead. Thanks

Dr. Matthew Cooperberg: Okay. And I do have some slides. Are you going to be able to show them? If not, I can just talk through.

Dr. Craig Haug: Yes. Just - no. I think they came in too late. So if you could just talk through.

Dr. Matthew Cooperberg: Okay. Yes, sure. I can make some comments. First of all, I'm listed on the agenda as a consultant to Exosome, but I'm really here in my - much more in my academic capacity, Professor of Urology and Epidemiology and Biostatistics at University of California, San Francisco.

I have done some work with Exosome and with other biomarker and other companies. The other hat I wear is, I'm helping the American Urological Association run the large national disease registry for prostate cancer, among other conditions called the AQUA registry.

So, I just want to make a couple of comments about the Exosome test in relation to the biomarker field in general and why this is so important for the whole endeavor of prostate cancer treatment and screening. As I'm sure most of you know, the prostate cancer epidemiology has varied tremendously over the last 20 years, with the (unintelligible) weighting of national stance toward PSA screening, which in turn, you know, the US taskforce recommendations against screening that came out in 2008 and 2012, were largely driven by prevalent problems with over-diagnosis and over-treatment of prostate cancers.

So we saw a crash in prostate cancer incidents to levels not seen since the early 1980s. And five years on, now we're starting to see prostate cancer mortality rates increasing. And in the meantime, the racial disparity has really not narrowed at all.

While we've seen a significant drop in prostate cancer mortality, there is still a substantial excess mortality for African American men, particularly for younger men. And all - what this all comes down to is the fact that we did not implement PSA particularly well.

If you think about it, you know, PSA is probably the best biomarker in the history of oncology. It's just the fact that it works much better for younger

men, not as well for older men. And most of the initial studies, and by far much - most of the implementation, was done among older men, men in their late 60s and 70s.

And so, we over-diagnosed a lot of prostate cancer, over-treated low risk disease, and under-diagnosed and under-treated higher risk disease, especially among younger men. Now, we are finally at the point of a consensus across most of the major guidelines that we should be doing shared decision-making in terms of PSA early detection, but there is really not a lot of specificity in terms of those SPM recommendations, in terms of what to do with the men with elevated PSA.

And this is especially important because the trend is really toward using PSA as an early baseline test when men have less BPH, when there's less mud in the water, so to speak. PSA, under the population median, which is around one rather than four, for men in their 40s and 50s, really takes prostate cancer out of the picture for a large majority of men. So they test with very good negative predictive value for men with a low PSA.

However, we cannot advocate for early baseline testing, unless we have tools to minimize over-detection and over-treatment when we start chasing PSA at low baseline values. I can tell you about UCSF after a long conversation with our primary care leadership over the course of a couple of years.

This was a primary care department who historically have been very opposed to PSA screening and early detection efforts. We now have a protocol in place baked into our EMR, which advocates for early baseline testing, and with one of the key planks being secondary testing between PSA and biopsies.

So we have been one of the leading sites advocating for active surveillance for men diagnosed with low-risk prostate cancer, but our preference beyond that is not even to diagnose low-risk prostate cancer in the first place. And the Exosome test is one of a number that we have studied and used over the years, and for the exact same reasons that I think we've just heard. It's particularly good in the COVID era because of this at-home kit availability.

I'd like to augment a couple of comments about, you know, these exclusion criteria. I'm very happy to hear that the exclusion for African-American men based on ethnicity has been dropped. African-American men, as I said earlier, bear an excess burden of mortality for prostate cancer, but there's really no evidence that PSA should be interpreted differently for them, or that, you know, an African-American man needs to go directly to biopsy with a marginal PSA.

In fact, PSA really has been shown to perform quite consistently across ethnic groups and some very large studies published really just in the last couple of years. You know, in terms of family history and DRE, you know, family history is not a dichotomous variable. And there's a huge difference

between somebody who's, you know, a great uncle, had prostate cancer and never treated it, and somebody who's got three first-degree family members who all died before 50.

And that sounds like an obvious statement, but the fact is, family history is usually considered a dichotomous variable in these analyses. We're now in an era of a lot of germline genetic testing for men with very strong family histories. But I think there - no one would argue that any degree of family history should drive someone straight to biopsy. And I think that that stance will, again, lead to higher rates of over-biopsy and over-diagnosis.

As far as the question of MRI, MRI frankly, competes directly with the liquid markers like the Exosome test in this space of what to do with men with elevated PSA who are contemplating a prostate biopsy. And, you know, what the appropriate use for MRI is, it's really quite controversial, you know.

In the UK, now you do not get a biopsy without a prostate MRI, but there are many of us that think that is not really the right paradigm, especially in the United States where MRI is substantially more expensive than most of the liquid markers.

the negative predictive value for MRI in the PROMIS trial, which was what really started the UK down this path, was only about 76%, meaning they were missing 25% of the high grade cancers, the Gleason grade group two or higher cancers, and some very well done studies from the NCI, from Stanford, and elsewhere, have shown a real problem with inter-observer variation in terms of interpreting MRI.

So, you know, in the Stanford study as one example, if you had a PI-RADS 5, which is the highest grade assigned to an MRI lesion, the likelihood of actually finding a high grade cancer on subsequent biopsy, ranged from 40% to 80%, depending on which radiologist happened to read the scan.

So, you know, this is not a test that is ready for community primetime as a reflex test, in my opinion. And we do a lot of MRI ECSF. We're a center of excellence for it, but we don't typically use it as a screening test. We use it as a test to augment biopsy, and there are plenty of scenarios where there's an equivocal lesion, which we do not think necessarily warrants biopsy.

And there are, you know, for the most part in our practice, we use a liquid marker like the Exosome test first to decide who should have an MRI, but there are plenty of other scenarios where the patient comes in with an external MRI already, and then we use the biomarker to decide how worried we need to be about what is sometimes actually an equivocal MRI finding.

So, you know - and so, I think I'll probably close there and, you know, really just emphasize the point. So, these tests really are essential to this whole concept of smarter screening and smarter management of prostate cancer, you know, are the planks we've really been pushing for a number of years

now, is early baseline testing, very liberal use of secondary tests before biopsy to minimize over-diagnosis in the first place.

And then, you know, universal active surveillance for men with low risk disease once it's identified to minimize the harms and costs of over-treatment. And, you know, this is proving to be cost-effective, very palatable to patients, and improves the accessibility, effectiveness, and cost effectiveness of the entire screening and management endeavor. So, happy to take any questions.

Dr. Craig Haug: Dr. Cooperberg, thank you. I think I misheard you say that you thought first degree relatives positive patients should go to biopsy. I misheard heard that, correct?

Dr. Matthew Cooperberg: Sorry. Patients with multiple first degree relatives, yes, obviously we take that kind of family history very seriously. Somebody with more of a remote family history, we may or may not be particularly concerned with. We're doing - no, I think the comment was that men with multiple first degree relatives, we are more and more commonly now doing germline genetic testing, looking for things like (BRCA) mutations.

Dr. Craig Haug: Okay. So one of the contraindications we got rid of was exactly that, the first degree relatives. We didn't say multiple first degree relatives with prostate cancer. Are you suggesting that we should have something in there related to the number of first degree relatives that should perhaps not get this test, but should either go to genetic testing or biopsy?

Dr. Matthew Cooperberg: I don't know that I would get that granular because, you know, somebody could have a first degree - somebody's father got prostate cancer at 85, and was managed for back surveillance and died of a heart attack three years later. You know, that is not a concerning history.

Somebody whose father died of prostate cancer at 52 is highly concerning, right? So these are - I think it's a very difficult criteria to dichotomize in terms of coverage decisions. And I personally think there should be clinical discussion allowed here in terms of, you know, is it worth getting the marker or not?

Because the first patient, I would say there's absolutely a role. Second patient, not the guy who I'd have a very low threshold for that.

Dr. Craig Haug: Yes. I don't think studies got that greenlight to be able to figure it out retrospectively.

Dr. Matthew Cooperberg: Yes, exactly.

Dr. Craig Haug: Reading your - the email comment you sent in, it looked like you were focusing on the need to repeat testing. I don't think I heard you talk about

that. Maybe you did, but does your EMI protocol that you referred to, does that have any proficiency guidance?

Dr. Matthew Cooperberg: We do not. We have done some internal studies, just looking at our own experience with repeat testing. You know, there are not a lot of data available yet to my knowledge. I think it is clear though that as time goes on and, you know, PSA is monitored, especially in the setting of, you know, early baseline testing, our goal is that men with low baseline don't get another PSA for at least five years. It could be even longer than that.

But we are anticipating screening men over - potentially over many years if we start early. So, you know, there's little question that a single snapshot in time is not going to capture a patient's risk forever. And while I wouldn't want to see any of these tests used annually, frankly PSA shouldn't be used annually, I think the notion that we can pay - that we can perform one test at once and have an accurate picture of risk for life, I don't think is practical.

I think there has to be some allowance for repeat testing if the scenario changes, if the PSA starts rising rapidly, if there's a new nodule, if there's symptoms. And there's a lot of scenarios where a repeat test could be quite valuable. But again, I would acknowledge there's no data yet.

Dr. Craig Haug: Yes. Okay. Thank you for those comments, Dr. Cooperberg.

Dr. Matthew Cooperberg: Sure.

Dr. Craig Haug: Operator, can you see if there are any other comments on this policy?

Coordinator: Yes. And again, if you would like to ask a question over the phone, please press Star 1 and record your name. I'm showing no questions at this time.

Dr. Craig Haug: Thank you, operator. Then comments on this policy for this open meeting are now closed. Dr. Duerden, I think you're up next.

Dr. Duerden: So, the third draft policy, which we'll be discussing today is the platelet rich plasma or abbreviated as PRP. This policy in our discussions, has analyzed the data and the PRP, I'm just giving you a little bit of background, has been - this substance has been espoused to be a form of regenerative medicine where they're trying to use growth factors to heal tissue.

PRP can be produced either in an autologous or an homologous fashion. Of course, the autologous fashion is when the PRP is derived from the blood of an individual patient, and then ultimately given back to that individual patient, as opposed to the homologous development of it, where the PRP is derived from the blood of multiple donors.

When PRP is derived, it is - and then has been used by physicians in clinical practice for treating a variety of substance or conditions, such as treating chronic non-healing wounds or open cutaneous wounds, and now even recently, soft tissue injuries and joint degeneration.

The difficulty is, is that there is limited clinical studies out there showing its efficacy. To that point, effective in March 28 - sorry, 2008, CMS received a reconsideration to use PRP for chronic non-healing wounds. And in their analysis in 2008, they determined that there was insufficient evidence to conclude that the autologous PRP was going to be - was reasonable and necessary in treating these chronic non-healing wounds.

Additionally, the evidence was also inadequate to show that autologous PRP was reasonable and necessary for treating acute surgical wounds or even wounds with dehiscence. And then subsequently, continued the national coverage determination for the blood-derived products of chronic non-healing wounds, which is 270.3.

So, in regards to this LCD, we have recognized that there is a lack of level one and level two A evidence, and no clinical guidelines by any organizations, and in the absence of medical necessity even by other carriers, then because of all those reasons, there is insufficient high-quality evidence to show that PRP is reasonable and necessary for the treatment of musculoskeletal conditions, such as soft tissue injuries or joint degeneration, and that it would only be reasonable to perform those type of active - or that type of treatment if it was being done within the confines of a well-designed clinical trial.

So NGS has developed this LCD to consider PRP, as well as PRP with stem cells for musculoskeletal injuries and joint conditions, whether it's used as a primary treatment modality, or as an adjunctive treatment modality. This form of treatment would be experimental and investigational. And the effectiveness of these products has not been established. Are there any questions?

Coordinator: As a reminder, to ask a question over the phone, please press Star 1 and record your name.

Dr. Marc Duerden: Seeing no questions or comments, I'll turn the time back over to Dr. Cunningham.

Dr. Carolyn Cunningham: Thank you, Marc. Is there anything - the official commentary, there's a slide up and it says, up to March 21 of this year, which will be about 45 days from now. And the next slide has a link for submitting comments electronically, which is so simple from our perspective, and hopefully easier for those submitting them. There's also a land address. Thank you everyone for attending today. We appreciate your support. Good night.

Dr. Marc Duerden: Thank you.

Coordinator: This concludes today's call. Thank you for your participation. You may disconnect at this time. Speakers, please stand by.

END