Please stand by for real-time captions

Hello. Good morning. We would like to welcome you to the training, Orthobiogenetics and Regenerative Medicine given by Dr. Reece. This session will be recorded. We ask that you silence your microphones. That was a reminder, if you would like to get credit for your CME you will find the files in the files pod. There is a sign in sheet to download and sign and return. You will find emails in the chat box. A quick biography. Dr. Reece is an Osteopathic Physician with his primary board certification in Physical Medicine and Rehabilitation were two additional certifications in Interventional Pain. He completed his internship and residency at Walter Reed Medical Center. He has an accredited joint pain fellowship with Johns Hopkins and the National Institute of Health and he is also certified in Medical Acupuncture and a Pain Specialist treating complex pain, neuromuscular disorders, acute and chronic musculoskeletal and sports injuries, dramatic brain and spinal cord injuries, headaches, trauma, and poly trauma rehabilitation. He incorporates an expensive variety of fluoroscopic and ultrasound guided interventional procedures and neuromodulation and regenerative orthobiologic along with acupuncture and osteopathic manipulation and other complementary modalities into his comprehensive pain management strategy. He is primarily at Walter Reed where he is the chief of Physical Medicine and the Director of Pain Medicine and he serves as the Pain Specialist for the White House medical unit. Academically he is the Associate Program director and Assistant Professor of Physical Medicine at the Uniformed Services University of Health Sciences. Outside of the military he is the Director of Physical Medicine and Rehabilitation and Regenerative Medicine at the Advanced Pain Management Institute in Chevy Chase, Maryland.

At this time, we will turn the presentation over to you, Dr. Reece.

Thank you. Thank you for joining. I'm excited to be here, to talk about a topic that is near and dear to my heart, Regenerative Medicine and Pain Management. This was intended to be a joint presentation with Doctor Miller the Program Director here at Walter Reed. Unfortunately, he had an unexpected conflict. I will give his portion and my portion.
Without further ado, we will get started. Let me share my screen.

If you have any questions, feel free to raise your hand and I will do my best to monitor that.

Will start to talk about platelet-rich plasma (PRP). A brief overview of the basic science and then take a break and jump into the orthobiologics for the spine. A little bit of the outline, some of the history. Preparation considerations which is a hot topic now with what concentrations we are using and what are best for different applications of PRP and briefly some areas of research.

PRP has been used to augment outcomes from surgery and there are a lot of studies in the literature involving injections around ACL reconstruction and even arthroplasty. Wound healing applications and minimally invasive injections. Some of the mechanisms for PRP involve primarily the use of growth factors embedded and released from the platelets themselves.

This involves cellular anabolism and the mediators play a huge role in the regeneration and recruitment of G regenerative mediators to the area and regeneration of tissue and the idea of the scaffold having a matrix or scaffold for the cells to adhere and migrate and proliferate.

This is a busy slide. This gives you an idea of how complex this is. With the coordination of the cellular cytokines and growth factors through different chemicals and some of the big players are some of these platelet agonists like ADP and ATP and serotonin, calcium and magnesium and the inflammatory factors. The growth factors and some adhesive proteins. This is to demonstrate some of what is going on at the cellular level.

PRP is utilized to facilitate tissue repair and some of the major growth factors are involved. This is involved in cell growth. New generation and repair of blood vessels and collagen production. This is involved with neon Genesis and epithelial cells and promotion of wound healing. Vascular endothelial growth factor and the generation of vascular endothelial cells as well. The fibroblast growth factor with tissue repair and self-growth collagen projection and hyaluronic acid production. The epithelial growth factor, similarly, with angiogenesis and cell growth. There are some bio reactive proteins involved in mentioned frequently attracting the stem cells and macrophages and fibroblasts. They all play a role in this cascade of wound healing and tissue repair.

This is a table of some of the same stuff we just went over. This is not by any means a comprehensive list, but it does give some insight into some of the growth factors. Some of the biologic mechanism fair, looking at the immune response and hemostasis and angiogenesis and anabolism. How these payroll. If you look at the immune response, these chemokine's are involved in the modulation of pain modification where we corral that kind of inflammation leading to a repair, and anabolic state as opposed to the catabolic destructive state which happens over time with trauma where you get scar tissue formation. Here we are promoting pro-inflammatory, organized inflammation. Angiogenesis and these factors have all been shown in multiple studies on the right with lower limb ulcers and ischemia and improvement with the hip and ocular surface disorders. You can look at these studies more in-depth at your leisure. At the bottom, anabolism. Some of the similar cytokines like TGF and beta and platelet growth factor showing changes in the structure in vitro and also, we've seen this demonstrated in vivo as well. Augmentation of plastic and reconstructive surgery and dermatology uses.

We know that PRP deals with modulation of inflammation. The growth factor leads to reduction of CO X 1 and 2 and PGE 2 and inhibits the nuclear factor pathway. Looking at this concept of leukocyte rich and poor and what we have from the data is that leukocyte-poor PRP may be preferred over leukocyte-rich. We will get into that later.

These are the newer concepts and areas of research. It's not so much whether PRP works -- I think it is universally accepted that we see benefit for it the degree of benefit is where we try to hone in and that is what we are trying to concentrate on and that involves determining

which types of PRP in which concentrations we should use for which conditions. That is the area of research now. PRP showed a decrease concentration of the tumor necrosis factor in vitro. These are concepts and areas that need to be incorporated into to the decision-making processes as we decide which type of PRP to use. With tendinopathy we see differentiation of stem cells. On the right you see a picture of normal and abnormal tendon. Schematically you can see the changes that occur with increased cellularity with increased matrix protein and collagen in disarray. We have seen this in cadaver work and also in operations for people with tendinopathy is. You can see the changes occurring clinically in the operating room translating into the tendon and that is how we see these changes. These are things we pick up. Now, are we using ultrasound changes as the outcome measure? Not all the time. That should probably not be the goal. If it is happening, great, but clinically, chemical change and improvement is the most important outcome measure with reduction in pain. If we do see changes on an ultrasound graphic, that is great. But some changes may have been and not transfer into pain relief, either. It is important to keep this in mind. We can see that in tendinopathy this inhibits the differentiation of adipocytes and osteophytes.

In OA we see different changes happening and that is why we are looking at the different concentrations of PRP in different constitutions, leukocyte-rich and leukocyte-poor concentrations and which are best for tendinopathy and which are best for arthritic conditions. These are some of the anti-inflammatory effects happening with PRP. Also, interim we are getting analgesic effects and stimulation of Proteoglycans and Hyaluronic acid secretion. We been using hyaluronic acid supplementation for quite some time with variable response. If we can naturally promote the production of hyaluronic acid in vivo as well as promote tissue reorganization at the same time that is the way to go. We will talk about this. When you look at OE and the use of PRP we also know that severe OA with bone on bone, not to re-create the entire cartilage or meniscus to the point where that person is not going to need it knee replacement. However, it has been shown to improve pain, not as dramatically as in the younger population or with less severe OA, but certainly it has shown improvement in pain in some function. There are limits.

When we talk about reparation of PRP, there are different systems out there. You should pay attention to the systems marketed so you know what technology in the type of centrifuge, centrifugation is happening. Most are using two boats pins where you have a soft and a hard spin and sometimes you get a Buffy coat in some of these and that is the primary layer that you will use. On the second spin, the hard spin will further concentrate to make it a leukocyte-poor solution. These come into play with the system you will purchase or use for your patients. It also involves timing. If you are looking at being time conscious and your clinic is not set up to allow for 45 to one-hour spin down time, take that into account.

In some preparations, traditional PRP has a rose-colored and short-term storage at temperature is not detrimental up to 2-8 hours. The idea of PRP with the fibrin scaffold was studied with rotator cuff repair. A couple of studies showed no difference in tendon to bone healing and the

scaffold had been shown to be a little more productive in areas where we had some type of tissue disconnect, again, usually with a partial tearing situation. Common sense needs to come into play as well. If you have a complete rotator cuff tear you cannot expect the PRP injection to fill the gap for lack of a better term. As long as there is some scaffolding of the tendon or ligament in place we've seen better success. These are some examples of the platelet-rich fiber matrix here.

Some challenges with this, again, there is no standardized preparation system. The blood volumes range significantly. You can take 60 milliliters or 10 milliliters and only get a solution of 3 to 32 cc. Most commonly we take about 60 cc of blood and get anywhere from 3 to 9 cc depending on the type of spin and concentration. Platelet concentrations will come into account. There are systems designed to give you specific and consistent platelet concentrations, but when we study this and you are looking at the various literature out there, rarely are you seeing specific uniform concentrations across the board. We know this will play a role in some way, shape, or form in the outcome. The various conditions you are treating. There are different types of activators involved and we will briefly touch on that. That is something to keep in mind. The presence of leukocytes and red blood cells -- we have alluded to this concept multiple times. Leukocyte-rich and leukocyte-poor concentrations to keep the blood cells and how much. The solution you are injecting has a heavy Rub-off -- red blood cell concentration with a reddish hue with the lower concentration being more yellowish.

This is a slide looking at the types of PRP. You've got the subtle separators in the classic PRP and some examples of the growth factors in these. I won't spend a lot of time on this. This is more for situational awareness so you can see the different compositions.

Again, some of the examples of how there are a ton of variations between studies. There has been a proposed classification system with the PLRA concept. The red blood cell presence in activation use and the platelet count is based on the absolute number of platelets per microliter. Leukocyte presents including the concentration of neutrophils again comes into play. This is when we talk about outcomes. The red blood cell presence in and activation use. Platelet concentrations defined as above baseline normal is anywhere from 150,000 to 350,000 microliters. The concentration thought to be ideal is around five times -- five times to 10 times. Concentrations that are too high can be inhibitory.

The ideal concentration is multifactorial. It depends on the tissue you are targeting, the severity of the disease and the actual pathology behind the disease whether it is tendinopathy or OA. Different patient factors come into play including metabolic disorders and immunologic disorders.

Some activators I have been referring to -- from been is the fastest. It is available and you also have calcium chloride faster than collagen, collagen present at the soft tissue site. Some others include bovine thrombin and these play a role in the activation of the cascade in the inflammatory response.

Activators -- natural activation may allow for slower release of growth factors over time. Activation may allow for fast relief over a short period of time, 90% in about 10 minutes. This is the chemical or synthetic activation. Most studies have not been using activators. Studies with OA, most have been published using calcium chloride. There is no comparison in the same disease model, unfortunately at this time. The presence of leukocytes whether it be leukocyte-rich or poor they contain the EGF. This could a quick, affect the quality depending on the target tissue.

These are used to promote inflammation and neutrophils contain enzymes such as the matrix and some function as macro phage in signaling to recycle cellular debris in the inflammatory mill you present. This can be beneficial clearing out the dead cellular tissue to leave behind a matrix or scaffolding for new regenerate tissue. White blood cells can be detrimental in certain conditions. The macrophages can be degrading, not just dead tissue but sometimes healthy tissue and cartilage and synovium. It is so they play a role in determining whether or not we leukocyte rich or leukocyte poor for conditions like joint OA versus tendinopathy. PRP without the cells may be beneficial in some conditions. PRP without red or white cells was noted to improve chronic jumping knee in a few studies, demonstrating the concept of the leukocyte-poor concentration.

Conversely, red blood cells can alter platelet function as well. Multiple factors include pH, the promotion of inflammation and chondrocyte death. Higher concentrations tend to have higher red blood cell concentrations. Your systems can reduce and remove red blood cells, but we don't know if this is a benefit at this point in time. Some of the injection considerations, you should use ultrasound guidance for most if not all regenerative orthobiologics. We are trying to be strategic about where we place this solution to have this regenerative effect, not just drop it where we feel and hope for the best. Similar to a cortisone injection. The next concept would be -- ultrasound is one form but we can also use fluoroscopic guidance to look at a joint such as knees and hip in particular is body habitus comes into play and we can't see through the depth. Some large patients with injection of the hip it might be easier and better to use fluoroscopic guidance. The idea of local anesthetics in conjunction with the injection, some studies have shown a reduction in platelet abrogation, but it may not hinder the growth factor released. That is not to say don’t use a local anesthetic.

Obviously, these are uncomfortable injections. Be careful about the amount that you use. Some people will put, even after the PRP has been centrifuged, into the injection. I would just locally anesthetized and people do really well with just a local infiltrate. Then using a small needle. Some of these tend to coagulate quickly if you don't have a thinning agent in the solution.

Then if you are using a small gauge needle it will not inject. Be cautious. Again, a smaller gauge needle can be used. I have gotten away with, the smallest is a 27-gauge and I do that routinely for knee joints. As long as the habitus is amenable. They don't make a 2-inch needle that I'm aware of.

For an inch and a half, they need to be pretty thin to access the knee joint. Most able tolerate that very well. In rare cases you can do a nerve block if the patient doesn't tolerate the injection. Particularly looking at the plantar fascia.

This is a very uncomfortable area to inject. Sometimes we will use a nerve block prior to injecting the punter pasha to reduce discomfort. The needling technique. This depends on the condition. The lateral epicondylitis is amenable and a lot of times we will go in and do this. Again, I don't recommend doing this with anything larger than a 25-gauge. You will need potentially some splinting depending on the gauge of the needle. Post procedure, talk about avoidance of anti-inflammatories prior to and after the injection. On average the safe bet is 10 to 21 days. 10 days or two weeks before the injection. Then up to two to three weeks after the injection. This is an area of debate, but it makes a lot of sense. If we are doing and inflammatory treatment and they are taking NSAIDs, we can hypothesize that maybe they will not have the same or as robust a response to the PRP. It is definitely a good practice to have them off anti-inflammatory fire and post.

I have seen shorter ranges. Some people just disregard this. I think it is a good practice to have this. This comes into play patients on multiple other NSAIDs. You have to caution them. Your other pain could flare up when you are off the anti-inflammatory. This is something to consider in patients on long-term anti-inflammatories. As a precaution, we talked about protection or splinting depending on the degree of the 10 not AMI performed. The area that should have pricing or splinting -- Achilles is a big target. The patellar tendon. These are high areas where there is a low threshold for potential rupture, and this can be a severe issue potentially leading to surgery if not protected. I think we will briefly touch on bracing in a minute. From a rehab perspective, we need to educate as it is with anything. Anything having to do with medicine in general, but these patients need to be counseled that we will do the injection and they will not be better tomorrow in a week or months. It's not just inject and go off and do your day today. A good rehabilitation program focusing on exercises particularly with tendinopathy is important. We don't want to inject and the next day or week with the exercises on the Achilles or patellar tendon or any tendon, for risk of potential rupture. There should be a gradual rehabilitation program. If they've had PT multiple times in the past it is reasonable to reconsider formal PT just to show how to do the exercises are properly and in the right timeframe. Even having them go for one session to review the exercises would be reasonable. A huge topic for debate is the idea of the frequency and timing of procedures.

In the military we are able to offer our patients that this modality in the civilian sector this is not covered, and it is a cash-based practice and it can be costly. We want to be careful. There are people doing PRP injections even weekly. There is no good evidence for this.

In fact, it may be too soon around the repair phase. Be careful of people marketing one injection per week. This is not like other therapies where we consider monthly or biweekly rejections. The general average at least in my mind and my practice is to do the first injection and give it three

to four months. I've had people who have seen no benefit for two or three months and then they do. That is a rare occasion. Most people notice some benefit at the month. It can be variable. For the first injection I would give it three months or so. Also, from a cost-conscious perspective as well, and from eight military side this is not cheap, either. We can be doing this every month unless we got good data to suggest this or a condition where we know the monthly regimen might be beneficial.

Some in vitro research out there. PRP plus some monoclonal antibodies in an animal model. Again, these are responsible for proteolytic enzymes. And the idea of PRP contributing to healing as well. The lipid fraction allowed proliferation and migration of fibroblasts in different areas. We are looking to see what is the most beneficial. Future areas of research, again, this classification is being used, trying to be used more consistently in the clinical studies. With these metrics, this needs to be determined. Retreating tendinopathy or OA? Are we looking at meniscus repair or improvement? Some of the optimal candidates we should target, again the idea of the severity of the disease and the age of the patient. As we get older our body's ability to heal is hindered. Will they have as robust a proliferative regenerative phase? And all likelihood if the answer is no. Obviously, the size of the lesion in the different pathology will come into play as well. Looking at the cost analysis in comparison to the standard of care. I was on the PRP review committee for TRICARE and we were able to achieve conditional approval for poor tendinopathy for PRP. It is out there for a 3-year term and we will revisit the studies and the data published after three years. Then, hopefully we will have enough to say yes, definitively, this is more of a proven concept and get it off conditional approval and get it covered. The downside is, if for some reason we fail to get these types of outcomes it may not be covered anytime in the near future. There is a lot of emphasis on publishing good data for PRP, trying to standardize these concentrations. There are a few studies that I will throw in.

Here is one from AJSM. PRP versus sailing. The endpoint was changed using a tennis elbow evaluation at three months. The secondary outcomes were sonographic changes in the tendon thickness and color. For those not familiar, again, we can throw Doppler on the tendons and look at neovascularization and sometimes we can see a significant change. This is the secondary outcome. Whether or not neovascularization confers clinical functional improvement or pain relief remains to be seen. Ultimately, neither the injection nor glucocorticoid was superior to sailing with regard to pain reduction at three months.

All these studies can be critically analyzed and you will see here what types of conditions they were treating. Again, lateral epicondylitis, the severity and the prior treatments, there was not a standardized post procedure protocol or rehabilitation protocol and so these will come into play and ultimately what a lot of the data is telling us is not so much that PRP is not working but we don't see the benefit at that early mark of study particularly the 12 week or three month cut off. We all know that PRP is not like cortisone where we see an immediate pain reduction, but then we see later on that the cortisone wears off and the pain comes back. Then we set these patients up, not for failure, but for repeat injections with cortisone and they get into a pattern where they keep

getting cortisone injections and over time the cortisone can be detrimental. It is detrimental to the tendon so, why start that cascade? It is reasonable, however, to consider a diagnostic injection prior to a regenerative orthobiologic to confirm the source and pain generator.

I will recommend that if they are adverse to cortisone at least a diagnostic joint injection. This is to see if there is any temporary relief. If there is no relief, does that preclude PRP? The answer is no. The one thing that is universal about PRP is that it is safe. It is your own blood. We spent it down and we need to caution about the inflammatory phase that could be uncomfortable, and it could last up to two weeks of discomfort. It should not be debilitating but such that they may not notice any difference, or it may require Tylenol the first couple of days or weeks here and there to account for some of this. Again, universally is three months the right timeframe? Should we extend it further to see better outcomes?

Another study for chronic tendinopathy. Patients ages 16 to 70. The average was six months of pain. They were diagnosed by a clinical exam or MRI or diagnostic ultrasound. Most failed conservative management with medication and bracing and stretching and strengthening. The PRP was done under ultrasound. 180 responded. Roughly 55%. Overall improvement was analyzed whether not at all or slightly more moderately or completely. The scores showed overall satisfaction. The distribution of tendons ranged from lateral at the condyle to patella and Achilles and then you had hamstring and the others. 82% reported moderate improvement to complete improvement. 50% to 100% relief of symptoms and 70% reported mostly complete improvement. This is pretty significant results with a range. The pain scores pretty and post-. Have arranged free being around 7 and down to 1.8. That was at six months. Over 74% reduction.

Here is another study. Improves clinical outcomes in patients with chronic tennis elbow. We are seeing the literature with lateral epicondylitis and you could extrapolate that to most tendinopathy these. Improvement in pain scores at 24 weeks. The control at 56 and 71%. Another study looking at PRP in treating knee joint degenerative changes. This is the review published in the archives of physical medicine and rehab. It was proven to be safe and effective and the benefits were generally better than hyaluronic acid with a longer duration of benefit than hyaluronic acid. Again, the concept and idea of having the benefit in earlier stages of OA than the severe bone on bone stage.

When we examine these studies this one in particular had poor methodology of how they set it up with the control of hyaluronic acid and non-standardization looking at the meta-analysis. The bottom line with the tendons and ligaments is that there is evidence to support disorders with PRP.

Evidence for acute injuries is lacking. Should we be using this earlier or later in the process? Should be the last resort of first resort? People are jumping into this earlier as opposed to using cortisone initially. We don't have good evidence yet. Again, are we causing harm? Chances are low that we are causing harm or setting the patient up for failure early on.

Tendon pain relief is the goal, but the tendon may never return to its normal state. Then when we talk about stem cells, briefly here, it is not often not needed for soft tissue issues. We have used it for more severe cases and gotten good results but not sustained benefit and then we switched to the stem cell reproach and we've seen longer-term benefit. Different stem cell sources. Embryonic, induced stem cells, placental he derived and have metal poetic and all different sources we can get. We can harvest the crest and then spin those cells down and get bone marrow aspirate and inject. We've seen pretty good results with that.
The issue is, it is another procedure for the patient.

The bone marrow aspirate is not comfortable, but usually tolerated with a decent amount of local anesthetic and we typically do that under fluoroscopy. The other types of stem cells are some of the amniotic stem cells. It is now no longer used in the military setting due to revelatory issues. We used it in the past on quite a few patients. We have had mixed results. They seem to have a heightened inflammatory response and a more painful period whether it was injected for tendinopathy or other things. They are no longer using this.

The other area where looking into, adipose stem cells. The patient comes in and it is a form of liposuction and we get the adipose stem cells from that. We inject these. The concept is that it is a seller and less of a growth factor although it comes into play. It is meant to be kind of a filler into a lesion or defect in a tendon or ligament. There is that idea of these pro-inflammatory. That is the last slide. This is the last one. Again, PRP is a promising treatment for OA. We just released guidelines for the DOD and the VA. The section I wrote was on regenerative medicine, but the evidence out there given the criteria we needed to use for that, again minimal low-level evidence, level five in some cases. But the safety profile is there and ultimately concluding that it can be used but it should not be first line at this point in time. Feel free to take a look at that. Again, it is promising. Than we're looking at leukocyte for PRP in the osteoarthritic degenerative conditions. Pain and function shown to be improved clinically best at six months but also at a year in some studies.

Now I will take a break. I will get ready to transition into the orthobiologic spine section and I will open up for questions.

I see one question.

Kaplan presented that these are [Indiscernible - low volume] cells. Any thought of changing the name?

I do not consider myself the foremost expert on stem cell therapy. My experience and my review of the literature, it would be reasonable if that is where the tide is heading. Just like the term of regenerative orthobiologics as opposed to other terminology, the shift is taking place. That seems reasonable.

Here is another question.

Have you used PRP in combination with hyaluronic acid?

Good question. I haven't. There might be one patient that came in being seen at an outside facility or civilian practice and they had been doing it. They may have been doing that for reimbursement purposes. I don't know that there is any data out there. I'm pretty confident there is no data out there to support it. I don't see a reason why it couldn't be used. I would caution that hyaluronic acid injections tend to -- they tend to take up a lot of joint space and distend the capsule depending on where you end. Adding PRP on top of that might be setting up the patient for an uncomfortable post procedure course. I would caution the volume that you are using. I think everyone can see this. Emory does this regularly. Again, my caution would be the volume you are using. Particularly for knees and hips. I would be concerned about doing too much volume. Five had patients asking for two files into their hip. They are adamant about getting it. I've seen them not do very well immediately because the volume is too much.

Here is a question from Dr. Phillips. Given the outcomes would you recommend going straight to PRP rather than HA?

Great question. With hyaluronic acid you don't have the overwhelming data that says this is the gold standard. We have reviewed this in the newest. A lot of the orthopedic specialists are not going to hyaluronic acid these days. It's not unusual to consider PRP ahead of HA if the patient is -- you have to take into consideration the cost-effectiveness. Can the patient afford the therapy versus access to the therapy? Obviously, we can get hyaluronic acid easier than a centrifuge and someone to run the centrifuge and do the PRP. If the setting is right and the conditions are right it is not unreasonable to consider.

How often do we activate PRP with calcium and if so, how much?

I don't. I do know that there are people doing it regularly. Particularly Emory and a couple of doctors using. There are some local groups that do this. As far as how much, I can't comment on that. I don't know that there is consistency or uniformity amongst practitioners similar to which condition you are trying to treat. These are good questions. These are areas we need to look into further.

With PRP CBT including imaging guidance how is the time being populated?

Another great question. In the military setting there is a neuromuscular group and they will look into this. Now its best, from a military perspective, code the T code with ultrasound guidance. Code the autonomy to capture the workload aspect and the time as well. That is what I would recommend as far as capturing this.

If there is a steroid injection, how much time do you have to wait?

Great question. From some studies we know that cortisone, depending on whether it is particulate or not particulate like dexamethasone, it can hang around the area of injection depending on the vascularity of the area, around four to six weeks. If they have had a cortisone injection, I

tell them they should not have this until at the earliest six weeks but on average eight weeks. There are some people doing it at four weeks. Is there data saying this is not the optimal timeframe? No. But, I think safely eight weeks to set the patient up for the best success is reasonable.

These slides are available, I believe. Troy might be able to chime in. It looks like Amy is chiming in. If not, I will make sure.

This is another great question. This is an area for further investigation. I don't -- I will document whether the patient is a smoker or not from a tracking standpoint. It is not a contraindication for me. I will counsel them on the potential effects of concomitant smoking with the regenerative outcomes, but I will not decline treatment if they are actively smoking.

These are good questions.

When we talk about this, herbal supplements is an area where not many people can comment because there are different herbal supplements where you don't know the changes affected at a cellular level with various herbal supplements. It is reasonable to caution up front. If you are taking some of these herbal supplements maybe you would want to hold off on them during the initial round of PRP. When you talk about this, most patients are having chronic pain and may have a con commenting depressive disorder. Similar to the concept of looking at Neuraxial injections. It is the risk-benefit ratio. Is there a risk of taking them off of this and risking depression worth it for a theoretical risk that the serotonin levels will be modulated, such that it will affect the outcome of the PRP and at this point in time? I don't think it is reasonable to assume it is a good approach. I think I would keep them on their medication because it's more of a risk to have them off and decompensate. We all know that anxiety and depression played a role in chronic pain. Having optimal mental health is much more important than the theoretical risk of not having the best outcome with the PRP. If you consider withholding this, I would make sure to consult with the behavioral health specialist that put them on this medication to make sure that you are on the same page. At this point in time, I would not.

Any other questions? We are going to take a break. Is that correct?

Then we will jump into Neuraxial Biologics. Or do you want me to keep going?

We will take a break. Then we will come back.

We will take a 10-minute break. It is 9:36 eastern. We will reconvene at 9:45.

9:46. Then we will get going with Neuraxial Biologics. If any other questions pop up, feel free to throw them in the chat box and I will try to address them prior to starting the spine section.

This event is taking a break and will reconvene at 9:46 Eastern Time.

[Captioner standing by.]

I've got 9:45 on my end. Can everyone hear me?

Great.

Here we will talk about some of the regenerative Neuraxial Ortho Biotics. We will run through all that etiologies. Discogenic pain. The epidemiology, a brief slide on that. The history, exam findings, some of the pathogenesis. Some of the diagnostic imaging and work up and the Neuraxial PRP options and the stem cell therapy.

Nonspecific back pain accounts for 80% to 90% of low back pain. I'm not sure how well you can see this, but we looked at the different generators involved, the pain generators involved. From history we know that it is multifactorial with difficulty narrowing down the specific pain generator. Specific low back pain is often neuropathic or a combination of nociceptive. Some of the nociceptive factors would include muscle and myofascial induced spasms, sacroiliac joint, vertebral body. There is a new procedure out there not related to orthobiologics with nerve ablation and this is a procedure we are doing now for this pain which has shown to be more common that we think and from a vertebral genic changes that are inflammatory. We look at the changes with high-intensity zones from the disc. And disc degeneration occurs from aging and age-related changing and loss of water content and injury to the disk or tearing reduced cellularity associated with poor healing.

There are the logic changes like disc prolapse or extrusion and spondylolisthesis and these nodes. This may or may not be symptomatic. Are often than not they are not. If they are associated with changes when he to pay attention to them. There are risk factors that can accelerate degeneration such as mechanical loading and trauma. Smoking again comes up. Unit inflammatory reactions and infections and different anabolic disorders. All of which can play a role in the degenerative cascade in the spine. The idea of discogenic pain, the prevalence being 22% to 56% in the chronic low back pain studies that were documented. We see this more often in a younger rather than older population.

The older you get, we tend to see that the nerve providing innervation to the annulus cannot, tens to not be symptomatic at older ages. It is more likely the arthritic component in that age group. Then when we look at annular disruption tears grade 3 has the strongest predictor.

95% had later than a grade 3 in this study. High-intensity zones are some of the associated factors with annular disruption and then Modic changes showing more likely to be symptomatic with some of these different types of changes which we will talk about. I wish this had come out better. This study was titled discogenic back pain, the definition of diagnosis and treatment. I think it was 2018. It was a recent study. Again, this goes into the diagnosis of discogenic pain and what we define as discogenic pain and some of the history and we will go into this. Sorry this flight is not showing up the way I wanted.

Here we talk about discogenic pain, the history. Most of the time it is midline in nature. We hear about radiation horizontally across the back. It has a positive protective value around 73% for midline location. We believe it is axial. The lower lumbar region is more commonly affected. It bears the brunt of the weight from the torso. This produces the most force on the disc, sitting. Rotational forces tend to exacerbate discogenic pain and an increase in aggressive pressure can provoke discogenic pain. Such as coughing, sneezing, rising from a seated position and pain alleviated with supine and standing are indicators suggestive of discogenic origin.

The exam for discogenic pain, again there is no specific exam maneuver to tell you definitively that the disc is causing the pain. We look at a constellation of factors and exam maneuvers and clinical history to put together the likelihood of the discogenic origin. It is midline tenderness, sustained flexion protective and 95.8 cases. There should not be significant radicular components. Negative straight leg raise and minimal lateral vertebral palpation. Some people will have midline tenderness that is somewhat spreading laterally, but more often than not lateral paravertebral tenderness is the predominant exam finding.

This is more consistent with other pain. There shouldn't be much SI joint involvement. We don't expect the disc itself to be causing reflects changes. The disc is extrusion will have straight leg raise positive and potential reflects changes depending on the level involved or new nerve root involved. This is to illustrate there are different types of discogenic pain. You've got the annulus enervated and if you have a tear and it's not a vertebral nerve being the primary source of innovation, innervation, you got all kinds of receptors. You've got chemical mediators released from the nucleus causing surrounding inflammation to the potential nerve roots extending into the periphery which can set off muscle spasms again throwing off and misleading the diagnosis of discogenic pain versus radiculopathy and/or muscle spasm. This needs to be taken into account. The red circle should say discogenic pain. We will talk about the pathogenesis. We talk about the mechanical aspect being the load on the disc. Annular tears and micro fractures of the endplate. Will go into this more. The chemical factors, again the cytokines being released. Reduced oxygen, increased lactate levels, decreased pH. Slow metabolic and reparative process. And to increase in chondrocyte activity. This can lead to this degradation.

This is a busy slide.

This is really just to give an idea of all the different factors that play a role in why the disc is degenerating and/or becoming a top source to isolate because of the contributing factors. The mechanical overload from trauma or overuse and also oxidative stress with free radical production. This can lead to signaling from the cytokines. Then you have underlying metabolic disorders and or genetics playing a role. The biomechanical instability, again with tears and herniation bleeding to a decrease in elasticity. You can have degradation of the extracellular matrix and loss of hydration and decrease in the proteoglycan concentrations which sets up the cascade for degradation and then you've

got the inflammatory cytokines. The list goes on. This contribute to the process. And different types of etiologies that play a role.

Next. Things that we look at as far as factors to distinguish inter-vertebral disc degeneration. Aging and degeneration itself. With the aging aspect of the degeneration we have lots of water content and increased collagen and advanced end product stimulation. You have endplate sclerosis and hypo osmolarity and reduced nutrition leading to reduced cellularity and increased senescence. You can have this regulated nutrient sensing and signaling protein kinase. Versus the degenerative cascade involving the inflammatory cytokines and different nociceptive stimuli. This leads to injury and neurovascular over the disc degeneration is age associated disc degeneration does not equal disc aging. This is a depiction of the seesaw balance between the synthesis and metabolism that occurs. On the right you are having a catabolic state where there is degradation of the disc material and the surrounding tissue versus on the left more of an anabolic synthetic state where there is building up of the tissue and regeneration.

The diagnostic imaging involved, again we use x-rays to assess the disc height and assess for arthritis, and you can see some degree of stenosis on the x-ray depending on the view and also bundle a lysis with fractures coming into play and also below a listhesis. On the MRI we talk about high-intensity zones and Modic changes. The idea of the grading system and the different sequencing of MRIs involved to look at not just basic morphology of the disc and extrusions but, but the chemical composition that we can pick up on different MRIs. Then, using discography to diagnose specific levels of discogenic problems.

When we talk about Modic changes, a lot of times the MRI or the radiologist may not comment on this and it's important and I have always advocated and taught the residents and interns to look at the MRI yourself particularly if you're dealing with the spine and pain management. In some changes, they can be not called at all or over called. The radiologist is basing their assessment and conclusion on static images versus your interpretation which has the exam that you have performed and also your clinical correlation. Hopefully there are no radiologists on this call, but the classic CYA is clinical correlation is indicated. Look at the MRI yourself. For Modic changes you will see bright on T-1 and dark on port type 2 you see bright on T-1 and T-1 and on type III we will see dark on T2 and T1 images.

Type one Modic changes have been shown to have the highest specificity for positive discography. This is an important point. This rings true for most of us doing spine management. This is that grading structure. Going from 1-5. Grade 1 look at homogeneous bright white, a clear distinction of the nucleus and handling, annulus and the signal intensity should be hyper intense or it is intense similar to CSF and the vertebral height should be normal. As with most of the grading screens grade 3 is the tipping point going from relatively normal to abnormal pathology. Grade 3 has a great structure with an unclear distention between the nucleus and annulus and that signal intensity can be intermediate and the height can be anywhere from normal to slightly decreased.

Extreme is grade 5 with a dark disc and loss of distinction of the nucleus and the annulus and hypo intense signal. Significant loss of disc height. Again, with this grading, again going through the visualfrom grade 12 grade 5.

I apologize. The issue is, it is around 70 megabits and it's tough for me to email it or send it. I will make sure that we have the slides available for you. Some people are saying file share is good. The recommendation is to download it and it will show up better. That would be helpful.

Next, a modified scoring. I don't know that clinically this comes into play. Breaking this down further, I don't know how much. From a research perspective it makes a lot of sense. If you are trying to be specific and strategic about what we are doing to characterize the disc and pathology before a treatment, but I think clinically probably not that relevant from your day-to-day practice with this scoring. Looks fine for documentation purposes.

Here is an example of a high-intensity zone. 13% of these high-intensity zones are asymptomatic. That is from a study in 1992. Here you can see the bright, high intensity area. If you look at the L4 -5 which has the disc collapse you can see some protrusion but it doesn’t have any intensity in that particular portion. I alluded to this novel sequencing. Again, is it clinically relevant? With more research it could be. Are we to order these MRIs on every patient? Right now, no, but from a research and as we investigate for the disc and chemical mediators and degradation cascade it can be useful. There is a chemical exchange saturation transfer and test sequencing to correlate between -- looking for correlation of pH with pain and what they see is that lower pHs have been more associated with disco-genic pain. Then it is measuring the signal changes known to be important in the degradation cascade and then you have the quantitative -- it has the potential to detect pH changes in the disc.

Quantitative analysis with the tissue has been applied. Higher resolution magic angle spinning. That is a mouthful. Qualitative and quantitative previously used to detect collagen breakdown. Now this is being applied for analysis of the inter-vertebral disc.

When we look at discography it has gone out of favor but it's not the kind of go to. We don't just jump to this off the bat anymore. Unless we are looking to isolate a source, a single level source. This is for multiple reasons. One of which is, most of the classic discography needs to have a control and we do know for sure that injecting a healthy disc, piercing a healthy disc has been shown to increase the degenerative change rate of the healthy disc. One disc that was previously healthy will degenerate quicker and that is a relative term. It's not like it will generate over weeks or months it could be years. But why are we injecting a healthy disc and risking the health of that disc? We have moved away from that unless we have to isolate unless it is clear that we don't know which one and we are only going to inject one. A lot of times the MRI and grading and clinical acumen will steer us in the right direction for which disc to inject and you can hold off on doing the

discogram. What we can do instead of provocative discography is anesthetic discography which I am a proponent of.

Instead of injecting multiple discs we are injecting just a single disc that we think is a pain generator with anesthetic to see if they have any change in the pain. Is that the best approach? A lot to be determined. The jury is still out, but I like it and it seems to work pretty well with the patients I have done treatment on or at least some tripe of therapy another techniques. It has gone out of favor as we have not seen sustained benefit. We do know that the nerve endings exist from the outer third of the annulus with encapsulated nerve receptors along the lateral surface. That ligament is also included. There is a high risk of discography and a healthy disc we worry about degeneration of the healthy disc prematurely. Also having a high false positive rate. The primary goal with discography is to determine whether or not disco-genic pain is a source. A primary source of the low back pain. Identifying the right levels to treat. The critical question being, is the pain [Indiscernible - low volume].

This is an important point. When we look at provocative discography we can inject these discs and look at the pressure and such but it really needs to be the patient reporting the pain versus what is causing the pain. This comes up often in the education setting.

How do we perform the discogram? This slide demonstrates the approach for the discography. It is not -- we will not spend too much time on this because most folks in the audience are familiar with this. Next -- this is where the needles and up for the discography and we do a degenerative medicine approach with provocative discography it is rare that we are doing this type of scoring, but I think it is reasonable. As we mentioned grade three is the more common levels are tearing. Anything above a grade 3. It is important to take into account per week and further characterized the extent of the tearing by doing the traditional discography with contrast and sending them for a CT scan to better assess the grading of the tear. This is the original scoring and then somebody comes out for modified scoring. Which scoring system you use, modified more in this setting versus the standard Dallas discogram score.

Some of the classic appearances you will see -- Again, normal discs look like a cotton ball. I usually say hamburger. The appearance of the contrast pattern. In a normal view versus the pathologic areas at L now 5 -- S1 were you see the importance of the pain during the discogram and then the L 4-5 the disc was injected and you didn't have reproduction of pain and there was no exacerbation of contrast material outside of the disc. It is important not to just have one thing that makes it a positive. You want to have all those things but up before you make the diagnosis.

This is new, is level being studied as novel diagnostic studies for back pain? That study is available and referenced in the reference section. In 2014, they looked at matrix laser absorption time, spectrometry I tell you, these acronyms get longer and longer. This will establish pain from other forms of chronic low back pain and complement levels in fibrinogen. Local biomarkers, in 2005, they looked at substance P, neural filament,

vasoactive intestinal peptide immune overactive nerve fibers and other areas where we can look and add to the diagnostic workup of the echogenic pain.

Next slide.

What we're using in the disc? We are burning essentially the annulus, to prevent the nerve from having and sending a pain signal.

Next slide.

So, the avascular nature of the disc create a microenvironment with relatively low cellularity and flow sell metal balls to meta-ball rates. That is important to keep in mind. That is where this idea of having growth rates injected as opposed to trying to get it to heal on its own with oral supplements and such.

Am I back on? Okay, for some reason the network cut off. I am sorry. I am not sure if people missed anything, but essentially, the last slide was discussing how the avascular nature of the disc was the ideal setting for regeneration, and so using the or the Biologics Orthbiolgics helps spur the regenerative tissue. Can we see the slides? It is not showing on my screen. Okay, everyone can see it that is fine. Although, I guess that will not help me, because I do not know which side you are going to be on. Nothing is showing up on my screen.

Okay, I am going to log off and see if that works. Okay, I am back in. Let me see. Let me see if I can wait for the lot. All right, in the interest of time is loading. Troy, can you pull up the slide that said guidelines, I will pull up my presentation on the other computer and then I will tell you or cue you when to turn, okay?

Can everyone see that? Guidelines, the guidelines slide?

Okay, perfect.

So, this was put out by a national pain organization, looking at the responsible safe and effective use of logics in the management of lower back pain. A lot of big names on this review of the guidelines or instruction of guidelines concluding that based on evidence that synthesized the level III incidents for stem cells or stromal cells, whereas the evidence is considered level IV, or lumbar facet joint, and sacral lack joints of PRP on a scale of 1-5, using a qualitative modified approach to the grading of evidence based upon the best evidence of this. The next slide said say PRP. And growth factors again, we did this in the beginning Dr. Miller's talk, going through different growth factors and what they do. I am not going to spend a lot of time on that.

Next slide.

Some of the advantages of PRP again, easiest cell type to obtain and can be done in the optician setting. It is cheaper than traditional stem cells therapy while still effective. This is a colleges transplant arrived from patient's own blood, and low risk of transmission of blood.

The disadvantages, unfortunately we eluded two it is not standardized or regulator. You get that particularly with the inter-disc treatment. 2-4 weeks, even, and there also is, you need to have a sterile technique, and I use, and most people these days are using a needle through needle technique to limit the transmission of skin flora through the needle into the disc for risk of death this -- risk of discitis. This should talk about leukocyte which PRP, along with platelets but load density fiber network. The share [Indiscernible] an increased concentration of leukocytes.

Next slide.

The next slide is a study by a former rotating resident at Sinai, a well-designed study looking at lumbar injections that are double [Indiscernible] and those that received PRP showed significant difference with pain and patient satisfaction survey controls. You know, again, promising -- you know, this is one of the first well designed and certainly gave us a bridge to start additional research.

The next slide is another study looking at platelet rich plasma injections and some of the preliminary results were done by Dr. Levin and Dr. Horn encouraging six-month findings using strict [Indiscernible] as a treatment for lower back pain and again, this one they elude to further randomized controls being needed to make inter- conclusions.

Next slide is a study by a meta-analysis review and ultimately you know, PRP shows significant -- statistically significant decreased pain after PRP, a 40.3 percent decrease at six months. A nice systematic review here, published in 2018, and I highly encourage you, in the interest of time I am not going to go through specifics here, but I highly encourage you to take a look at that well-constructed meta-analysis. This included the study and other really, really good quality studies. There are more quality ones included in there as well, but they did a good job at finding and singling out the ones that had the best design. And, so to flip through the next two slides or three slides and get you stem cell therapy. Then, we will jump into the next slide after that that says cell types. The different cell types that are out there are harvested purses off the shelf. You have autologous, self-versus donor, and injecting scaffolding versus matrix.

Next slide.

Some of the mechanisms again, in 2013 they talk about mitigating inflammation with nucleus proposes, we hiding the nucleus. Remodeling the tissues or recruiting peripheral cells and nutrients and restoring the disc height to remove pressure on adjacent hers. All of which decelerates or reverses the degenerative process by putting rail like Ganz [Indiscernible] the advantages here are relatively easily harbor to harvest. The yield is smaller number of NSC's per ML aspirate and this number decreases with the age of the donor. It may need to be combined with other for transportation into larger sites due to the small cell count. They are hypo immunogenic.

Next slide.

This should show disadvantages and again here, they are not standard and not regulated. They yield lower cell counts that often need cell expansion to increase the numbers of the cell numbers cannot be expanded in the U.S. per guidelines at this point in time, for FDA guidelines. They may differentiate uncontrollably into an undesired lineage and they may decrease in quality in the age of the donor.

Next slide.

It should be mesenchymal. It will be related by the FDA as a drug with rigid oversight, there is lower risk as opposed to tissue, and there is lower risk of infection due to decreased need for processing. And again, it may need to be combined with scaffolds with larger sites.

It is hypo immunogenic. The disc of the neck turn some of the trials are on the next slide, I highlight three of them. There are bone allografts with steel conductive 3-D scaffold, that was as if I believe March or April role, that may have changed at this point, or it could be longer, just because of COVID-19. That is the mesenchymal precursor cell line, and that is an investigation that was in phase 3 trials and then the IDCT which is in phase 1 trial.

Next slide.

This is a study that looked at cell-based therapies for lumbar discogenic back pain and a single arm analysis in 2017, in the spine Journal. Again, it looked at six eligible studies from 2006 two 2015. 74 patients. There were no serious adverse events, and thankfully no tumor formation, which I hope is not something that we ever have to worry about with this particular modality, but something that we may need to pay close attention to. The next slide will go into again, different studies and breakdown of those studies. You can present at your leisure, feel free to look at the individual studies yourself.

Next slide.

This is a slide demonstrating decreased pain score after treatment, again, in this systematic review. The next slide shows eight decreased in the ODI score. One of the outcomes from this meta-analysis -- the next slide is a breakdown of some of the results of these individual studies, you know, from Noriega all the way to [Indiscernible] the next slide is more of studies that were included in the systematic review. And the next slide as well.

I will jump to this idea of -- this was published by an interventional radiologist, the VAST clinical trial, looking at safely supplementing tissue lost to degenerative disc disease. Ultimately, the study is supported by immense trading improved with supplemental disc matrix. Subject receiving the bio disc achieved things terrible at 12 months. It was a quality study and I think I go into, on the next slide, a few of the results there, if you hit the next slide. This is the 6, 12-month one level versus two level treatment with the bio disc. You look at your baseline and going all the way out to the levels, anywhere from 53%

decrease in two levels up to 76% decrease at two levels. All the way out to 12 months.

Next slide.

They did MRIs pre-and post, and it did show some changes in the disc matrix. If you look on the left, the VAST, a six-month follow-up for a random subject, you can see on the right, post treat, at six months, we can see that the VAS at 17 ODI at 18%. The changes in the disc that occur are very subtle, but you do see some change in the intensity of the disc, and some minor resumption of the disc material, and are you going to citizen everyone? We do not know, right? There were a few patients that did show more changes. This is a 12-month follow-up of another random subject. Here you can see almost near complete resumption of the disc on the axle image and also on the sagittal you can see the disc resolved. Is intimately related -- have we seen discs resort on their own? Absolutely. But in the timeframe it can be variable. There are often disc resumptions on their own in the 6-12 month range as well. So, is this directly related to the bio disc matrix? I don't think we can definitively say, but we do note that the patient had clinical improvement and I think that is the most important thing to look at particularly as we are looking at the RCT and seeing the control, if the control is not doing as well from a pain and functional perspective as the treatment arm.

If we go to the next slide, this should again some of the outcomes and characteristics of this trial. The VAST study was the only study at the time on therapy to demonstrate sustained clinical improvements at 12 months. It is the largest study to demonstrate cynical improvements and significant improvement in high responder group as well. The only RCT of any size treatment at 1 and 2 level indications. And the supplemental allograft appears to provide an effective resolution of pain to enhance functional recovery and sustained disc height not only at the end level, but at levels rostral to the treated level, as well.

Next slide, this should say other treatments. Some of these are older concept that we have kind of moved away from, the idea of ozone or methylene blue using two chemically oblate nerve endings. This complex biomarker, fibrin sealants and scaffolding for stem cells that are unregulated, looking at fibrin and thrombin.

Next slide.

The other treatments, again, prior to or even certainly prior to, I wouldn't do PRP and then jump to an IDET type of thing, if you are heading down this pathway, still, you know, we just haven't seen the data work out in its favor. And it is not being done as often. And again a similar concept in Biacuplasty, nuclear plasty and something like total disc replacement cup which I can doesn't have really great data on it, from a back pain perspective.

Next slide should say complications. And there are a couple of quick slides on this, and this is specifically related to interdiscal orthbiolgics. There is a lot that can happen, but the most reported of the stem cell orthbiolgics was this idea of, if you hit the next slide,

bio-flare. You have an MRI and a CT, this shows erosion into the M Plate after entered the school treatment. It is not without risk, these particular procedures. This is very rare. This is something we need to pay very close attention to, counsel the patients on the risk and the next common question is this even symptomatic? And, the answer is largely not, believe it or not, patients are not complaining of more pain, but incidentally we are finding these from a bio-flare perspective. Over time will this cause issues? It will, unless further research is done, and you find that that heals or fills in [Indiscernible] and bone is being laid in that bone.

And, on the next slide, we will talk about obviously the risk of discitis and changes that can occur there with an active in infection. This is not regenerative orthbiolgics, so having a sterile technique and using this needle through needle technique, I think all -- giving prophylactic antibiotics, I will say that I do oral antibiotics prior to a discogram. There are some that inject directly, I do not -- that is definitely not standard protocol, but something that certainly needs to be investigated further, as well. And I know we are 10 minutes over, so thank you all, I open it up for questions.

Thank you for your time and attention. Please let me know if you have questions, if we have time, I will answer them now. If not send an email and I will get back to you with the answer. We can go from there. I don't know if the chat room is open, you can type in questions or if you want to unmute microphones, we can have an actual verbal discussion, if possible.

Any thoughts on nanogram dexamethasone use with PRP or BMC?
I don't know, I do know that the concept makes a ton of sense to me, if I am thinking that as a steroid. I would be concerned I guess, but maybe there is something to nanogram dexamethasone that I am not trekking.
Do you want to comment on that verbally?

The nanogram dexamethasone?

He is saying he doesn't know how to unmute.

It should be on your screen on the upper portion, there should be like a microphone and a person with a hand raised and WebCam, usually just click that and it will say mute or unmute. If not, no big deal. We can talk off-line, or you can share your thoughts, but if I am interpreting that for face value, I would be concerned about using a steroid with a regenerative orthbiolgic.

Hello? Hello? I am just going to talk.

Can anyone hear me?

Yes, who is that?

So, it is good to hear from you. I have a thought on that go there has been studies that they do a nanogram dose of nanogram dexamethasone, they have to either get it made or just diluted several times like five times.

Then, they use it with MSC or BMAC procedures. They do it based on a couple of those studies, and it has been shown in the lab to be protective of the actual cells.

I want to know do you have any thoughts or have you seen that? Orthobiolgics is that at an extremely low dose, it has been shown to be protective of themselves. Thank you.

They curate longer and when they look at you know, when they get their numbers and their cell counts, they have are seeing in a lab that their numbers are higher, they use a very small dose.

Great, so, again, I don't claim to be like Sampson or anyone on the forefront, but I will certainly look into that, and do a review myself. I may even start to incorporate that, thank you for bringing that up.

Absolutely, I will see if I can find the studies and have they sent to Ibis -- I was wondering if you had any thoughts.

All right, cool. Thanks.

Does anyone else have any questions? All right, I think they are going to leave the chat room open. I will stay on for a little bit, if there are more questions. I will put my email in the chat box if other questions arrive. I meant to have that on the slides but I forgot. My email is there, and my phone number is there if there are other questions that come up. We will make sure that you have access to the first presentation. I will get uploaded, soon.

If there are no other immediate questions, oh, hold on.

Dr. Phillips is asking, is your facility using "New Cell" at all for intradiscal injections?

No, we have strictly moved in the direction of leper Jens [Indiscernible] unfortunately, I cannot comment on that in particular.

All right, well again, thank you everyone for your time and attention. This is an exciting era, and field, where there is a lot of research to come. I think we have the potential to do a lot of good for our patients particularly in the military setting, and our readiness, a lot of people have back pain that have been adding random cortisone injections or getting them too frequently. I have seen that too often, what extensive tendon ruptures and Achilles tendon issues. And, so, I'm looking forward to kind of doing good work in this field, and also, collaborating with everyone, to move the science forward.

[Event Concluded]