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Jurisdiction M (JM) June 1, 2020 Open Meeting Transcript

Dr. Garrett:
In accordance with PIM Ch. 13, Section 13.2.4.4, we are going to make an audio recording of this Open Meeting and, as part of the LCD record, assure the recording is maintained on our Palmetto GBA website. On behalf of Palmetto GBA, I consent to the recording of this meeting. I will now start the recording. Okay, we have started the recording of this Open Meeting in compliance with CMS. For the record, prior to doing so, I announced that Palmetto GBA would make an audio recording of the Open Meeting and consented on behalf of Palmetto GBA. Are there any questions on this issue?

Those of you that are on call and not speaking please mute your phones. Okay, again I'd like to welcome everybody to this Open Meeting and what we're going to do is we're going to have a series of talks addressing some of our draft LCDs, and then after that we will have a period of questions. The first presenter is Mr. Matt Salkeld from PROCEPT BioRobotics talking about the fluid jet system and the treatment of benign prostatic hyperplasia.

Matt Salkeld:
Hi, Dr. Garrett this is Matt Salkeld. Can I be heard?

Dr. Garrett:
Yeah, I can hear you quite well.

Matt Salkeld:
Okay. So then just to give you a little bit about me, I've been in the industry about 20 years in pharmaceuticals, biotech, diagnostics, mostly commercial roles. I'm Matt Salkeld, the Vice President of Healthcare Economics & Reimbursement. I'd like to thank you Dr. Garrett and Palmetto for the opportunity to speak as part of the Open Meeting process. I'd also like to acknowledge Palmetto for being on the leading edge of the Medicare Administrative Contractors in terms of retiring and addressing the non-coverage category III CPT® codes, as well as following that up quickly with a proposed LCD for Aquablation.

What I'd like to review over the next 15 minutes is to touch on some of the evidence that was highlighted in the LCD, as well as review some recently published evidence that was not included in the LCD as it came out late in the process, but it is relevant to the LCD. I submitted some slides in advance, and according to Melissa the Palmetto attendees have the slides, and so I'll go through those slides and just reference where I am as I go through them. I am an employee of PROCEPT BioRobotics and an employee and shareholder.

Slide three and four of the presentation is really a summary of our position and what I'd like to cover. First, we want to support coverage of the fluid jet system. It's medically reasonable and necessary based on three things: one is the body of clinical evidence, second is society support both in the US as well as outside the US, and then the national coverage determination from CMS of Aquablation is a substantial clinical improvement.

In terms of the body of evidence I'll touch on three studies, and while we have many more studies

available the three that I'll touch on are really the core ones. There's the water study, which was Aquablation randomized to TURP, transurethral resection of prostate, the water II, which was a large prostate study, and then open water was our first commercial registry. The three-year data was recently published confirming safety up to three years with no additional adverse events after two years, a maintaining of efficacy in terms of both symptom improvement and flow rates I demonstrated durability with no retreatments, and then lastly, which we'll touch on more, is Aquablation demonstrated statistically superior safety and efficacy compared to the gold standard in a subset of patients with larger prostates in the study.

Aquablation is included in the American Urologic Association guidelines for BPH surgery, the European Association, as well as the Canadian Urology Association guidelines as well. And then lastly, and while I understand CMS, the NTAP and the transitional pass, so I understand that's payment methodology and not coverage methodology, I still believe it's worth noting that the process that is done in terms of CMS determining a substantial and designating a substantial clinical improvement requires a thorough review of the evidence. At that time, we had our one-year data of water and water II that CMS reviewed and determined Aquablation to be a substantial clinical improvement both in the inpatient and the outpatient setting using that data and as a result awarded NTAP and transitional pass-through.

On slide four, what we would recommend in the LCD in terms of the proposal is modifying the upper limit to 150 grams, and this is based on clinical evidence that has been recently published, as well as the FDA labeling. The FDA labeling has no size restrictions. In terms of clinical evidence, the water II two-year outcomes, again this is the large prostate study, was published at the end of April just as the LCD was being finalized and is not referenced in the LCD, but I think warrants further consideration and discussion. In addition, the recent publication of the open water, which was our commercial registry prostates in the size of 20-150 grams and showed predictable and reproducible outcomes.

I'll jump to slide five please, which is a summary of our core clinical evidence on Aquablation, and there's two studies that I would say are our foundations for the clinical evidence. The first one is the water study, and again this is the only FDA pivotal study that's been done randomized to the gold standard, which is transurethral resection of prostate. There have been other technologies come through that have randomized to a sham procedure, but this was randomized to the gold standard. The inclusion criteria was similar to what we see with many BPH studies looking at 30-80 grams, it was a two to one randomization, and I think worth noting that's not reflected here is it was double blinded, so the patient was blinded and each hospital staff had a team that was blinded, so the follow- up was blinded out to three years. In summary, the Aquablation demonstrated a superior safety, and comparable efficacy profile, the TURP in all prostates, a subgroup analysis and looking at large prostates, and I'll go into a little more detail demonstrated.

Aquablation's superior both in safety and efficacy, and the three-year outcomes were durable as you'd expect with a resected technique. The water II study, knowing that many surgeons would want to use the technology on larger prostates, we did a single on registry, it's the only FDA prospective study that was completed in large prostates, 80-150 gram prostates, 101 patients, and the two-year data was recently published, and it's worth noting that many of these patients would have been random, or would have been an open prostatectomy at that size of a prostate, not a lot of surgical options, and what the results demonstrated were durable outcomes out to two years, really clinically normalizing. I'll go through the outcomes in more detail, but as you look at the water which were smaller prostates, and water II and you compare them, they're virtually identical, and what this study showed was that normalizing outcomes are predictable and reproducible outcomes in large prostates, and ability to take an inpatient procedure. So open prostatectomy, which has several days in the hospital, and now you can offer the patient an outpatient procedure with a majority of these patients staying just one night, and as you'd expect with the

resected technique, lower retreatment rate.

Next slide on slide six is a summary of the three-year outcomes from the water study, again this was 30-80 gram prostates randomized to TURP, and on the left you see the efficacy which is symptom improvements out to three years, and this is using a validated international prostate symptom score referred to as the IPSS. On the right, our flow rates are more of an objective measure using peak urinary flow rates, and there's I think three points to take here, one is a statistically significant improvement from baseline in both arms, two is stable outcomes to three years, so you're not seeing deterioration either in symptom improvement or flow rates, and then three, consistent outcomes or comparable outcomes between both Aquablation and TURP.

So, again, TURP being the gold standard comparable outcomes, and I think Palmetto, as you noted in the LCD, the three-year results were essentially unchanged from two years, so no changes from two years to three years as you'd expect with a BPH surgery. On slide seven is a subgroup analysis, a pre- specified subgroup, to note the average prostate size in this study was about 54 grams, so the 50-80 category was about half the patients in this subset, and I think it's important to note as prostates get bigger and bigger, and I'll let again Dr. Singh and Dr. Kriteman who are following me speak to this, they get more complex from a surgical standpoint, more dependent on the surgeon skillset, what this showed in the water study in the subgroup analysis was that Aquablation was superior both in safety and in efficacy compared to TURP at three years in this larger subgroup, and noting, the authors noted that the three-year results combined with the other data show that compelling long-term evidence for the safety and effectiveness of Aquablation and then with less. So, good outcomes out to three years.

I'll move to slide eight. The reason this is in here is just to reiterate that Aquablation is a tissue retreatment technique. I think there's been some confusion on this in the past, this is tissue retreatment, and as you look at other tissue retreatment techniques the two primary ones are TURP, and then laser as well, and this is an analysis of looking at nearly 12,000 patients discharged, and out to four and a half years, and the freedom from retreatment, and you can see here both with laser and with TURP, it's roughly about 2% per year in terms of retreatment, so at five years about 10%, at three years you'd expect about 6% retreatment rate, and what we've done here is added the Aquablation and the TURP arm from the water study out to three years, and you can see as you'd expect, again, it is a retreatment technique, and you'd expect durability and retreatment rates within that, which is what we're showing here.

On slide nine, the AUA guideline from 2019; they were redone in 2018 and amended in 2019. In 2019, the Aquablation was added as the only new surgical approach added, and I bring to your attention, you'll note one kind of the upper left there, the first thing a surgeon's supposed to do when determining which technique to use from a surgical standpoint is to assess the size of the prostate, and that's because when the prostate gets bigger, the two main options are open prostatectomy, and enucleation using laser, which is less than 5% of the procedures being done due to the surgical complexity of the procedure. There are some challenges in terms of surgical options for patients with large prostates, and that's why the water II study was very relevant.

On slide 10 is our FDA labeling, and I just note here, again, you can look at it later, there's no limitation on prostate size according to our FDA labeling. Moving to slide 11, I've touched on the water study so far, so again that was our pivotal study randomized to TURP, now getting into water II, which is the large prostate study, and this compares the patient inclusion criteria of water and water II, I think very similar inclusion criteria with the distinction of prostate size. The average prostate size in the water study was 54 grams, in water II it was 107, so nearly double the prostate volume between water and water II, and as I mentioned earlier, bigger the prostates get, the more complex they get from a surgical perspective.

What we've done on slide 12, and I'll jump to the results of water II, and what we felt was relevant here was to compare it to the outcomes of water. So you're talking about a prostate that's nearly double in size, and now you're looking at the symptom improvement at each of the data points out to two years, and what you'll see here is virtually identical outcomes in the larger prostate at each data point out to two years with water II even having a slightly higher reduction in symptom score, but it's not statistically significant, so it is virtually the same outcomes at each data point out to two years in terms of symptom improvement.

On slide 13 it looks at the sub components of the International Prostate Symptom Score, which are voiding in storage and total IPS, and looking at baseline three months, six months, 12 months, and 24 months, and again are virtually identical in terms of the outcomes and symptom score improvement, so you didn't see this in the water studies. You look at the TURP arm in the water study, when the prostates got bigger you saw a deterioration in symptom improvements because the outcomes are more dependent on the surgeon's skillset with a TURP, with Aquablation based on the robotic component, it's automated, you can get predictable and reproducible outcomes.

So jumping to the conclusions of the waters II study, as we said, normalizes the outcomes regardless of patient prostate size or shape, the benefits that we saw in the water study were shorter or at times length of stay maintaining antegrade ejaculation, we saw both in small prostates and large prostates now, and I think very important, the learning curve in these studies, two-thirds of the sites in the studies had never used Aquablation before, so even though the prostates were larger, two-thirds of the sites had never touched Aquablation, so it speaks to the learning curve, and the conclusion there obviously is the durability on the large prostates.

Last few slides here, and slide 15 just compares other surgical approaches for large prostates, and primarily looking at open prostatectomy, and you'll see here that this was a meta-analysis looking at 35,000 Medicare patients that had open prostatectomy, and you'll see that it had an average length of stay of 5.4 days, and a perioperative transfusion rate of 24%. What we're reporting in the water II study is 1.6 length of stay, and 6% perioperative transfusion rate, and this was really the data that we used in discussions with CMS on the safety profile, and being able to offer the patients that may require an open prostatectomy inpatient stay obviously more complex and complicated, being able to offer a transurethral procedure that can be an outpatient setting is significant.

On slide 16, the open water was our first commercial registry, this was kind of an all-comers study, five sites globally, 178 patients, average prostate volume was 20-148 grams with an average prostate size of 60 grams. You'll see the safety profile was at similar rate of 22% adverse event rate, and 2.7% transfusion rate, so similar safety profile, no retreatments at one year, and here we plotted the results from open water, both in terms of symptom improvements and flow rates, and you can see we plotted those outcomes relative to water and water II, and very much right in line. The conclusion from the authors, the real-world evidence shows that Aquablation is safe and effective for the treatment of BPH, so again predictable and reproducible outcomes.

On slide 17, this is just a summary, and you can review this later, just some of the outcomes of these other surgical techniques for BPH enlarged prostates, variety of complications associated with them including retrograde ejaculation, some of the techniques such as a TURP, a laser, are very dependent on the bigger the prostate the longer the resection time, and obviously complications can be higher, but as you compare it to Aquablation, shorter a lot of time, length of stay better for the patient at the end of the day.

In conclusion, slide 18, we support the proposed LCD that considers Aquablation a reasonable necessary request, the indication to be increased to 150 grams, and aligns with the FDA labeling, and well based on the new data that's been published, and so based on the evidence ... so we demonstrated the water study, durable out to three years, and there were no changes in outcomes from year two to year three, we've demonstrated that the water II outcomes now published out to two years were very comparable to water at two years, and would not anticipate anything from year two to year three as well.

Society guidelines recommendation, despite not having the recent clinical literature, and then obviously recognizing that NTAP and transitional pass-through are payment methodologies and not coverage still required a robust study of the evidence, and looking at it, and designating Aquablation a substantial clinical improvement, and then as I mentioned, the recently published water II two-year data that is not reflected in the LCD. So, again, thank you for the time here, and I'll stop and turn it over to Dr. Singh or Kreitman, are happy to answer questions, so thank you Dr. Garrett.

Dr. Garrett:
We'll have two more presentations on the same draft LCD, so we'll hold any questions concerning it until after those. Next presenter is Dr. Singh from Potomac Urology who is also talking about DL38549, Dr. Singh.

Dr. Singh:
Hello, good afternoon. So, thank you for giving me a chance to speak about this water jet system, Aquablation. My name is Inderjit Singh, I'm a partner with Potomac Urology Woodbridge, Virginia. To give a little background about me. I did my urology residency from SUNY Downstate in 1992, and then I started my urology practice in Woodbridge, Virginia. I'm a board-certified Urologist and have been in practice for 28 years. I have special interest in BPH treatments, so just to give you historical background, when I started my urology practice TURP transurethral resection was the main surgical option for BPH.

Overall it produced good results but was associated with hard undesired morbidity. There have been lots of procedures that have been tried and used for the past three decades. There was initial excitement followed by four results that led to discontinuation of some of these modalities. There are some that have helped in the office setting, and they have made a niche in the aqua setting like Urolift, Rezum, and found a role in a smaller to medium sized prostate.

So, when Aquablation was introduced I was skeptical because of my prior experience with other modalities, but I was surprised with the results, and in my experience, it has worked better than my expectations, even with larger glands. I commend CMS for doing due diligence prior to proving this therapy, or any other therapy, because sustained results are important, that's why I am so excited about this treatment, or similar results to TURP but with lesser morbidity compared to TURP.

Now you have my slides, they're not many slides so it's not going to take that long of time. First, I have no conflict of interest, I have no association with this company except for patients. Go on the second slide, experience at Potomac Urology includes 33 patients from May 2018 to February 2020, the average volume was 63 grams, and 11 out of 33 patients had a size of 80 grams. So even though we try to select patients, not very large prostates, even then there are 11%, almost one-third of patients have larger than 80-gram prostate, and you can see the results on the next slide. So, on the left side of this slide number four, you see the procedures, number of procedures, and the prostate size, and on the right side it is actual time. So, we can see the procedures vary from 20 grams to 120 grams, and the average would be about 60, 63 grams as it says there. If you go on the right side, the learning curve, really there's not much of a learning curve needed, I mean, every patient, even the smaller gland may sometimes take longer, it depends upon the time to set up the equipment, the treatment time itself is like five minutes, so overall

the time taken for it is like 50 minutes on an average, and that really has not really changed much from the beginning to the end.

This includes the larger glands also, so even for larger glands you can see that you can use this treatment with similar efficacy, and you avoid having them stay in the hospital for data during the procedures like open surgery that requires transfusion in a lot of situations. In other results have been excellent, I had one reoperation, all of the patients did very well, they were catheter free after three days, most catheters were removed the next day, some of them to be done in their office, except for one retreatment no other patient required retreatment.

I'm very excited about this treatment, I think this is a game changer as far as comparable results with TURP, with additional benefit of reduced morbidity on sexual function, and ejaculatory function, which is very important for some men, especially with a relatively younger and sexually active. So that really is, in a nutshell, my experience with this procedure, I'll be happy to answer any questions, and I'll save some of your time so you can utilize for questions.

Dr. Garrett:
Our next presenter is Dr. Lewis Kriteman from Georgia Urology also talking about Aquablation, Dr. Kriteman.

Dr. Lewis Kriteman:
Yes, thanks Dr. Garrett, and I appreciate the opportunity to speak to CMS and Palmetto about Aquablation. I think Dr. Singh's done an excellent job of summarizing sort of where we were as far as BPH is concerned, and hopefully what we can show you is kind of where we are and where we hope we're going in the future as far as BPH treatment is concerned as well.

I have very few slides, just to give you a quick background on me, I am a partner with Georgia Urology, and specialize in voiding dysfunction in both males and females with a special interest in BPH. I do all types of BPH procedures, laser procedures, and Rezums, and Urolifts, and started to do the Aquablation about two years ago. I've got a huge referral base not only from my practice, but also around Georgia and the southeast for sort of the big, bad and ugly prostates that we would normally be using other modalities to treat, which quite frankly really don't give us the same results that the Aquablation has.

So let me go through my slides quickly to give you a real-world experience as far as my experience is concerned so that we do have time for questions, because I think it's important that we help you guys to understand why we think that this is the procedure of the future. The first slide really is the conflict of interest, I do serve on an advisory board for the manufacturer of Aquablation, I'm a speaker, and I help teach other physicians how to do this procedure, both in my own operating room as well as teleconferencing other physicians in from around the country and around the world.
My next slide summarizes what makes Aquablation a better procedure and a more attractive option for a lot of my patients. The fact that it's a standardized result and a very straightforward, the procedure is important, the skill of a receptionist for a TURP, for a greenlight procedure really depends on that experience of the surgeon and how good they are at doing that, we don't see that with Aquablation. I mean, we're going to get a standardized result every single time, and we expect the same channel through the prostate every single time, and from a research standpoint because we do a lot of publishing on BPH, I find that very exciting.

Size really doesn't matter, and when I show you my next slide, you'll sort of see where I've been as far as the patient sizes that I've done. This is a good procedure for 30 prostates, this is a great procedure for a 100 gram prostrate, a 200-250 gram prostate, and so it really is a Swiss Army knife of BPH treatment,

whereas some of our minimally invasive procedures like Urolift or Rezum require that the gland be smaller, less than 80 or 100 grams, it doesn't really matter, and we're going to get the same results regardless of the size.

Sexual function we're finding is more and more important to our patients as we come out with these new procedures, and so some of the minimally invasive procedures that do maintain sexual function both from an erection standpoint as well as an antegrade ejaculation standpoint have really impressed upon us urologists how important sexual function is, and ejaculatory function is for our patients. We finally have a procedure that we can use on any prostate size that will in the vast, vast majority, greater than 90% of the time, maintain the patient's sexual function, and ejaculatory function, as well as the sensation that they have that ejaculation, and we're finding that to be more and more important.

Let me go to the next slide quickly, which is my real-world experience just in our first 20 patients. We've done, I'm pretty sure, close to 60 or 65 greenlights in Georgia Urology, this is the first 20 patients because we had data on these patients, but these are my first patients, and what you've seen on the left there is what's the most important thing, and that's the AUA symptom score for the IPSS, the International Prostate Symptom Score. This is what the FDA mandates that we use, approximate points, for all of our trials, and what you see in there is about an average of about 26 on their IPSS pre-op down to about four post-op, and that's a really good result especially when you compare it to any other operative procedure, extraoperative procedure, whether it be a TURP, or a GreenLight, or a HoLEP or even open prostatectomy.

Average PSA reduction also from eight down to about three, which is very important for us to know those numbers so that we can follow up patients appropriately post-op. My average size above that was 111 CCs on these 20 patients, and I think it's also important to note what the average procedure time was, and that's from the time we start the procedure putting the ultrasound probe in the rectum, till the time we finish when we put the catheter in the prostate. I've done every type of procedure out there for BPH, I will tell you for 111 CCs, you can't even come close to doing that in 28 minutes regardless of which modality you use, and that's really going to speak to more efficacy and efficiencies in the operating and in schedule time.

On the graph that you see to the right, you see the sizes, the smallest size I think we did in the first 20 was 50, the largest size was about 235, and that goes again to the average prostate size of 111 CCs. I know that PROCEPT and Matt earlier asked that you guys increase the size to 150 as far as the limit is concerned, I would actually ask that you don't put a limit at all on the large glands, when you see what the alternatives are for what we have, we as urologists have at our disposal to take care of these large glands, you're really looking at robotic simple and open simple prostatectomies for these super large glands, and those are going to have a lot more morbidity, more mortality, they're going to have a much longer hospital stay, and really aren't going to give you any better outcomes with less safety. Sexual function was preserved, and 90% of the patients who are still sexually active. The other set of patients noted a decrease in their volume of ejaculate, but we sort of count that as being not preservation of their ejaculatory function. So, in summary, the last slide just shows an IPSS improvement, post-void residuals went from 130 out of 25 CCs and as mentioned earlier the sexual function really is a big plot, and so hopefully both Dr. Singh and I have given you sort of a real world view of what we think, as far as our option for taking care of these patients with any size gland including the large glands, and with that I'd be welcome to answer any questions that you guys might have.

Dr. Garrett:
It's Dr. Garrett again, thank you all three. We are open for questions for now. I have one request of Mr. Salkeld, I have not seen the new water study, and I would suggest that since we'll now be entering the

comment period for this draft, if you could send the comment requesting or suggesting the increase in size either along your recommendations, or Dr. Kriteman's recommendations with a hard copy attached to that, the new water study that you quoted, it would be greatly appreciated.
Any other questions? Hearing none we'll proceed to a MolDX presentation on Prognostic and Predictive Molecular Classifiers for Bladder Cancer DL38576, Dr. Gibb.

Dr. Ewan Gibb:
Yes, so much for the opportunity to present our classifier. So, my name is Ewan Gibb, I'm a Senior Scientist and a Bladder Cancer Program Lead at Decipher Biosciences, that's for slide one. So on slide two, a little bit of background about bladder cancer, so to give people sort of a sense of where we're working, bladder cancer really is a tumor that arises from the transepithelial layer, lining of bladder lumen, so this is the aligning of tissues surrounding the lumen of the bladder, the space in the bladder that holds urine.

US and Canada are actually quite common in cancer, fourth most common cancer in men and twelfth in women, and has a higher instance in men, three times more common in males and in females. It tends to be a disease of the elderly, so the median age of the diagnosis is 73 years of age. One of the challenges with bladder cancer is its extremely aggressive disease that's associated with a high risk of both morbidity and mortality, and this can be true whether it's non-muscle invasive, which I'll get into, or muscle invasive.

Muscle invasive disease, for example, has about a 50% mortality rate of five years with no treatment. It's also a very expensive cancer, in part, because the high rates of recurrence require repeated visits to the clinic for updated screening, but also there's a lot of decisions that need to be made in how it's treated, so it can be quite costly.

So in slide three, this is an overview of how bladder cancer is regarded clinically, so there's basically two different kinds of bladder cancer, that's non-muscle invasive bladder cancer, which is about 35% of cases, this is where the tumor has not actually invaded into the muscle layer surrounding the bladder. You can see a schematic on the left where I indicated the kidneys and the bladders, and on the right the diagrams indicating the scope view of the bladder wall.

Muscle invasive bladder cancer, which represents about 25% of cases is actually where it has penetrated the muscle layer, and the deeper it's penetrated through the muscle or into the fat layer, even outside of the bladder wall, impacts the staging. So, in slide four, this is to show really how complex bladder cancer management is, and so on a non-muscle invasive side, even for a patient who's just been diagnosed with probably a different bladder cancer, they have a series of decisions to makes, and this is just for the first step.

After they've gone through their first round of treatment there's often a second level treatment, and these treatments increase in intensity typically. Muscle-invasive bladder cancer, and this is just a subset here, where we're looking at clinical stage II patients, again, the patient has numerous decisions that need to be made, and a lot of different treatment options, particularly now there's a lot of different drugs and treatments that are emerging sort of becoming increasingly challenging, how one would treat these patients.

The small inset on the left, there's another indication for small cell bladder cancer, which again is a rare tumor type, not as rare as one might think given some data that we've published recently in retreatment decisions, and so this is not a very important indication for the tumor.

So, on slide five we have basis of our test. Our test is based around a content called molecular subtyping. So this is not a new tool, it has emerged originally with breast cancer actually, but has been recently developed in bladder cancer as well back in 2012 and as you can see from the string of publications presented in this slide, has been refined and updated and been changing and evolving over the last eight years or so.

So, the Decipher Bladder TURBT test is an assay built on this long-standing literature, and basically separates tumors in the most broad sense into basal and then luminal tumor, we'll get into details of that. Our test is indicated for patients diagnosed at TURBT with bladder cancer for any high grade non-muscle invasive clinical stage T1, all the way up to locally advanced clinical stage T4, and none of the patients are indicated to have received a radical cystectomy at the time of our test is run.

So, slide six is the background of the actual technology. The test uses a clinical grade whole transcriptome assay to look at the bladder cancer biology. We use a total of 209 genes to classify the patients into one of five molecular subtypes. So, this is a categorical model, and not a continuous model. It must be extensively, analytically validated as a sole source laboratory test and it's CLIA-certified.

So, on slide seven this is a snapshot of one of the panels of our test report. On the left is the diagram to give a patient and physician sort of a sense of what type of tumor they're looking at, but on the right is the actual test readout. So, again, it groups patients into one of five categories, and the patient's given a probability score for each of the indications, each of the possible subtypes with the highest probability being the most likely called subtype for that patient. We typically see a much higher probability for one subtype versus the others, so this is quite consistent, quite robust.

On slide eight, this is some of the indications, I think, appropriate for the patients based on the consensus guideline. So, for example, if a patient were to have a luminal subtype or a luminal bladder cancer, these patients really have a much higher probability of being organ confined, meaning that the bladder tumor has not spread outside the bladder itself, it's not metastasized, and they really have a limited benefit from neoadjuvant chemotherapy based on current literature.

On the other hand, patients of a basal subtype are much more likely to be non-organ confined, meaning the tumor has penetrated the bladder wall, and these patients are observed to have significant increase benefit from cisplatin based chemotherapy in terms of overall survival or a period of about five years. Patients with a claudin-low tumor we found to have the greatest benefit from immune therapy Pembrolizumab, for example, but really don't have a favorable response to cisplatin-based chemotherapy, and this is based on new data as well.

Finally, we have the neuroendocrine-like subtype, and this is a very interesting tumor type because these patients have a biology that's extremely consistent with small cell bladder cancer, but the patient tumor actually presents as a conventionally urothelial carcinoma. So, on diagnosis you wouldn't actually know whether the patient has this aggressive tumor type, but the clinical and biological behaviors of the neuroendocrine tumors are identical to small cell.

Bladder cancer and these patients, according to the NCC, and guidelines would be clearly most benefit from more aggressive chemotherapy regimens including etoposide and cisplatin-based chemotherapy. Finally, on slide nine, we believe based on the cover of this criteria indicated in the LCD that we actually meet all these indications again and we're set to meet the criteria for coverage and DL38576.

Lastly on slide 10, we have a series of literature for those who are interested in following up on this presentation and slide 11 is a thank you slide. So, I want to thank everyone again for their time and for

the opportunity for us to present this model to you. So, I'm happy to take any questions if there are any from the audience.

Dr. Garrett:
Are there any questions on Dr. Gibbs presentation?

Dr. Brito:
This is Dr. Brito from Palmetto. Can I just ask one question? You're saying that you can determine neuroendocrine differentiation because the histology doesn't look like neuroendocrine cancer? I just wanted to clarify that.

Dr. Ewan Gibb:
Absolutely. So what's very interesting about this, it's a neuroendocrine-like subtype, so when we do a profile with a TURBT sample, we haven't in the past accepted any neuroendocrine or small cell histology, these tumors look like conventional urothelial tumors, so when you look at their genomic profile they're identical to small cell tumors. So, it's as if the tumor hasn't quite presented, or has some of the phenotype of a small sub-disease. Did that answer the question?

Dr. Brito:
Yes, thank you.

Dr. Garrett:
Okay, any other questions? Thank you, Dr. Gibb.

Are there any other comments? I'll make a couple of announcements then while we're waiting. Those of you that did not register need to email Melissa Robinson to note your attendance. Her email is Melissa.J.Robinson@PalmettoGBA.com. Secondly, the comment period began on 4/23/20 and was set to end on 6/6/20 but because of the COVID-19 pandemic, and requests from multiple shareholders, we've extended that comment period to 7/7/20. If you want to make a comment on the presentations today, or additional comments on the draft LCDs, please send those. Melissa, where do you want the comments sent?

Melissa Robinson:
The mailboxes are notated on each proposed LCD.

Dr. Garrett:
Okay.

Melissa Robinson:
That would be a.policy@palmettogba.com, b.policy@palmettogba.com, or MolDX.policy@palmettogba.com. Also just to let everyone know, the changes for the end date of the comment period will be reflected on each proposed LCD this Thursday, so if you were to go out to the Medicare Coverage Database and view the proposed LCD, those changes will be reflected.

Amanda Patterson:
This is Amanda Patterson again, Dr. Rapp's practice manager, they are planning to both present, Dr. Clayton was going to begin, and then Dr. Rapp.

Dr. Garrett:
Hi Dr. Clayton, we're ready for you whenever you are.

Dr. Clayton:
All right sounds good.

Dr. Garrett:
Dr. Clayton is going to be talking about the Stretta Procedure, DL34553.

Dr. Clayton:
Well, greetings and thank you for allowing me the opportunity to talk to Palmetto GBA about the Stretta Procedure in hopes and consideration that we might be able to provide this to our shared customers and patients. A little bit about me, my name is Steven Clayton, board-certified Gastroenterologist, I'm at Wake Forest Department of Medicine, I am their esophageal expert.

I have no pertinent conflicts of interest and I'm not employed by or have any financial interests the corporation. So, a little bit of an introduction, so basically multiple observational studies from different institutions have consistently reported Stretta improves GERD, symptoms, quality of life based upon validated metrics. Similar to the results of randomized studies, we have several meta- analyses, there are reports that the Stretta procedure can significantly reduce distal esophageal acid exposure time, and patient satisfaction and symptoms.

Long-term results of Stretta are similar to those of Nissen fundoplication, essentially decreases or reduces the reliance on proton pump inhibitors and other anti-secretory medications, and the Stretta procedure has been endorsed by two different society guidelines, SAGES in the surgical community as well as the American Society of Gastrointestinal Endoscopy, the ASGE, support the use of Stretta in properly selected patients.

Overall our objective today is hopefully to gain parity with other endoscopic anti-reflux procedures, such as the TIF procedure, allowing physicians to offer an effective, and to be honest, probably less invasive solution for patients with GERD that would greatly benefit from the Stretta. So certainly, as I'm talking, if I go over the time allowance, or if there's questions let me know. Initially this was supposed to be a PowerPoint introduction, but so my next slide was going to talk about how the Stretta procedure is performed, but it's performed endoscopically with a radiofrequency catheter that's placed into the esophagus at the level of the lower esophageal sphincter. It has four essentially hooks that deliver the radiofrequency energy, and you move these around the LES in the lower esophagus, they deliver thermal energy which stimulates esophageal remodeling, and overtime tighten the sphincter similar to the way that a fundoplication augments the sphincter and provides an effective barrier for reflux. So, I think you guys are all familiar about GERD, I mean, it is the most common GI tract ailment. Approximately 30% of the United States adult population suffer from GERD, proton pump inhibitors, kind of the medical mainstay, have definitely made vast improvements in the treatment of GERD but still about 33% of patients out there have incomplete relief of their symptoms with GERD, and then we all know about the media, and they really like to villainize the PPIs.

Every time you turn on the news there is another report about how PPIs are associated with acute kidney injury, dementia, and albeit studies usually don't pan out when we do better observational studies. It does cause a little bit of apprehension in our patient population and you have certain patients who have significant GERD, poor quality of life as a result of it, who want something else other than medications to control their symptoms. From a surgical standpoint, laparoscopic fundoplication's kind of been the mainstay, it certainly is the most robust operation for treatment of GERD, but it has inherent disadvantages, it's invasive, can have up to a six-week recovery time, it permanently alters the patient's anatomy, and side-effects are not uncommon, patients will complain of dysphasia, gas, bloating, inability

to belch are not uncommon side-effects, and furthermore there is the risk of buccal nerve injury and subsequent gastroparesis.

Stretta is an important part of the kind of the continuum for GERD. Stretta augments the LES function reducing GERD, and if you look at long-term data, 80% of patients are off of daily anti-secretory medicines at four years, and at 10 years 64% of patients are off their medications at 10 years. There's been over 40 studies including sham trials, and randomized control trials, it had proven durability in multiple long-term studies, and it's significantly more cost-effective than alternative surgical options, and even probably the TIF procedure.

This is something that's done same day, we do them quite often here before COVID, these things the patient comes in, we perform the procedure, and we have not had to hospitalize any patient's post-procedure here in our experience in Wake Forest. It doesn't preclude other treatment options, so if the patient doesn't do well after Stretta they can still go for traditional anti-reflux surgery, basically it's very easy to pick up the learning curve, not terribly steep, and it's got a very low complication rate, less than 1%.

Patient selection, the Stretta procedure is not for everybody, there are certain patients that would do better with reflux, anti-reflux surgery, and traditional laparoscopic Heller myotomy, but Stretta really is for the patients with mild to moderate GERD, and this is key, they can't have a big hernia, we recommend that Stretta is best for patients with a small hiatal hernia who partially respond to meds, for patients who just don't want to be on PPIs, or they're concerned about long-term side effects, drug interactions, my own personal experience as an Esophagologist, I get referrals for some of the toughest patients with GERD to evaluate.

So Dr. Rapp and I collaborated quite a bit when I was at University of South Carolina School of Medicine, Greenville, one of the hardest patient groups to treat from a reflux standpoint is somebody who's status post gastric sleeve, we would have patients on multiple different medicines including PPIs, H2As, Carafate, and still have significant evidence of bad reflux disease. These patients initially treated by Dr. Rapp come back to me in follow up and say, "My reflux is significantly better," and we'd be able to de-escalate some of their medication regimens.

So, it's really been a game changer in post sleeve reflux. So, contraindications, who really should not have a Stretta Procedure? For people under the age of 18, pregnant women, you really don't want to do this on somebody without a proper diagnosis of GERD, and you don't want to do it on hiatal hernias really that are bigger than two to three centimeters. Obviously, you want to make sure that the patient doesn't have some form of underlying esophageal dysmotility such as achalasia, or somebody who's not a good surgical candidate.

Mechanism of action, it basically uses low-power radiofrequency energy, and is delivered to the tissue through these small hooks, for lack of a better term, and we treat multiple levels to maximize exposure to the esophageal, the muscle of the lower esophageal sphincter, and the gastric cardia. Over time the esophageal musculature remodels and becomes a more taunt, or tight barrier for reflux. This has been well-documented on multiple different models, both human and animal, there was a trial by Herman and Holt where they did a blinded randomized control trial with pigs, and they showed significant increase and hypertrophy including muscle tissue.

Back in 2013, there was a similar study done with canines for seven months, post- treatment they saw significant muscle hypertrophy. In humans this was demonstrated with endoscopic ultrasound back in 2004 by de' Angelis. In our clinical efficacy, Stretta has been around for a very long time, they're going

on 20+ years, this has been examined by numerous different studies, and we've got pretty good evidence at this point in the form of two meta-analyses showing with a combined patient population of over close to 4,000 and a really nicely done meta-analysis by Ronnie Foss in 2017, and another one by Perry in 2012.

We also mentioned the other 40 clinical trials supported by two different medical societies. Ronnie Foss in 2017 had a very high-quality comprehensive study, large ranks, and the top 1% is systematic review and meta-analysis, looked at 28 studies with a combined 2,468 patients, and had up to 10 years of follow-up, and that's one of the great things about Stretta is it's been around for a while. So, we get to see how long people benefit from it.

Overall, the summary of this meta-analysis to a significant improvement and health-related quality of life scores, symptom significant reduction in heartburn symptoms, the majority of the patients were able to wean off or deescalate on their proton pump inhibitors, we had significant healing of erosive esophagitis, and on objective PH impedance monitoring showed a decreased distal esophageal acid exposure time, and a low adverse complication rate of less than 1%.

So patient safety, that's always a major concern. If you look at Stretta versus EsophyX versus LINX, Stretta is typically done with MAC anesthesia compared to the other ones that are done with general, Stretta is about $500 less expensive than EsophyX, which is covered by Palmetto GBA, and way less expensive than the LINX procedure which is about $12,000. So it's about $8,500 less than that, Stretta over 20 years we've treated over 30,000 patients with this, and FDA reported adverse events is extremely low, at the time of January 2020 when these slides were put together it was just three reported adverse events, compared to EsophyX with 109, and LINX with 500.

Basically, after an investigation of the three adverse events they were investigated and found not to be device related, so it has a 0.0001% adverse event rate, so we've established that it basically works, improves symptoms, basically in and out of the office, but how durable is it, how does it compare long-term to, for instance, Nissen fundoplication? De Guerra et al in Gastroenterology research in practice volume 2014 had 26 study participants with refractory GERD that were treated with Stretta, and they followed them for eight years, and at the end of eight years 76.9% were completely off of all anti-reflux medications with just the reported only occasional symptoms.

In that study, the primary outcomes were achieved greater than 50% improvement versus baseline, they saw a significant and sustained improvement in GERD, HQRL scores saw improvement on an esophageal acid exposure at four and eight years, VB and LES pressure showed no significant changes from baseline, and they saw no disease progression, and what this means is that they showed no worsening of an erosive esophagitis on the LA grade, no Barrett's or cancer related.

So, they concluded that Stretta at eight years compares very favorably than the more invasive Nissen fundoplication. Mark Noir in surgical endoscopy in 2014 published another study showing long- term maintenance of effect of radiofrequency, energy delivery for refractory GERD, he looked at 99 patients with refractory GERD and followed them for 10 years, in that 10 years 41% were still off of PPIs, now that's very comparable to the data that we see with fundoplication, about 50% of patients after a fundoplication will need some form of anti-secretory medication.

Once again, he also treated patients with Barrett's, and he said that he saw demonstratable improvement in Barrett's tissue in 85% of cases, and he even showed some disappearance of the metaplasia, no reported cases of esophageal cancer, statistically significant sustained improvement in GERD measured by the HQRL scores patient satisfaction, two studies looking at long-term data shows

it's pretty comparable to traditional anti-reflux procedures, and in bariatric patients, like I said, the sleeve gastrectomy patients are certainly one of our most challenging referrals, because these patients as a result resecting the fundus have lost the reservoir capacity of the stomach which increases gastric pressure.

In terms of physics, things go from high pressure to low pressure, well the lower esophageal sphincter is one of the weakest sphincters in the body, the upper esophageal sphincter has significantly higher basal pressures, the pylorus has significantly higher pressures, as well as the anal sphincter, so it's really one of the weakest sphincters in the body, and basal pressure's somewhere between 15 and 18 millimeters of mercury. So, it doesn't take much pressure to overwhelm the LES, and is part of the reason why reflux is a major problem, especially in your obese patients, where intra-abdominal pressure is elevated.

So, you take somebody who is obese, and then you give them a gastric sleeve, it's like the perfect storm for reflux, and these patients at that point they don't have a surgical option because you've resected the fundus, and the fundus is essential to doing a fundoplication. So, the Stretta has been a real game-changer in bariatric patients with GERD. If you look at GERD after the laparoscopic sleeve gastrectomy in Roux-en-Y or gastric bypass, when you talk about the sleeve gastrectomy, 84% of patients with existing GERD will still have GERD afterwards, we kind of went through this slide pretty well.

Routine patients do a little bit better from a reflux standpoint, because you've increased basically the gastric opening, so things have a chance to go downstream better, but you've also bypassed the bulk of the parietal cells in the stomach. So, the advantage is the Stretta for bariatric GERD is non- surgical, these patients have already gone through one surgical procedure, so attempting to do another surgery is going to be limited by adhesions and it's in and out, so there's less risk from a sedation standpoint. You can do it both in patients with routine, and laparoscopic sleeve gastrectomy, it doesn't preclude any future or more invasive options such as the LINX.

Dr. Garrett:
Dr. Clayton, you have three minutes left. I'm sorry.

Dr. Clayton:
Oh, three minutes left? All right, so how am I going to basically convince you guys, well ASGE gives a strong recommendation with a high level of evidence of the strong recommendation, the ASGE in June 2015 basically said adverse effects were infrequent, and typically minor, the technique appears to be durable to leave GERD symptoms up to 10 years, and this is a major GI guideline.

Basically, the summary was that endoscopic anti-reflux therapy may be considered for select patients. Financial impact, there's been several budget analyses showing that it's significantly more cost-effective, there's a trial done by Dennis Gregory who concluded that adding to the clinical importance of radiofrequency ablation, and filling in the gaps between medical and surgical management, the economic analysis demonstrates to payers that the adaptation of Stretta can create notable savings to their plans when compared to surgery or medical management, and I suspect that's one of the things that you guys are keenly interested in.

It is a cost-effective way compared to Nissen fundoplication, LINX, TIF, and even medications. So in conclusion, multiple observational studies from different institutions consistently reported that Stretta improves patients' GERD symptoms quality of life based upon validated patient-centered metrics, similar to the results of randomized control, the meta-analyses that supported the Stretta, and that it can significantly improve symptoms and decrease distal esophageal acid exposure, it's durable similar to Nissen fundoplication, has the support of both the surgical and the gastrointestinal society, and that I

hope that you will consider to gain parity with the LINX and TIF procedures, which is already covered by your network, and removing the experimental label, and designating Stretta as an approved procedure. Thank you very much for your time.

Dr. Garrett:
Dr. Rapp, did you ever get online?

Dr. Rapp:
I am here sir, I apologize. I just got out of the operating room.

Dr. Garrett:
Do you have any additional comments?

Dr. Rapp:
I'm a bariatric surgeon. The problem that we run into whether we've had these patients who have had bypass, or sleeve, is Stretta gives me an option that is much stronger than TIF because we can't do TIF in that environment. LINX is something that I have some strong, strong reservations about, but Stretta is a nice option, if I can convert a patient who is currently on PPI therapy to nothing, or even just H2 blocker therapy, it's a much stronger foundation for the patient.

Steve has already given you the lengthy study analysis, but particularly with Medicare patients, I am just struggling to give them other options other than taking a sleeve patient back and doing a bypass on them or keeping them on long-term maximum PPI therapy. So, I would love to have that option, and for those who are covered by it, it's a fantastic opportunity.

Dr. Garrett:
That concludes our presentations for the morning. Does anybody else have any comments or questions of the presenters?

Dr. Brito:
Wait, I have one quick question. This is Dr. Brito from Palmetto, for Dr. Clayton perhaps, using this Stretta Procedure, what measures can be taken, or how do you know that you're not going to end up with the same complications you would have with the Nissen in terms of dysphagia, and gas, and bloating, and inability to vent, how do you know that muscle is not going to hypertrophy aggressively?

Dr. Clayton:
I don't think you know anything for certain. I certainly haven't seen it in my experience here, in fact, if you compare the bloating, and the inability to belch to Stretta or to traditional fundoplication. These patients are able to vent their stomach, so basically they're able to belch, so all that air that normally would have went through the GI tract with a traditional fundoplication is able to be vented, and they don't have the significant belching or flatus, and bloating symptoms.

As for dysphagia, dysphagia is not uncommon in the initial stages, so as they're recovering from it most patients will transiently report dysphagia, but that subsequently resolves within about six weeks post-procedure, and I haven't seen any significant dysphagia. So there's always the option too that you haven't altered their anatomy, so if they did have significant dysphagia you can still do traditional esophageal dilation, it doesn't preclude, and I certainly haven't seen the complications that can arise, or the adverse events that can arise post-fundoplication. Ed, would you care to elaborate on that?
Yes. I mean, I have never seen that level of hypertrophy from Stretta. Clearly the Nissen fundoplication, or the LINX, they create such a significant obstruction at the distal esophagus that you get the symptoms

that you mentioned, but not with Stretta. Stretta is just there to augment the lower esophageal sphincter and not create that level of hypertrophy.

Dr. Clayton:
One other options here, I'd like to say as an Esophagologist is a lot of our patients have significant dysmotility that would basically keep them from having a traditional fundoplication, so a lot of these patients will have what we call ineffective esophageal motility, and if you put something that causes mechanical topical gastric junction outflow obstruction like the LINX procedure or fundoplication, these patients would have significant dysphagia, but where Stretta doesn't actually cause a physical barrier, just hypertrophy is the normal natural barrier to reflux, you can do it in patients who otherwise wouldn't be able to; a candidate for fundoplication or LINX, I mean you can significantly improve these patients' quality of life and deescalate their anti-secretory regimens.

Dr. Garrett:
Are there any other questions? That concludes the Open Meeting. A couple of closing remarks, as I said earlier, if you were unable to register but did sign into the meeting, please email melissa.j.robinson@palmettogba.com with your attendance. The comment period will end on July 7th so please submit any comments to the email that's addressed on the draft LCD which will either be b.policy@palmettogba.com, a.policy@palmettogba.com, or MolDX.policy@palmettogba.com.

I'd like to thank all of you for attending, and unless there are any other comments, which I'll wait for a few seconds, that concludes this meeting.