TRANSCRIPT: MULTI-JURISDICTIONAL CAC MEETING- AMNIOTIC PRODUCT INJECTIONS FOR MUSCULOSKELETAL INDICATIONS, NON-WOUND - MAY 12, 2021

Linda Meyer

Thank you to everyone who is attending today we'll go ahead and get started with our meeting.

Good morning, or afternoon, depending upon where you may be joining us today.

My name is Linda Meyer, and I am the Noridian Medical Policy Manager for MAC Contracts.

I would personally like to welcome you all to the Multi-Jurisdictional Contractor Advisory Committee Meeting for Amniotic Product Injections for Musculoskeletal Indications, Non-Wound.

I'll be assisting the Noridian Contractor Medical Directors with facilitating today's meeting, and that is on behalf of all of our partnering MACs.

We would, first and foremost, like to thank all of our CAC panel members who have taken time out of their very busy schedule today to join our meeting and share their expertise on the various topics. We also welcome those attending in listen only mode, sharing your interest on this discussion today.

As mentioned, this is a Multi-Jurisdictional CAC meeting, meaning a group of partnering MACs, they're working collaboratively to potentially develop an LCD.

On the next slide, we have a list of those Contractor Medical Directors assisting us today. While Noridian leads these efforts, we are joined by these individuals in partnering in these efforts.

Those included are from Noridian Healthcare Solutions, Dr. Janet Lawrence, Dr. Anne Marie Sun, and Dr. Eileen Moynihan. From CGS Administrators, Dr. Meredith Loveless, from National Government Services Dr. Marc Duerden and Dr. Carolyn Cunningham, from Novitas Solutions and First Coast, Dr. Andrew Bloschichak, from Palmetto GBA, Dr. Judith Volkar and Dr. Jason Stroud and from Wisconsin Physician Services, Dr. Ella Noel.

We thank them for their effort in, not only just attending today and listening to the discussion, but for their hard work and effort in developing a potential LCD.

Moving on to our agenda.

The meeting will start with a few housekeeping items, I will then turn it over to Dr. Lawrence, who with Dr. Moynihan and Dr. Sun, will be leading the CAC panel evidentiary discussion on behalf of all of the MACs today.

Today, Dr. Lawrence will introduce our expert panel and lead into the discussion questions thereafter.

Now we have broken down the discussion items into various topics, from two more general areas, to four more specific medical condition.

Discussion questions were provided to our CAC panel members prior to today's meeting to facilitate today's discussion.

Members of the panel were identified to lead the discussion for different specific topics with all members welcome to contribute to all topics.

This ensures we have sufficient time to address each topic, and we hear from each panel member as a lead discussion.

After the discussion of each of the conditions, the panel members will be asked to respond via a polling system to six key questions regarding their confidence in the evidence of each topic discussed today.

They are to respond on a scale of 1 to 5, with one being low competence, and five being high competence.

At the end, we will conclude with a brief summary of the next step in the LCD development process.

Moving on to our general housekeeping item. All lines are muted except for the CAC panelists and meeting facilitators.

The chat feature within the meeting is to be used for technical issues only, and questions specific to those topics discussed here today will receive, will not receive a response.

The meeting is being recorded as required by CMS, and the recording and written transcript will be available after the call on all of the participating MAC websites.

Housekeeping for our CAC panelists.

For the panel members, we have tested your microphones and appear to be working correctly.

We are still troubleshooting with Dr. Gulur, but the majority have successfully tested through, and we will continue to ensure Dr. Gulur can be heard and speak.

When not speaking, we do ask you and any other facilitating members to be on mute, to minimize any background noise that might impact the quality of our recording, and for our attendees to hear the comments being made.

We will conduct introduction shortly, and please indicate for the meeting record any conflicts of interest when Dr. Lawrence does call your name.

Throughout the call, we ask you to announce yourself prior to speaking, especially if you haven't spoken in some time, so that it's clear for the audience, and for the record, who is providing each comment.

As part of our meeting, you are asked to respond to questions on competence of evidence on today's topic. We are aware some panelists may need to leave the meeting unexpectedly or early, and with all the panelists, we will work with you to obtain a complete set of responses to all of the key questions that are asked in today's meeting.

Any incomplete responses will be communicated after the meeting, and we will obtain a complete set from you.

Lastly, to ensure we are able to discuss each topic today, we have set an estimated timeframe for each topic discussion.

When nearing the end of the time I will interject to communicate, we are low on time.

I mean no disrespect to any expert speaking at the time, this is only to ensure all topics get attention in the three hours we've allotted today.

With that, I will now hand the meeting over to Dr. Janet Lawrence.

Dr. Lawrence.

Dr. Janet Lawrence

Thank you, Linda, and good afternoon everyone and again, welcome to the Contractor Advisory Committee meeting for Amniotic Product Injections for Musculoskeletal Indications – Non-Wound.

We appreciate our panelists, and we also appreciate the attendees, recognizing that everyone is busy, and we appreciate everyone's answers.

As you likely already know, but I will reinforce the CAC process changed effective January 8, 2019, per CR 10901.

Prior to, that time, a CAC would be convened with regularly assemble members, and draft will be brought to them by a contractor medical director, and they would discuss it. Subsequent to

the CR, the purpose of the CAC meetings now, start at the beginning of the process, and the purpose of the CAC meeting is to discuss evidence and literature of a topic.

The meetings are held to determine if a local coverage determination is necessary and what its scope should be.

The CAC members role is advisory in nature, and comments, and opinions are on the evidence, not personal experience, and the contractor medical directors use this to assist the appropriateness of any proposed LCD. The CAC process supplements the Medicare Administrative Contractors, internal expertise and is to help to ensure an unbiased and contemporary consideration of newly developed technology and science.

CAC meetings are now open to the public, as observers, not participants.

CAC meetings are recorded, and the audio recordings and the written transcripts are posted on each participating MACs website.

For further information regarding the LCD process in general, or the CAC process specifically, please look to Medicare Program Integrity Manual, Chapter 13, or the CAC section, look to Chapter 13.2.4.3.

And with that being said, we will go forth and introduce our esteemed CAC panelists.

They will be introduced in alphabetical order, not speaking order.

First, we have with us, Dr. Nicholas Beatty, DO, he is Board Certified in Sports Medicine and Physical Medicine and Rehabilitation. He is a member of the American Academy of Physical Medicine and Rehabilitation; he is an assistant clinical professor of Rehabilitation Medicine in the Mount Sinai Medical Center system. He specializes in interventional spine care and regenerative sports medicine and focuses on injuries of the upper and lower extremities.

Dr. Beatty, please say hello and discuss any conflicts of interest you may have at this time.

Dr. Nicholas Beatty

Hello, and thank you for the introduction and introduction and there are no conflicts of interest.

Dr. Janet Lawrence

Thank you.

Our next panelist is Dr. Mark S Block, doctor of podiatric medicine.

He is the Chair of the Insurance Committee of the Florida Podiatric Medical Association. He is a Medicare CAC representative for the Florida Podiatric Medical Association, the chair emeritus

of the Health Policy and Practice Committee of the American Podiatric Medical Association, Vice Chair of the Florida Board of Podiatric Medicine, he is a diplomat of the American Board of Foot and Ankle Surgery and is certified in foot and ankle surgery.

Dr. Block, please say hello and discuss any conflicts of interest you may have at this time.

Dr. Mark Block

Yes, Dr. Block, thank you. No conflict of interests at this time.

Dr. Janet Lawrence

Thank you.

Our next panelist, is Dr. James Gajewski, MD

He is a Master of the American College of Physicians, is board certified in hematology oncology with a focus on stem cell transplantation, he is a pioneer researcher in alternative donor transplantation, including unrelated donors, haplo identical donors and umbilical cord blood transplant.

He has been very involved in the regulatory field, having served on several FDA stem cell therapy advisory panels, and was advisor to the AMA, RUC and CPT Advisory Committee for over 20 years.

During that tenure, he wrote or revised, all of the stem cell therapy codes for collection, processing, and fusion, as well as the diagnostic bone marrow aspiration and biopsy codes and was part of the E&M reform effort at that time.

Dr. Gajewski, please say hello to our audience and discuss any conflicts of interest you may have at this time.

Dr. James Gajewski

Hello, the only conflict I have, I serve as a [inaudible], chairman of a scientific advisory panel for Avalon Global Care. Avalon Global Care is developing stem cell therapeutics for cancer, but they are, their whole product focus is on China, they have no products, currently or plan for the US marketplace.

Dr. Janet Lawrence

Thank you, Dr. Gajewski, hopefully she's gotten in. Our next panelist in alphabetical order is Dr. Padma Gulur, MD, are you on yet, Dr. Gulur?

Dr. Padma Gulur

Are you able to hear me?

Dr. Janet Lawrence

Yes.

Dr. Padma Gulur

Hi, yes I am on, thank you. I'm Padma Gulur, and I have no conflicts or disclosures.

Dr. Janet Lawrence

Okay, to introduce her further, she is a Fellow of the American Society of Anesthesiology, she's Professor of Anesthesiology at Duke University, and is in the Department of Population Health Sciences. She is an Executive Vice Chair for the performance and Operations, she is Director of Pain Management, Strategy and Opioid Surveillance, she is the Medical Director of the Acute Pain Consult Service and has been a member of both the CPT Advisory Committee of the AMA and the FDA Advisory Committee on Pharmacy Compounds.

The next panelist is Dr. William Harvey.

He is a Fellow of the American College of Physicians and is Board Certified in Rheumatology, he is an Associate Professor of Medicine at the Tufts University School of Medicine, and Clinical Director of the Division of Rheumatology, Allergy and Immunology, he is a Chief Medical Informatics Officer at Tufts Medical Center, he currently serves as the Chair of the Committee on Registries and Health Information Technology for the American College of Rheumatology, and is one of the authors of its 2019 guidelines for osteoarthritis management.

Dr. Harvey would you please say hello and discuss any conflicts of interests you may have at this time?

Dr. Will Harvey

Hello. This is Will Harvey, thank you for the introduction. I have no relevant conflicts of interest.

Dr. Janet Lawrence

Thank you.

Our next panelist is Dr. R. Andrew Pavelescu, Doctor of Podiatric Medicine.

He is a board certified in foot and ankle surgeon, he is a Fellow of the American College of Foot and Ankle Surgeons, he is the clinical director at the New York State, fifth beat Special Olympics

International, he is faculty at the New York University Langone Hospitals, and is a podiatric ankle surgeon with the Metropolitan Foot and Ankle Group.

Dr. Pavelescu, could you please say hello and discuss any conflicts of interests you may have?

Dr. R. Andrew Pavelescu

Hi, good afternoon. I have no conflicts of interest.

Dr. Janet Lawrence

Thank you.

Next we have Dr. William Ritchie, MD he is an orthopedic surgeon specializing in conditions of the shoulder and knee, occupational medicine, sports medicine and trauma with the New Mexico Orthopedics Associates. He is a fellow of the American Academy of Orthopedic Surgery, and he is affiliated with Presbyterian Hospital in Albuquerque, New Mexico.

He served in the Air Force where he was the chief of orthopedic surgery, and he is a member of the New Mexico Orthopedic Surgery Association.

Dr. Ritchie, would you please say good afternoon and discuss any conflicts of interests you may have?

Dr. William Ritchie, MD

Good afternoon and thank you for the introduction, I do not currently have any conflicts of interests.

Dr. Janet Lawrence

Thank you.

Next, we have Dr. John Tassone, Doctor of Podiatric Medicine. He is an Associate Professor at Mid-Western University, Arizona College at Podiatric Medicine, he retired from active clinical practice after 23 years, and now pursues teaching and research full-time, he has authored a number of publications and he is on the board, he is the Board Director for the American College of Podiatric Medicine.

Dr. Tassone, please say hello and discuss any conflicts of interests you have.

Dr. John Tassone

Good afternoon, thank you for the introduction, I have nothing to disclose.

Dr. Janet Lawrence

Thank you.

Next, we have Dr. Will Whiteside, MD

He's a fellow of the American Academy of Orthopedic Surgery, is an affiliate assistant professor for the Family Medicine residency program at the Medical University of South Carolina in Charleston and its affiliated Tidelands Waccamaw Community Hospital System, in North Myrtle Beach. He is board certified diplomat of family Medicine. He completed a foot and ankle fellowship at the Andrews Research Institute in Pensacola, Florida, he is a member of the American Orthopedic Foot and Ankle Society, a member of the American Academy of Family Physicians and the South Carolina Orthopedic Association.

Dr. Whiteside, would you please say hello and discuss any conflicts of interests you may have?

Dr. Will Whiteside

Hello and no I have no conflict of interest. Thank you.

Dr. Janet Lawrence

Okay and our final panelist is Dr. Barton L. Wise.

He is a fellow of the American College of Physicians, and is a board certified rheumatologist, he is a Professor of Rheumatology at the University of California Davis School of Medicine, he's an interim Associate vice chair for Clinical Research and he was also one of the authors on the American the American College of Rheumatology, 2019 guidelines for osteoarthritis management.

Dr. Wise, would you please say hello and discuss any conflicts of interest?

Dr. Barton L. Wise, MD

Hello, thank you for the introduction. I have no conflicts of interest.

Dr. Janet Lawrence

So that is our extended panel, you can see that they are representative of a number of specialties, and also a number of locations across the country.

With that being said, we will get right into the formal CAC by beginning with our first speaker, Dr. Gajewski, who will discuss the FDA labeling and general safety, of these products.

Dr. Gajewski.

Dr. James Gajewski

So, my perspective on these products having been part of several FDA liaison meetings, for the licensure and regulation of stem cell therapies, that there are a couple of things that FDA has asked for licensure and regulation of all products.

Any allogeneic cellular therapeutic product has to be registered with FDA. Also, any cellular product being used for non-homologous use, and the human body that is autologous, must be registered with FDA and licensed by the FDA.

So, from my perspective, amniotic fluid cannot be acellular or always have fetal cells in it.

That makes it an allogeneic product subject to licensure.

I also have had strong conversations with FDA, and they agree that the issue of use of a bone marrow asper for joint repairs or fracture repairs, or injection to facilitate, wound repair, that that also is non homologous use, of cells because those cells are for hematopoietic reconstitution hematopoiesis.

That does not include joint repair. That does not include wound repair.

So that is also subject to FDA licensure.

Couple of other comments in terms of that.

These products if you are using them for related donors, must be very, very cautious.

And I know Janet advised against anecdotal issues, but I was at UCLA in the early years of the Gann Act where we were required to ask patients if they wanted to have designated blood donors.

At that point in time, we only irradiated first degree relatives so parent, child, siblings.

We had a grandson who donated blood for his grandfather, and we got [inaudible] those cells a few white cells and red blood cell product and grafted and [inaudible] fatal graft versus host disease.

Graft versus host disease from cellular therapies, I'm like where I'm dealing with in the context of a stem cell transplant, has an 85 to 100% fatality rate in about two weeks. The only way to prevent it is use of irradiation. So, with FDA licensure, comes various sterility testing assays. There is no uniformity on amniotic fluid. Each product has a certain uniqueness given the genetics of the, of the potential child, as well as of the mother.

[Inaudible] the FDA has now come up with this RMAT approach for allowing some of these products to be used, but that's in the context of licensure, and that's to me, where these products should be going.

I would also say, having served on RUC and CPT, as both a voting member and as an advisor, and, yes, I wrote all those codes relating to bone marrow and stem cell transplant as well as the Diagnostic Bone marrow codes, there was some code put up for fracture, repair of use of stem cells.

When I was at that time, I was a member of the, of the RUC, a voting member of the RUC, I raised the issue that that was subject to FDA licensure, the, the RUC chair said it [inaudible].

It is not the purview of RUC or CPT to determine whether FDA licensure is granted when they grant a code, that is for the providers utilizing those products.

So just because you can find a CPT code with RVU value does not mean you have the [inaudible], of the FDA for approval for use.

So, I just wanted to start the discussion with those, I know that we have other questions about review of the articles in place, but I will, at this point, be silent, unless there are some other questions for me.

Dr. Janet Lawrence

I actually had one follow up question Dr. Gajewski [inaudible] you mentioned the graft versus host cells that are present in the products and the need to irradiate them to prevent that very tragic complication from occurring.

So, in preparation of these cells or these products, how does, how does the means that are needed to make them be “safe to use”, how does that affect the effectiveness of the products for their intended use?

Dr. James Gajewski

So, a couple of comments there, Dr. Lawrence.

First off, the risk is primarily when it's a related donor where the donor, where these cell products will share partial HLA matched with the intended recipient.

They don't have to be completely HLA matched in fact, that's the, the real dangers when they are partially matched, because that, that is such a mismatch.

The issue of amniotic fluid becomes a little bit more because you don't you, when we use umbilical cord blood transplants, we are often using those that are only half matched with the intended recipient and that's HLA typing there from umbilical cord blood is low very low resolution, not the sort of high resolution molecular typing that I use with an unrelated, an adult unrelated donor and an adult unrelated recipient.

So, that's where the concern will be if the products are completely HLA mismatch with the intended host than the host immune system unless they are immunosuppressed, which some of the rheumatologic patient are, they would automatically be rejected by the host immune system and destroyed so the risk of engraftment there would be very small but it's incumbent upon the users of these products to know and know that the relationship and any risk of those products being a partial HLA match with the intended recipient.

Dr. Janet Lawrence

And with that, I will open the floor to comments from other panelists or my colleagues, Dr. Sun and Dr. Moynihan.

Do we have any questions or comments for Dr. Gajewski?

Dr. Ann Marie Sun

Yes Dr. Gajewski, this is Anne Marie Sun from Noridian, thanks so much for joining us, trying to better understand, and I think in and reviewing the literature, and in just the products that seem to be out there, how do you, how do you look at these products, when there are some requirements that the, that the FDA have the four main requirements that the FDA have determined for human cells or tissue products.

When some of the things such as you mention homologous use and you mentioned the cellular versus acellular type composition, I think, where folks get confused relate to how you apply the FDA concepts of healthy human cells and tissue products, and how do you apply that concept to something that's injected into joints and tendons. I think there's a disconnect, or at least, a confusion out there, as to how do you apply these FDA concepts to these products.

Dr. James Gajewski

In my discussions with FDA, and in my advisory roles there, the assumption is, all these projects for this stuff is subject to, FDA licensure and FDA review and FDA approval. I recognize that not all clinics doing this work have felt that they were subject to FDA jurisdiction. I think the FDA has had major concerns and is moving forward with more aggressive investigation of these products.

Beyond that, I cannot comment, but my, everybody who's using these products in clinical settings needs to, from my perspective, submit data to the FDA and give the FDA right of refusal for licensure. But, given what I stated, not homologous use of cells or allogeneic cells are subject to licensure.

Dr. Ann Marie Sun

Thank you. As far as, have you had your experience, have you had experience, though, in some of these products that have been used, whether it be discussions with other researchers, discussions with the FDA as to and any, anything on the horizon regarding future regulation, maybe even a new section or section or Department of FDA that would look into these more closely as far as paying attention to the new products that are coming out on the market?

Dr. James Gajewski

So, the FDA, this is all subject to the Center for Biologics, CBER section directed by Peter Marks have some fame or infamy lately with all the COVID vaccines.

And then the sub-section of Peters of CBER is the Office of Technology Transfer, used to be the center for LaSalle Gene Therapy branch of CBER, that has direct responsibility.

I think the new RMAT designation and pathway is a reflection of FDA trying to get more involved here, the other issue that is a little less clear with these cells but very clear for the anything that's genetically modified or allogeneic stem cell transplant is that they [inaudible] we are, you are subject to the registry reporting to the SCTOD, the stem cell, I forget what the OD stands for. The SCTOD is, the Nationals tracking age registry or outcomes for this, they have not, and that's contract for the SCTOD, [inaudible] for the Center for Blood and Marrow Transplant Research based in Milwaukee, Wisconsin.

I don't know how aggressive they've done here. They have clearly stepped up to the plate and are doing the long-term tracking of the immune effector cells, which are primarily now the car T cell therapy.

So, but that's the best I can tell you, I'm not.

I think FDA is obviously looking at. They've also been very stretched for resources here.

Dr. Ann Marie Sun

Thank you.

Dr. Janet Lawrence

Do we have any further questions or comments from our panelists?

Dr. Eileen Moynihan

This is Eileen Moynihan.

Hi. I'm just curious about some of these preparations are cryo-precipitated, et cetera. Given the various preparations do you think they all could have cells or might have other factors?

Dr. James Gajewski

I think you have to make the presumption that all these cryopreserved products could potentially have cells and the cryopreservation process, the other risk is that you may actually fracture cells with the freezing process.

An infusion of fractured cell, your products can actually create, create an immune cascade, similar to what we're seeing with some of the COVID patients.

As also the TRALI reaction that we see with blood transfusions, particularly cryopreserved platelets or plasma when we thaw them and infuse them, that we occasionally have that type of reaction.

Dr. Eileen Moynihan

Thank you.

Linda Meyer

Dr. Lawrence, we have one-minute remaining on the topic, so if there is one last question or any other comments.

Dr. Janet Lawrence

Dr. Gajewski, building on the last question from Eileen. For any of the literature that you have reviewed, have you seen where these potential complications from the fracturing or other things other then bruising or allergy have been addressed?

Dr. James Gajewski

That were very small patient trials, usually on the order of 10 to 20 patients that may be, they are insufficiently powered to look for those things, or have those things happen.

So, I don't know.

I also don't know how well they track long term toxicity most the outcome reporting was relatively short follow up.

So I don't think any of the studies that I reviewed adequately addressed some of those safety concerns.

Clearly, any of them actually also, [inaudible] what their conversations and their approval process with FDA was.

Dr. Janet Lawrence

Thank you, Dr. Gajewski, any further questions as we are at the end of our time for this panelist?

Are there any further questions?

If not, thank you Dr. Gajewski we hope you can stay around for the rest of the CAC discussion.

We're sure that you will have some interesting comments or insights.

So, we will now go into our second general discussion which will be conducted by Dr. Barton Wise and he will discuss the general concepts of use.

Dr. Barton Wise

Hello, can you hear me?

Dr. Janet Lawrence

Yes.

Dr. Barton Wise

Can you hear me? Okay, thanks. So, yeah. This is just going to be a very general discussion about the studies that we were given and that we reviewed and amniotic related products in general. So, amniotic related products were apparently first used in 1909 and have been used since then to support and treat wound, healing, burn treatment, and other indications over the years.

And recently, they've been investigated, begun to be investigated for use in tendon and joint related conditions, such as tendinopathy at various sites and osteoarthritis including such joints as the knee.

As far as I understand, the theoretical basis for the use in these conditions is predicated on a variety of arguments in part depending on which preparation is being used.

Some of the potential mechanisms for explanation of potential efficacy include or have included presence of stem cells and apparently, in some ways of higher quality than stem cells derived from other sources, and perhaps Dr. Gajewski would have something to say about that, pro- angiogenic properties, immunomodulatory properties, and components of some of the preparations that have fibrous protein, scaffold elements, or growth factors in them.

There's at this point, been a range of animal studies in different species that, which have reported some promising findings with regard to tendon and joint repair and reduction of pain.

And recently, a number of studies in humans have been published, investigating the products, some of which have reported benefit from their administration.

However, overall, there's a relative paucity of human studies published and there, I would say reasons for caution in interpreting and deriving policy from the currently published literature.

In the overview and an overview of sort of the State of the research field for amniotic product injections, for non-wound, musculoskeletal indications, there's some high-level patterns that can be identified that give me some pause.

Perhaps most importantly, the variety of the products of this type available and used in these studies is incredibly heterogeneous, and represent profound variation in the contents, and therefore in the potential mechanisms of action for the products.

Depending on which source one examines, for example, outlined in the Sulton article table 4, McIntyre table 2, Riboh table 2, there are at least eight different products or types of products available and used in different studies.

The products represent varying mixtures of different tissue components and there appears to be no unified approach to preparation or storage.

Even if, even if products that appear to contain similar source tissues. Based on these observations alone it does not appear possible to evaluate this class of products as a unitary treatment. And therefore, many of the published studies should really be considered entirely independently of each other.

And in many cases, cannot be joined, or contribute together toward demonstration of efficacy or safety.

Also, these published studies represent enormous heterogeneity in approaches, which limits the ability of the studies themselves, which limits the ability to draw conclusions on efficacy or safety of the products.

Delanois describes this amongst some of the other authors, number one, body structures and types of conditions treated, are variable and not carefully defined, and vary both between studies but also even within single studies.

An example is MacIntyre who lists multiple studies which are classed as foot and ankle, but actually represent even within a single study very different entities such as posterior tibial tendinitis, Achilles tendinitis, injuries to extensor muscles of the foot, plantar fasciosis and even nerve involvement.

Another one is Huddleston of the articles given.

Some studies such as Gellhorn include distant sites in the same study such as spine and knee and glenohumeral and femoral subtabuary and subtalar.

There are important differences, I would argue, in manifestation of pathology between these joints in terms of pain, functional limitation, and other things and lumping them together like this prevents appropriate and joint specific measurement of outcomes. Rendering the studies that combine multiple distant sites essentially uninterpretable.

There are also conditions treated that vary widely as well ranging from tendinopathies of a variety of types of injuries to osteoarthritis of various joints.

These studies are mostly very small numbers. Studies are mostly low-quality evidence level 4 or 5 only a few level one as described in a few of these articles, and the outcomes are evaluated over short time periods on the whole, mostly a few weeks or months, with only one that I saw that was evaluated after two years.

There are also many [inaudible] by design, the majority of, which are not randomized controlled trials.

So, in summary of sort of a general overview of this, some preliminary data appears potentially promising. But the available evidence is highly heterogeneous, and often low quality for a variety of different reasons.

Dr. Janet Lawrence

Thank you, Dr. Wise for that summary. That was really thorough and clear.

So, if I could briefly paraphrase you then, the studies that are out there are very, to use your word heterogenous. The preparations are not standardized in any way that you could see, whether that's preparation, storage, dose, timing and the amount of time that we've looked at these, as well as the number of patient studies, is insufficient to draw conclusions?

Dr. Barton Wise

Yes, I think that all of that is the case, and there are other elements that are concerning in terms of differences between the studies, as I described, and in terms of trying to understand them, join together, to provide a coherent picture that would support use of the product to this point.

Dr. Janet Lawrence

Are there any questions or comments for Dr. Wise from the panel?

Dr. Eileen Moynihan

This is Eileen Moynihan.

I just want to comment that I, I thought that was a very succinct and thorough discussion.

And you kinda left me without any further questions on your topic. So, thank you.

Dr. Barton Wise

Thank you.

Dr. Janet Lawrence

I think it's probably safe to say from the reactions that most of us would agree.

So, thank you very much, again, for that Dr. Wise.

It was very informative. Okay, we're moving right along.

So, we will go to our third topic for discussion which will be our first polling topic and that is the discussion of osteoarthritis of the knee and hip, and other joints.

And this discussion will be led by Dr. Harvey, followed by Dr. Ritchie.

Dr. Harvey?

Dr. Will Harvey

Thank you and thank you for your time.

I was asked to review the available literature focusing on use of these products for treatment of osteoarthritis, and I think you will hear through this summary, that I will echo some, many of the things that Dr. Wise just reviewed. Rather than reviewing them in chronological order, I thought I would them, actually, in sort of ascending order of evidence, starting with the least strong evidence that we have for review out to the, the most significant evidence we have.

So, I was asked to review and found in the literature two papers that were primarily review articles discussing other author's work, as well as some of the background information on these types of therapies that Dr. Wise just reviewed. One was actually a very well-done system, systematic review and analysis that suffered not from the skill of the authors but from a paucity of evidence.

They reviewed one article, which I'll talk in more detail about later, and another that focused on the use of umbilical stem cells with hyaluronic acid injected into microfracture drill holes as part of a surgical procedure. So, I will defer any further discussion about that to my orthopedic colleagues who will speak next.

Another review article, by Hannon et al published in 2019, really only discusses again, one of the articles that will come up subsequently. In fact, that article is by Vines and colleagues. It is an open label pilot of six patients who got one particular therapy in this category it was

published in 2016. Their primary outcome was KOOS and for those of you who are not familiar with this, it's a very commonly used standardized outcome. It's actually quite a good outcome for measuring knee pain and other knee outcomes in osteoarthritis. So, the good news is that they are using well established standardized measures. They saw some short-term improvements in pain, but did not do any statistical analysis due to the small sample size. Two of the six people had transient pain at the injection site and as was suggested earlier, not a large enough study to truly assess the safety or efficacy of this product.

The next paper was a pilot study of 20 individuals using a different outcome called Womack, W, O, M, A, C, which is also a very well standardized and commonly accepted outcome in knee osteoarthritis research. This was an injectable amniotic membrane, an umbilical cord particulate. They saw very dramatic improvements in pain stiffness and function using that outcome that I just mentioned, at 12 weeks.

The, they also saw some improvements in bone marrow lesions, which are particular factor, a particular artifact in an MRI that has been associated with pain in [inaudible] knee osteoarthritis and other studies. The difficulty here is that this was an uncontrolled study of an injected therapy and the risk of bias in this study, which is the main factor I use when interpreting studies to determine whether the results are believable is extremely high because the study was not controlled, not blinded. And external data suggests that, that studies involving injection therapies have very large placebo effects. So, I find it difficult to assess the efficacy or safety of this product based on this study alone.

The next one was a case series of 50 consecutive patients, which by the time they were done, this was one of the studies. This is Gellhorn, et al, published in 2017. This is the study that Dr. Wise mentioned used to disparate. It was used in disparate joints. So, eight knees, two tibial tailored joints, two subtalar joints, three glenohumerals, and so on. And so, it's very difficult again because of the heterogeneous nature of the application of the product in the study, not to mention the disparate outcomes that were used in the study again make hard conclusions very, very challenging for this paper.

Next is, I will not attempt to butcher the good Dr. Bhattacharya's name. But that's my best guess at the pronunciation, it was published in, in a book chapter actually in 2011 and as a report of a single study over seven years. And it compared triamcinolone to 10cc's of freshly collected amniotic fluid. With all of the caveats that were mentioned previously, you know, it's somewhat concerning the way in which this unlicensed product was used in the study.

Nonetheless, they again found quite dramatic benefit as measured by visual analog [inaudible] and multi-dimensional health assessment questionnaires. And the things that concern me about this study is that it was very, it was not reported well. And so I can't, I can't confirm much of the aspects of quality study design. And, in fact, one of the things that they report is that over the 24 months of follow up, there was not a single drop out of participants in the study.

And having done large osteoarthritis trials, that certainly raises some questions because that's a feat that is almost impossible to have happen. So, I do not feel as though the results of the study can be used to determine efficacy.

The last two are, are better design studies. The [inaudible] one is again, a case series and you'll notice a theme here that almost all of these are uncontrolled studies of a 100 milligrams of injected amniotic chorion membrane. It was done by a single physician over 14 months. And this was a retrospective chart review design again, used a very standard outcome of KOOS and they saw a very large [inaudible]. However, again, because this was a non-controlled, non-blinded study, in a highly selected population who chose to pay for the therapy that they were getting, I find the risk of bias in this study unacceptably high to use it to adjudicate efficacy or safety of these products.

The last one is, by Farr, the best quality study is, by Farr, et all, published in the Journal of Knee Surgery in 2019. It is truly a randomized study design 200 participants. One to one randomized to an amniotic product, versus hyaluronic acid versus placebo use very high-quality outcomes, such as KOOS and the EQ5D for quality of life.

One major methodology, deficiencies that they did not identify primary outcomes, so they analyzed all outcomes together, which, for us methodologists, means that there's a high risk of, of a random chance of a positive result. And they did find significant improvements although small, in EQ5D, and KOOS pain for these products in question compared to hyaluronic acid. They also used an outcome, called OARSI-OMERACT Responders Group which is another very well standardized outcome, and there were more such responders, meaning people who achieved a better outcome in the Amnion Group, compared to the other groups.

The risk of bias in this trial is moderate, it still was not blinded, and there are some other methodological deficiencies, but this one trial really represents the best evidence that we have for use of these products.

If I were to take them in summary, I would echo a lot of the things that others have said, that, that these studies may be promising, but the quality and volume of the evidence, not only in efficacy, but particularly around safety needs for these products. As well as the fact that each one of these studies used different formulations of different products, and so cannot readily be compared. In a single class, as Dr. Wise suggested, that I have the feeling that these therapies may hold promise, but we do not yet have sufficient evidence to recommend their use outside of ongoing research study protocols.

That concludes my summary of evidence.

Dr. Janet Lawrence

Thank you, Dr. Harvey.

That was, again, that was an excellent summary and you, you went in order from worst to best, and essentially even the best study that they have is, still has flaws and there's just insufficient evidence at this time from what we can see.

Are there questions or comments from the panel regarding Dr. Harvey's presentation?

Okay, hearing none again, that speaks to the thoroughness of your presentation.

Dr. Ritchie, are you ready?

Dr. William Ritchie

Yes. Thank you. It's kind of a tough act to follow. Harvey did a very good job summarizing that, the studies that were provided, and I agree completely with what he said and his ranking of the studies.

The last one, the Farr study, is the best of the group. But, again, has problems. It was funded by one of the, by one of the companies providing the amniotic membrane and cells that I've dealt with as well. Just trying some of their products. It did have some long-term results that are promising. But, again, many, many of this, these studies, are, are more like white papers, then, truly good, randomized, double blinded controlled studies.

I also found a site, it's been accepted by the Journal of Arthroscopy, but has not yet been printed on amniotic allograft injections into hips. And, but, again, it is like some of the other studies. It's a pilot study, with just 10 patients, with, with promising early results, but still lacks not only the power, but the standardization, the selection of cohorts, you know, many of the, the problems that have been brought up already, so, I don't have a lot to add except to echo that, that, we do need more data, that, there are still questions, all these studies say, there's safety and efficacy, but again, they're short-term, and there's still questions, as brought up at the very general section, on safety. When I've worked with these companies, or, or had them come and present their products to me, that is definitely glossed over, the safety aspect, the potential graft versus donor problems that really does not appear in their literature or in their presentations.

Nothing more to add to that.

Dr. Janet Lawrence

Thank you, Dr. Ritchie.

As an orthopedic surgeon, then you did not appear to find anything in the literature that you read to support its use intra-operatively?

Dr. William Ritchie

There was there was just one study that, that spoke of using it with the micro fractures.

And, I have used these products intra-operatively on several occasions, both on tendons, and in the knee and the shoulder, and, have anecdotal, you know responses to that, but do not have good trials, long term series, long term follow ups.

And so, you know I think it does have a place, I think we will get there with biologics. But we haven't expanded the, the study sufficiently to cover all the, the concerns, both from a safety standpoint but also from, in, in how the products are treated. How, you know, when do you use them? And then these studies, they're so low powered, the cohorts aren't really segregated sufficiently to establish who they work for. For instance, many of these studies, exclude anyone with a BMI over 30, or some of them over 40. So, we still need data, and intra-op, yes, I've used it with primarily good results, but on a limited basis than in a case by case basis.

Dr. Janet Lawrence

Thank you.

Any comments or questions for Dr. Ritchie and/or Dr. Harvey on this, this section because in osteoarthritis is one of the largest areas where we are seeing the use of these injectables.

Any questions for them at all or comments from our panel?

Dr. James Gajewski

This is Jim Gajewski, I have a question where, where you actually did these injections for the micro fractures? Where these products registered and licensed with the FDA and part of an IRB approved clinical trial?

Dr. William Ritchie

I have not used them in conjunction with, with microfracture.

I have used, them as, like I said with tendon repairs, as far as in the joint, I have injected fluid at the end of a surgery when doing, Chondroplasties, and, then also, when dealing with an osteochondral defect, and they were not part of an IRB study.

Dr. James Gajewski

And I presume that the products were not registered with FDA, either.

Dr. William Ritchie

To my knowledge, that is correct.

Dr. Will Harvey

In partial answer to that question, one of the review articles today, I looked at, cited an article by Park et all, all that used this technique of microfracture injections that was part of an IRB approved protocol. I do not know if the product was licensed at the time that study was done.

Dr. Janet Lawrence

Interesting.

Anything else from our panel?

Yeah. Yes. Who was the last speaker, I'm sorry? Who identified the study?

Dr. Will Harvey

Sorry, that was Dr. Harvey.

Dr. Janet Lawrence

Okay, thank you. Okay, so again, very informative, very helpful and sort of reinforces what we determined from our own literature reviews.

With that, we will move on to the polling. Linda, please take it away

Linda Meyer

Alright. Thanks Dr. Lawrence.

We are now going to ask our CAC panel members to access the polling system, either via your web app or your web link.

The questions should be available, and those on the app, I know you should actually be able to see all 24 questions you'll need to speak to today. Right now or excuse me, respond to today. Right now, we'll just ask you to do the first six, that is for condition one.

After we get responses to this, those six questions will be removed, so the next six questions, when the time comes, will be moved up in that order. If you're not able to see, hit refresh, because the questions should be loaded.

I will go through and read the questions for this first series. They are the same six questions that you will be speaking to regarding safety efficacy and post-operative outcomes. However, we ask that you rate for each specific condition at the time, that condition is being discussed.

With that, the first question is, how confident are you in the evidence that amniotic product injection to treat, to treat the osteoarthritis demonstrate, short, or intermediate term safety?

Question number two, how confident are you in the evidence, that amniotic product injections to treat the osteoarthritis demonstrate long term safety?

Question three, how confident are you in the evidence that amniotic product injections to treat the osteoarthritis, demonstrate, short or intermediate term efficacy?

Question four, how confident are you in the evidence that amniotic product injection to treat the osteoarthritis demonstrates long-term efficacy?

Question five, how confident are you in the evidence that amniotic product injections or placement intra-operatively improved short or intermediate term post-operative outcomes, for this condition?

And the final question, how confident are you in the evidence that amniotic product injections or placement intra-operatively improve long term post-operative outcome for the condition of osteoarthritis?

And again, one is low confidence, five is high confidence.

We'll just take a moment to allow them to submit their results.

Dr. Will Harvey

Hello, this is Dr. Harvey. I continue to get a survey unavailable error when I click on the questions.

Dr. Padma Gulur

Same for me, this is Dr. Gulur.

Linda Meyer

Okay, are you, you're on the web ap?

Dr. Will Harvey

Actually, it just loaded, the first question just loaded.

Linda Meyer

Oh okay, good.

Dr. Gulur, you're still having the issues.

Dr. Padma Gulur

Yeah, unfortunately, I've tried refreshing it and I just tried it again and survey not available.

Linda Meyer

Okay, we'll make note, and as we indicated, because we know technologies and where our individuals are at, we will obtain your results most definitely, if not today, or after the meeting.

Dr. Padma Gulur

Thank you.

Linda Meyer

Thank you.

And, give everyone another moment.

Dr. James Gajewski

This is Jim Gajewski, I'm getting an error message 503 survey not available.

Linda Meyer

Okay, I think you have the same that, Dr. Gulur has, I'll make note of that. Thank you.

Okay. I do see that we have five individuals that have completed.

And, looks like, we have seven so if were having some technical issues, it does appear we are, we have everyone.

Is anyone still completing, I will wait another moment, if not, we'll move on.

Okay, Dr. Lawrence, I'll turn it over to you to move on to the next condition.

Dr. Janet Lawrence

Thank you, Linda.

Moving on to our specific condition two, which is the discussion of plantar fasciitis and Achilles, tendinopathy, tendinitis, and other conditions of the foot.

We will have presentations from four of our panelists and they will proceed in this order.

We will first hear from Dr. Tassone, then Dr. Block, then Dr. Pavelescu followed finally, by Dr. Whiteside who will give the orthopedic perspective.

Dr. Tassone.

Dr. John Tassone

Yes, good afternoon. Thank you. Appreciate the opportunity to speak. What I'm going to do is go through each study briefly and just bring out what I looked at as strengths and weaknesses.

And then at the end, give an overall summary of my thoughts, if that's okay.

So in no particular order, the articles I looked at were 9, 12, 14, 21 and 23 and we'll start with article 12, the use of dehydrated human amnion and it was a case series involving 40 patients.

So just to look at the strengths first. I'm a big proponent of diagnostic ultrasound, especially in guiding injections and especially Amnion injections, which I've used clinically for, for a few years. And I think that that's imperative. I think you need to have guidance, and this was the only study, as far as I could see, that utilized it. And so, I think that's a strength in regard to this study.

Another strength, is that, is that the cohort showed improvement in pain reduction and, and function over time, and that was statistically significant. Also, a strength was that it showed a decrease in medication usage among, among the, the patients. And that was also statistically significant, and that was unique to this, to this article, the others did not have that.

However, the big negative for me, is that this was not a randomized control study. So, it was, it was a case series, a case study. So, a level four, in regards to evidence.

Going on to the next article Number 14 and this was the Cryopreserve human amniotic membrane injection for plantar fasciitis. And this was a randomized, controlled, double blind pilot study. And so, trade in the title, a strength is that it is a controlled trial. So, a level of evidence of one, seems like the big point coming from this article that it appears to be safe, seems that that was the big statement they were making. So, they did look at that so I would list that as a strength.

But there was kind of, in my opinion, quite a few weaknesses. First, it's a pilot study. So very small population size. 14 patients receiving Cortisone and nine the Amnio, so a low power, in regards to evidence, in regards to the sample size.

There was little to no significant difference between the study group, and the control group, for three of the most relevant outcomes, which included foot pain, general foot health, and the BAS pain scale.

Another thing that I saw this in a couple of other, other studies was that they included after the injection stretching of the Achilles and the fascia, which is okay, but they didn't adequately assess that in the results. So, we don't know how much that impacted the results. Then, a big negative for me was that this was funded by Amniox Medical. An amnion product, and an amnio manufacturer. So, in my regards was big negative.

Going on to the third article, which is numbered nine, and that was the Randomized, Controlled Trial of Micronized Dehydrated Human Amnion. In my thoughts, this was the best of the studies. It is a randomized, controlled trial. So, level one evidence, excellent sample size, with a power analysis of 90%, 73 participants in the study group, 72 in the control group. So, very good.

They had really great inclusion, exclusion criteria. The results were good, statistically significant results in pain reduction and improved function. But this was also funded by an amniotic company and for me, that was a big weakness.

Also, another weakness is that the subjects in the control group also reported a significant reduction in pain, and improved function over time. And, as I mentioned in the previous article, they threw in standard of care treatment afterwards, offloading, night splints, orthotics and, again, was not, I don't think, adequately addressed, and how that factored in, in the results.

Going on to the next article, this was actually the systematic review, and the amnio did provide significant relief after two months, 0 to 2 months. But there was no data for long term relief past two months. The best data for long term and what they concluded overall was the botulinum injections that they did in this study. And this was a systematic review, but it had a limited number of trials with a large number of treatments, and thus did not produce good statistical, powerful results.

And then the last article, number 23 was the prospective randomized blinded comparative study, of micronized dehydrated amniotic allograft with planter fasciitis. It was a randomized control study, so that's a strength. But it was a very small sample size. Also, it was a very short study, only eight weeks. All groups, including the control group, showed significant improvement, another negative. And once again, patients were given some random other treatments at the end, tramadol. They were off loaded in this study and night splints and again no adequate discussion on how this could factor in with the results. And then finally, another big negative was that it was also funded by an amniotic company.

So just to summarize, overall, we have three randomized controlled trials that I mentioned that were all funded by amniotic companies. As I mentioned, the lack of ultrasound guidance and all, but one. All three trials included other inventions without addressing their impact on the results plus the other assorted negatives that I mentioned. And so unlike wound care, which I feel we have a lot of good literature on in regards to the use of this product. There's just not strong enough clinical evidence over placebo or any compare towards or standard of care in the literature at this point.

So, I just don’t think, there's significant literature to show that it's better, and also in regards to pain reduction, and improved function, I don't really feel that there's strong literature, at this point, I think, I think it shows promise, and I've used it anecdotally, I've used it in the clinic, but there's just not strong enough evidence to support it. Thank you.

Dr. Janet Lawrence

Thank you, Dr. Tassone.

Very detailed and thorough overview of the articles.

Yes. I think I'm going to have people respond unless someone has, feels that they'll forget their comments. I think we'll hold the comments until the end of the section.

So, we're going to proceed on to Dr. Block

Dr. Marc Block

Thank you.

I have a number of comments here, but many of them have been addressed, so rather than being redundant, I'm going to try to segregate as I go down my list. Those that may not have been addressed previously or that I felt I wanted to elaborate on. So, I apologize if many of these are redundant, but we can deal with that as we move along.

Let me preface by saying, again, a lot of the comments that were made by the other Dr.'s, I, I strongly agree with them, so I'm not going to go into any detail on those.

That being said, just as a general overview. I had the same group of articles that Dr. Tassone had reviewed. I was focusing on some different areas. Some of the issues that I had in as a generic overview was, I didn't think these articles or these studies, in some cases, with that strong to make the points. And I think the, the number of candidates and possibly those that were selected, may not have been the best. There may have been some bias there.

The control groups were varied, the different types of controls they used. The timespan for evaluating the results, was not necessarily consistent. Most of them went out to three months. I think if I recalled one went out, I think about six months to a year, a number of the articles did agree that they needed. They recommended moving forward, that longer term studies or evaluation should be considered.

In article number nine, it showed a decrease in pain with just placebo amniotic products. In this particular one, the control used sodium chloride, and interestingly enough, there was some impressive, positive results from the sodium chloride as well as the amniotic product. Although, in the end, they indicated that the amniotic product was superior.

The, there was another study using cortisone. Initially the cortisone as the control seemed to have, equal or maybe even a little better after the first, I believe month that it seemed the amniotic exceeded the results. But interestingly enough, one of the articles and it wasn't specific, referred back to studies where cortisone was utilized and it stated that at the very beginning, the amniotic product was superior to the cortisone yet, in this the study I just

referenced, it was just the opposite. So, the credibility in that particular article is, comes to mind.

The other, the other issues that came into play is a methodology in which the actual procedures were done in one, they needled the plantar fascia, as they injected the amniotic product. So one has to question whether any positive results was the result of the actual amniotic product or if it was the actual procedure of needling the plantar fascia there have been articles and papers done on the efficacy of needling the plantar fascia and positive result just from that.

There was, let me see. Another study, again, it was mentioned previously, in particular, this study was sponsored by one of the companies that markets one of these products. One of the investigators, did disclose that they had stock or shares in the company and they were on the advisory committee. So, that also, raises kind of a red flag on any bias.

I would have to say that overall, generically, the article seemed to weigh a little bit more in favor or in favor of positive results when using an amniotic product. Although, again, I questioned the number of candidates and how scientific these studies were.

There was one other, also, there was another individual, he was 1 of 5 investigators, and his observation was 100% improvement as far as pain, which I also found extremely suspect. So, the question is, was there bias there, was it the wrong group of candidates that were being examined? Were there some flaws in the actual study?

As, as an overall treatment, it's an option. I think it's a tool that a clinician may want to consider in their armamentarium. Is it a first line of treatment?

At this point in time, I personally would say, no, I would say some of the more traditional methods should be utilized first. And I also question whether some of these studies really weighed that and did a comparison, an adequate comparison of the traditional methods versus using this as opposed to using this is the first line of treatment.

That's basically all I have to share with you right now, and if there are any questions, I'm available. Thank you.

Dr. Janet Lawrence

Thank you, Dr. Block.

You brought up some additional interesting points. So, thank you for that.

We will proceed unless someone has a question that they'd like to ask Dr. Block right now, we will proceed to Dr. Pavelescu.

Dr. R. Andrew Pavelescu

Good afternoon, everybody.

So, I'll try to be as brief as possible. I also had the same review articles, as Dr. Tassone and Dr. Block.

So, I'll forgo the summaries, but and my area of focus was harm and adverse events, and both conservative and then operative applications of these products.

So, I just wanted to preface my answers first, that, you know, level one studies for foot and ankle are few and far in between. So, we're lucky that we have two, as part of these packages, some of the other problems that were already addressed is that, most of these studies, if not all, were short-term in nature, they were relatively low powered. And I'll get into some other concerns.

So, in terms of looking at harm and adverse events associated with a single injection, just based on these studies, there were no major adverse events that were reported in any of these studies. Minor, adverse events, such as, you know, injection site pain, were reported, but not statistically significant, for any of these studies, in terms of harm or adverse events with multiple or repeat injections. I don't think any of these studies looked at a series of injections for any specific problem. I think one paper gave their cohorts the option of having a second injection and their inference was that there may be a dose dependent effect because they did see a significant decrease in pain and increase in functionality, but I don't think that's explicitly uniform for all the literature.

There's also variability in the, the volume of some of these injections and some of these studies, and so the variability questions. Whether low volume, high volume, multiple injections are effective, and I don't think there's any answer as to frequency of injections in terms of outcomes.

And looking at these amniotic products, as far as side effects, if they have lower adverse events versus standard of care, I, none of these papers really addressed. Yeah. It, you know, looking at it. I think the answer is no.

I think one paper inference that. These amniotic products may have at least a similar, similar efficacy to cortisone injections. But again, this is a conclusion just based on a small cohort.

And then in terms of operative applications, there's really only three papers that look at operative applications for, for lower extremity problems. And there, they're actually summarized in one of the review articles into general concepts. And, again, these are very small studies with low number of patients. Which, in looking at these results, there is some, positive support for these products.

But, again, I don't think there's enough literature to 100% support their use. And, again, as I said, everything, you know, all these studies really address short-term outcomes. There's really

no intermediate or long-term assessment of these products. And that concludes my, my portion for these, for, for plantar fasciitis and Achilles tendinitis.

Dr. Janet Lawrence

Are there any questions for Dr. Pavelescu right now, from my panel?

Dr. Barton Wise

I have a question. This is, this is Dr. Wise, and this is really, addressed to any of the three people who just spoke. I won't go over the, again the issue of there being very different preparations.

But one thing that I noted while reading these studies is the multiple different types of conditions that they included in the patients that they were treating, or including in the studies, and I know that I'm more familiar with osteoarthritis. That's more my area. And I, as I stated, I think that it's pretty problematic to just lump together the different joints. But I have less ability to understand whether it might be a problem that in foot and ankle, for example, they were really putting together multiple different types of tendinopathies, one of them even included people with nerve problems. I'm wondering if any of you could comment on whether that was concerning to you, that these studies were really not on specific individual conditions in the foot and ankle.

Dr. Marc Block

This is Dr. Block, if I could comment. One thing I wanted to mention, I'm glad you brought this up, is that, plantar fasciitis or the inflammation maybe the results, for example, of this strain or it could be due to a partial tear. So, one has to question whether the efficacy of the product is in repairing the plantar fascia in fact, as a tear? Or is the efficacy more in just reducing symptomatology without a tear? And I think there should have been some studies where there was imaging, high quality, either ultrasound or MRI's to differentiate whether the symptoms are associated with a partial tear or with, were no compromised anatomy, just enough an inflammation. So, I don't know if that answers your question, but that was one of the things that I was going that that came to mind and that was really not stratified in any of the articles that I read.

Dr. Bill Wise

Thank you. Yes. That is definitely partially what I was asking about.

Dr. Janet Lawrence

Anyone else like to comment.

Dr. John Tassone

This is Dr. Tassone.

Dr. Janet Lawrence

Go ahead.

Dr. John Tassone

Oh, I'm sorry. This is Dr. Tassone, I think you also need to look at, it's an excellent point that you bring up is that we also have some biomechanical differences as well. Different forces depending on what structure you're looking at, the plantar fascia versus the Achilles tendon versus the peroneal tendon. And so I think that's also a factor. You have different forces, for instance, the peroneal tendon a [inaudible] function going around the [inaudible]. So, I think that's also clinicians, too, as well. So, excellent point.

Dr. Janet Lawrence

Okay, thank you, panelists, for that discussion in that, and those, that clarification and expansion.

That's greatly appreciated. Are there any more comments on the previous three discussants?

Okay, then we will move on to Dr. Whiteside.

Dr. Will Whiteside

Hey, yeah, Will Whiteside here. Yeah. I agree with a lot of the discussion we just had.

And I think they hit on the main point, and it seems like we agree.

I reviewed these articles as well and some of the take on points and advantages to review what I just said. There was funding by, you know, MiMedx which is associated with EpiFix. And that's certainly concerning when you look at any kind of peer reviewed literature that there can be underlying benefit to having good results for your company. And a lot of the other thing with these articles is there are really short studies. I mean, some of these only had results for eight weeks, up to 12 months, is the longest study, number 12 article by Gellhorn, something we just mentioned, I mean, there was 40 patients, but they injected the cervical spine, the knee, the ankle, the tendons of the elbow, the shoulder. So that kind of level four evidence no control there, and just kind of a smattering of see how you do with these injections.

Other thing and a number 14 with Robert Santrock, Hanselman know essentially the effectiveness is similar to steroid injections. One thing to think about when you're looking is

there's no, there's really no guidelines, and I think that's why we're trying to discuss this stuff. No, AAMS has clinical practice guidelines for osteoarthritis, and really, even for injections, for osteoarthritis, will shrink the recommendation remains inconclusive. And that's kind of a longer condition, and it's been studied a lot longer than that recommendation for PRP for Osteoarthritis is inconclusive, growth factor injections are inconclusive.

It's kind of one of those things even for a broader topic and something that's a little more studied. We still don't know. And so that's something to think about that I've thought about when I was looking at these.

Another take on point, I think that we could conclude is that it seems safe, certainly in the short term, you know, if you look at objective data, that's all the data we have based on these few articles, but no more than 12 months. It does seem safe, I think that's an okay thing to say but some of these other ones, eight weeks of data, know, that was a level one study with another with Andrews, number 23 but again, that was funded by MiMedx as well and so I think, you know, just be brief, I think we do need longer study to determine the true effectiveness of these. But I would conclude that I do believe it is safe in the short term.

Dr. Janet Lawrence

Alright, thank you, Dr. Whiteside. Are there any other comments from the panelist or from my co-workers?

Dr. William Ritchie

This is Dr. Ritchie. I have a quick question to Dr. Whiteside, and just to the group. Coming from a surgical standpoint, what we, it wasn't addressed here, or included in the topics, and, and I have not found papers on it particularly, but in using amniotic membrane to decrease scarring in tendon repairs. Those alluded to in a couple of the papers and I've used it as such with very good but anecdotal results again. And it's almost like the wound, wound indications. Where you are using membrane or external wounds. But this is for surgical procedures and decrease scarring. Post-operatively but not an open wound. I don't know if that is a subject to just a topic that is too, there's even less information about, so, there's not much to discuss, but I was wondering if anyone had a comment on that.

Dr. Will Whiteside

This is Will Whiteside, well the only comment I can make is kind of what you said. I've seen it anecdotally, I've used it for revision cases, revision peroneal tendons, probably specifically some of the Achille's indications that I've used it for but that that is purely my experience in talking to others. I mean, I can't say, I have data that I can back it up, you know and I'm not sure that they want to hear about that here, but anyway, that's all I can speak on that. I didn't really

come across that too much these articles they specifically pointed at. I agree, I understand. And I think for the revision cases, you know, you kinda throwing everything at it and this, in this setting here, I'm not sure we can back it up with evidence.

Dr. R. Andrew Pavelescu

Hi, this is Andrew Pavelescu, I was just going to agree with everything that's been said I think anecdotally. You know, I've used amniotic membrane products for revision cases specifically tendon revision cases, peroneals, Achilles, PT tendon, but you know, with respect to all the literature that were reviewed, I just don't think. I just don't think there's enough evidence to support the widespread use.

Dr. Barton Wise

This is Bart Wise again, just with regard to the safety. You know, I'm not sure it's appropriate if, as we've discussed several times now, to kind of lump all these things together. But even if you do, you put together a whole bunch of these studies together to look at the safety issue and you get maybe a couple thousand patients total in all of these studies is, that's the kind a very quick and not accurate estimate. But let's just say it's a thousand or two patients, something like that, and it does appear that there isn't any large safety signal that I saw in the papers that we read.

However, I just would caution that Dr. Gajewski mentioned earlier the possibility of, you know, a little bit more rare, but very, very problematic conditions such as graft versus host. And, I'm not sure that this collection of studies necessarily represents the true safety profile that you would see if it were in very large studies are, or in very large use in society in general so, I guess I would be a little bit less sanguine about the safety based just on these studies.

Dr. Janet Lawrence

Anything further from the panelists?

Dr. James Gajewski

Hi, this is Jim Gajewski, I guess I would echo that concern there. The other issue, since almost all these studies are company funded and not from an independent analysis, we're missing that unbiased view of safety, that is so necessary.

Dr. Janet Lawrence

Yes, and that is very important. And just to emphasize, as MACs, we are required to form our policies, or local coverage determinations based on the evidence. While, we all have experiences and different procedures, or things may work. We have to, formulate our policies

solely based on the review of the evidence. And at least at this point from what we're hearing, it's pretty sparse, So, with that being said, we're ready for another poll.

Linda?

Linda Meyer

Great, thanks, Dr. Lawrence.

Again, for those, we will be in contact with those who are not able to access the website.

You can, you can try to refresh again, but Jocelyn will be in contact and we will get you the survey, the survey will be out here shortly, or access or trouble shooting it.

The next series of questions and we'll go to the polling questions again. They are the same questions.

This time we ask you to rate you're confidence in the evidence and that the amniotic product injections [inaudible] or as they're related to plantar fasciitis, Achilles, tendinopathies, and tendinitis.

There are two questions related to safety, two question to efficacy, and then. Okay. But we'll just watch it. And then the last two for post-operative outcomes.

Take a moment.

This is condition 2 questions.

Looks like.

Looks like we're getting near the end.

Okay. Looks like, we're waiting for maybe a couple more questions, and then we can move on, just give it another moment.

Okay, I do see the survey questions responded to. so, Dr. Lawrence, we can move on to the next condition.

Dr. Janet Lawrence

All right.

Moving right along to Condition 3 the discussion of Rotator Cuff Tendinopathy, Tendinitis, or Tear; Lateral Epicondylitis, Carpal Tunnel, Trigger Finger.

And our discussant for these topics will be Dr. Beatty followed by Dr. Ritchie.

Dr. Beatty.

Dr. Nick Beatty

Thank you very much.

So, I will review these topics as discussed based on the research at hand. And since some of these studies had multiple tendinopathy conditions, some of them may crossover versus being discussed individually.

So, one of the themes that we're all recognizing is the paucity of high level of research. And the foot and ankle on the lower extremity actually had higher level research than looking at the upper extremity. It's was pretty limited in terms of level four research.

So, we've all discussed the Gellhorn and Han 2017 study. Although you know, from a clinician point of view, it was had some elegant aspects of it that was practical, feasible, cost effective, image guided, and you designed well from a retrospective case series and the fact that this study keeps coming up. I'm sure the authors would probably agree as well that that's a sign that the literature is thin. But I just want to review taking away the arthritis cases, the 20 cases of tendon pathology and just list them again.

There were seven common extensor tendon cases, which is the tendon treated for lateral epicondylalgia, or epicondylopathy, or tennis elbow. There were three supraspinatus tendon cases for the shoulder. There were three conjoined tendon, or proximal hamstring tendon cases, two gluteus medius cases, two patellar tendon, one Achilles tendon. and there was no specifics as to whether it was insertional or mid-portion or tendinous junction. There was one fibularis longus, and one iliopsoas.

So, I'm going to touch on just the numbers which are seven for the common extensor tendons and three for the supraspinatus. So it's quite limited. The study used AmnioFix, which was a dehydrated human amnion chorion membrane, it was ultrasound guided. And they also, or did, the performing interventionist did 5 to 10 passes of percutaneous needle tenotomy, and that's not something to gloss over because there are other studies such as Kirshner et all, and Mountaineer, that show, when comparing PNT versus PRP. You know, there was a big question of is it the needle, is it the passing of through the tendon that’s actually invoking the response versus trust the other injectate. So, this was an AmnioFix injection plus 10 passes of PNT.

Primary outcome measures we discussed already overall were fairly positive and they weren't broken down too much beyond the tendon versus arthritis subdivisions but there was upwards of 3 to 6 months at pain change. 30% was the MCID that they use which was pretty generous and then they had a secondary functional outcome measure using the patient specific functional scale. So, at three months, they were functioning better significantly, although that's still not too far out. There were no adverse events, which we discussed as well.

In terms of limitations, there was no control, those very small sample size questioning of whether it was the PNT or the actual product itself, is only up to three months in the first

author. Although, there were no details. There was honorarium from the company that makes the AmnioFix as part of this study.

Moving forward to, an Ackley et all 2019 study. This was, again, a case series, this was a pilot, which is you're typically looking at safety profiles and not really making any conclusions from pilots. 10 patients with partial rotator cuff tears, they injected amnion, and then, umbilical cord particulate matrix called, the CLARIX FLO was the name of the product they used, based on the pen shoulder score range of motion and MRI. Findings showed a 75% improvement in the shoulder score. About a 28% increase in range of motion overall. The MRI was blinded by the radiologist to the radiologist. And there was no change in the rotator cuff anatomy. It's didn't get worse, but there were no improvements based on this. These were floral guided intra-articular injections, which is not typically the norm for a study design if you're trying to treat a rotator cuff tear, and the baseline MRI shows, synovitis, capsulitis, effusions, and you're injecting into the joint, to treat the tendon above it particular[inaudible]. It's not necessarily without confounding variables. No control, small pilot, and again, level 4 study.

And then lastly, I'll just touch on a trigger finger, tenosynovitis, study. They were trying to treat the A1 pulley. This was by Quinet et al in 2020. This was a pilot study with a larger and there were 111 digits. I guess you can get a little bit higher and more easily, in this case, from 96 patients, they were blind injections or palpation guide injections using one mil of amniotic fluid product and they never said, and the materials and methods what the product was, which was a little unusual. They had to thaw it in warm water. So, it wasn't reconstituted in saline. They use the DASH score for disability of the arm, shoulder, and hand. And they actually had reasonable outcomes. They had a strict success rate, and they had 51.4% success rate. And if they changed the success rate to being converted to surgery or not, it jumped up to about almost 70%, the limitations of this, so that it was also a pilot with no real applicability beyond the pilot safety measures they were looking for and the injectate was never mentioned.

There were no studies, non-surgical for carpal tunnel. There is some research for nerve hydro dissection using everything from saline to prolotherapy to PRP to other just corticosteroids. But in terms of the literature looking at amniotic products for nerve hydro dissection, particularly for trauma neuropathy at the wrist, there was no literature. There was a surgical study which I can defer to Dr. Ritchie or discuss later if you'd like. So overall, I would just conclude or comment that definitely a limited research significant in the upper extremity.

There were a few other papers that are relevant in terms of what we're dealing with, I think, and that's a commentary by Dr. Scott Rodeo and AJ Asam, where they really called for some type of standardization for these biologic products. And, basically, the need for minimum reporting standards for studies of biologics in sports medicine.

Similar this issue has been brought up with PRP. And there was a call for standard classification for biologics with PRP nomenclature, that was by Mountaineer et all. And then Dr. LaPrade was

you know, well published as well. He came out with his MIBO Standards or Minimal information for studying biologics and orthopedics.

So, there's a clear consensus across the field that we need some type of nomenclature, and the amniotic and placental derived products are just letting us know that as well. I mean, in terms of, we're basically going by the white papers of what these manufacturers say are within them. We know that they're typically acellular by the time they get reconstituted. But none of these studies are actually doing growth factor analysis, or anything in depth beyond. See if you can to see if there are any cells are just basically giving some type of nomenclature, whether it's autologous or allogeneic, or just the steps that are taken. So that was my takeaway from this is that the literature was limited, and the nomenclature is desperately needed.

Dr. Janet Lawrence

Thank you so much Dr. Beatty for that informative overview.

Are there any questions or comments from the panelists or my comrades for Dr. Beatty?

Hearing none, we will go back to you, Dr. Ritchie.

Dr. William Ritchie

Thank you. And I really agree with Dr. Beatty about about what he was just saying. Dr. Rodeo et al, it really pointed out how there needs to be more data and more study and more standardization.

And so, of the studies, when I went through them, you know, certainly, the, the, they lacked power. But, in particular, you know, the study with the 40 cases, again, it sounds like a lot case, but it lacks power because half, or articular, and half where were tendon. It was a variety of tendons. You know, they show good results, but there's no control and way too much heterogeneity and where they’re injecting it [inaudible]. The trigger finger study, that one, it has a lot of numbers. But the problem is, the numbers really aren't favorable, [inaudible].

What I took away from it was the corticosteroids worked, basically, just as well. Or [inaudible] plus, it's the standard of care for an initial treatment and when that fails the surgical procedure, is very small, very minimal, very safe, that's done in the office now. And so, I think that may be a technology in search of an indication.

And, you know, I'm not sure there would ever be indication for trigger fingers, when it comes to municipal or to rotator cuff pathology and I have used it to augment rotator cuff repairs, the study that was done, I again, echo that. That it was intra-articular injections, but to be honest, many, probably, most rotator cuff injuries, particularly partial thickness tears, are on the bursal side. And so, they really weren't injecting the amniotic membrane or amniotic the more size, amniotic cells membrane, whatever, where the pathology is.

They, they don't really have, a control group is not prospective randomized. Short follow up, there were many problems with that. Again, it was a case series, not really powered for anything beyond safety and, as we've discussed earlier, I'm not sure there's still enough power there or longevity to discuss safety.

So, from a surgical standpoint, again, there were not studies looking at augmentation of surgery using the amniotic membrane, [inaudible], et cetera, to say [inaudible] a search group here and the studies, just are not out there yet. And so, again, I'm not sure there's data here to support using this, except in studies to gather more data, to establish whether it's safe and efficacious.

Dr. Janet Lawrence

Thank you, Dr. Ritchie.

So from your reading of this literature, and in your searches, independent of the articles that we gave you to review, you've not found any evidence out there to support the use of these products intra-operatively for rotator cuff surgery, is that?

Dr. William Ritchie

The only, the only data that that I've found that I've been exposed to, to be honest, white papers from the suppliers. There, I have not seen, but I did not make it a very extensive review, but over the course of the years, I have not found articles from peer reviewed journals with anything but anecdotal reports on their usage in surgery.

Dr. Janet Lawrence

Thank you very much, Dr. Whiteside. Are there any other questions from the panel, for Dr. Whiteside regarding this topic?

Dr. Ann Marie Sun

Yeah, this is Anne Marie Sun from Noridian. So, I think one of the things, as far as we were doing, several different passes at an extensive literature search bringing out and pointing out plantar fasciitis, osteoarthritis, some rotator cuffs, and Achilles, tendinopothy type articles out there. We were very hard pressed to find other specific articles to even other conditions not just mentioned. Understanding like, for instance, the Gellhorn article number 12, there were a hodgepodge of 40, 40 patients with all sorts of different ailments would that be fair to say that out there, and this may be for anybody on the panel here, trying to find literature to even, that's not such, such as a white paper that doesn't support, I mean trying to find that literature to support other types of ailments or conditions has been difficult, and I would assume that that would be the same for everybody across the board?

Dr. Padma Gulur

Yes, we would agree.

Dr. Ann Marie Sun

Thank you.

Dr. James Gajewski

One other thing that should probably be mentioned is negative studies are rarely make it into the literature, the other issues, to make sure each and every one of these studies, had IRB approval to do. And they should be stating that in every study because the IRB, would also mandate all reports of toxicities and could institute a chart audit. If they're not IRB approved, then the toxicity value of any of those articles is completely specious.

Dr. Ann Marie Sun

Thanks, Dr. Gajewski, this is Ann Marie Sun again, I actually, the aha moment that I just had was your statement, which is completely true, that there is a possibility that negative studies wouldn't even be published in the first place, right. So, I think that's a very interesting point. Thank you.

Dr. Janet Lawrence

I agree Dr. Gajewski. Very good point that any evidence out there to show that these products are either not efficacious or not safe, would likely not see the light of day. Are there any other comments on this topic from any of the other panelists?

Dr. Barton Wise

Just, this is, this is Bart Wise, just following up on the question of publication bias. I completely and absolutely agree. I will point out though, that one of the articles and I don't remember which one actually did have a funnel plot, that is a way to look for publication bias.

And I just kinda glazed over it pretty quickly. But it actually looked like there, it looked from that, like there wasn't a lot of publication bias in that particular little subset. But I completely agree that I would highly suspect that overall, in this area, there is publication bias, in other words, negative studies not being published. And that does call into question how to interpret all this.

Dr. James Gajewski

The reality as a 30 plus year academic medicine, you only get credit for promotion and tenures for papers that help move the standard of care. That is one of our problems also right now, since all of us in academics are clinically overburdened. We prioritize our publication, our efforts on publications that come at 10 o'clock at night, on things we think will actually help get us through promotions and tenure committee.

Dr. Barton Wise

Totally agree. I do not disagree at all.

Dr. Janet Lawrence

Thank you for your, insite and honesty Dr. Gajewski. These are all points well taken. If there are no other comments then we are ready for the poll for condition three. Linda, it's all yours.

Linda Meyer

Thank you, Janet.

Again, we ask the CAC panel members to access the survey condition three questions. Condition three questions should be available.

Again, the first two questions are related to safety and the topic this time is Rotator Cuff Patellar, Lateral Epicondylitis, Carpel Tunnel, and Trigger Finger.

Second, two questions are for efficacy.

And the last two again are for post-operative outcomes.

Give everyone a moment.

Looks like some who were having problems appear to be able to answer these questions, that’s good to see.

Okay, looks like we're almost there.

Looks like, we're just waiting for a couple more results.

Jocelyn, why don't we leave those questions open for a moment and we'll let everybody complete the survey, but we'll have Dr. Lawrence move on with our final condition.

Dr. Janet Lawrence

All right. So, thanks to Dr. Gulur for waiting so patiently and for everyone to stick it out. We're changing gears somewhat and Dr. Gulur is going to give us a presentation on back pain and cervical facet joint pathology.

Dr. Gulur?

Dr. Padma Gulur

Thank you very much for inviting me and for this opportunity to speak on this condition.

As you just pointed out, I've had the pleasure of hearing some excellent discussion on other conditions, many of which actually, which have more evidence, if we can summarize it to be that, compared to the conditions I will be presenting on today, which are back pain and cervical facet joint based therapy. I'll start with just some general observations, which I think are well in keeping with what the other speakers have pointed out. At this point. In the studies that I've reviewed, you know, regarding these conditions, key point to note, are the products itself, extremely variable. They seem investigational at best, unclear of any FDA regulatory process that they have undergone.

They are very heterogeneous in terms of active content. It's unclear if the products are stating that they're active materials, growth factors or stem cells, per se. And as another speaker has very well pointed out, no real growth factor analysis. Mostly these are acellular, but this is all by inference. We truly don't have appropriate labeling or information on any of this. There's no real dosing guidance which speaks to the potency of these products, and how, you know, what decision support is provided on appropriate use. The concerns from a safety standpoint, graft versus host, that has been brought up quite a few times.

And then storage of these, storage of biologic is of significant concern, given the potential to introduce infections, et cetera, as well. And so that is also something that you are hard pressed to find enough information on.

As far as the studies of the whole, before I get into the four studies that I reviewed today, I just wanted to take an overall perspective on this, and, you know, I would also agree with the recognition that's required for publication bias.

And this especially when you consider that the product itself is something that, you know, acquiring this product is not a standard process. Many times, it is driven by industry. These studies themselves are hydrogenous just as the other speakers have brought up, variable populations within the same study and very small numbers, which makes it very difficult to adequately power any of these studies. Some of them were randomized, but not really controlled or blinded and mostly they were case series.

They lack a true comparison to placebo or standard care, which would be important, especially conditions such as low back pain and cervical facet for the existing literature itself, shows significant variability and efficacy of many treatment measures. And the outcomes used were variable within these studies, as well.

And, again, just to summarize, not adequately powered, to truly detect any safety signals, [inaudible] every one of them had no adverse event. Which may speak to the fact that were these, you know, IRB approved studies that went through a stringent study design and collection of adverse events, et cetera. And, again, not adequately powered to truly detect efficacy. So, in summary, investigational at this stage, I would agree that there's some promise for biologic for the whole.

However, the presence of adequate data to come to a conclusion on use for standard care seems to be lacking. With that going into the individual studies, the first study that was part of our literature review was Cryopreserved amniotic membrane, and umbilical cord particulate for managing pain caused by facet joint syndrome. Which was a case series. Here, the condition being treated of course was facet joints in the lumbar region, which were injected with the volume of one ml.

Depending on which region, cervical versus, you know, lumbar that were being injected. Which again is of concern, because, again, it's very hard, given that, again, this was small, number nine patients. Interestingly, they state, that they've treated 30 patients, but only nine patients met their criteria for follow-up, which makes the, it makes it difficult to come to any conclusion based on the results presented. As there is an intention bias here. The product, itself, 50 milligrams of particulate and you see, it was a single center case series. Again, as we said, and of the nine patients, seven were males and two females.

The duration of follow-up was about six months. Instruments that they used, it was essentially descriptive statistics on data collected on an excel sheet as they described it, and the outcomes were six-month post treatment. They report that average pain has decreased from severe pain greater than 8 to .4 and they found that statistically significant, again, difficult to do that with nine patients but that's their conclusion. All patients, the remarkable part of this has ceased use in prescription pain, medication including opioids and no adverse events, repeat procedures are complications were reported.

I'm assuming that this is their statement with nine patients that they did choose to include in up to 30 treated in the report. Such results, I think, with the review of the literature, literature and also for any of us who have done these studies are, are fantastic if they can occur but hard to reproduce. In another study, forget general care.

The second study that we reviewed, I reviewed was Amniotic Fluid Cell Therapy to Relieve Disk-Related, Low Back Pain and Its Efficacy Comparison with Long Acting Steroid Injection and this was, Bhattacharya, again, and a chapter, I believe. Here, we compared, they compared steroids versus fresh amniotic fluid at the site and it was injected at the site of maximum tenderness. And the product itself and as was stated was, 10 ml of freshly collected amniotic fluid from mothers undergoing hysterotomy and ligation, can lead you to wonder what happened to the

fluid. When they say fresh do they mean they was injected within what period, et cetera. So that gives you pause.

It was randomized, but it's unclear if it was truly blinded. They did, they do. A follow-up period was 24 months and one of the longer ones. They used [inaudible] score. The walking distance in meters, the health assessment questionnaire and the Oswestry. So, they did use some well-respected validated instruments.

And their patient population was about 42 patients who participated, and they were randomized into two equal, equal groups. Their outcomes were sustained relief compared to steroids. They did show that steroids showed some relief as well. But their conclusion was that the with the amniotic fluid, it was more sustained. However, they were also surprised to see recurrence toward the end even with the amniotic fluid patient.

Dr. James Gajewski

Just out of curiosity with that study with that being relatively fresh, fresh fluid, how on earth do they do sterility testing, as well as test the donor for HIV, hepatitis B, all those things that you are supposed to be doing when you're doing that sort of fluid injections.

Dr. Padma Gulur

Again, I couldn't agree with you more on the story. You know, the whole processing of the fluid the testing was, obviously, and that was not information shared in any great detail, in the material that was available to review and left more questions than answers.

Dr. James Gajewski

That's an indictment into the peer review process of that journal, as well.

Dr. Padma Gulur

I don't believe, if I'm not wrong, this wasn't there. This was not one of your standard journal.

Point well, well taken.

Dr. Eileen Moynihan

This is Eileen Moynihan. I just wanted to say, for the record that last comment, was Dr. Gajewski, Thank you. Sorry.

Dr. Padma Gulur

Not at all. Is it okay to continue?

Dr. Eileen Moynihan

Absolutely.

Dr. Padma Gulur

Thank you. Moving on to the next paper, Amniotic Umbilical Cord Particulate for Discogenic Pain. This was Derek Buck. And this again used AMUC. It was injected intradiskally, and varied dose 50 to 100 milligrams of particulate for cervical, lumbar, and lumbar sacral disc. So again, varied groups here that you can see, and the range of dose was 50, any choice of 50 to a 100. Some had single disks injected others had multiple. They had 11 patients and they said they injected 20 discs.

And this, the note that the particulate used in the study has been commercially available since 2013, in the United States, as a 361 human cell and tissue-based product. The particulate is derived from donated human placental tissue following healthy live caesarian delivery, full term births, and then, stored at low temperatures. I'm unclear, again, I do not have adequate information on what they mean by low temperatures.

The follow-up period was six months in this and the instrument used was percentage of pain relief, which is again, a unique way to look at outcomes. The outcomes of reported based on this was pain relief of 40%, 50%, and 75% at one month, three months, and six months per se, again.

This study itself from both a methodology, product, and, you know, power, stander, standards that are used, as well as instruments for measuring outcomes left a lot to be desired or, you know, definitely would not lead to robust conclusions that people could draw.

The next paper was Effectiveness of Epidural Amniotic Fluid Injection for Low Back Pain. This was published in The Spine Journal in September of 2020, Buttermann, and here what they did was they had multiple conditions. And so, they had 20 patients in each group. And the groups were patients based on their diagnosis, HNP, degenerative disk disease and spinal stenosis. And each of these patients would then receive 2mls of amniotic fluid in the epidural space at a symptomatic level using imaging transforaminal.

The follow-up period for this study was two weeks, six weeks, three months, six months, and one year, and the instruments that they use, where a pain scale for back and leg pain, pain diagrams, the stress disability index, and patient report to the PROMIS measures physical. Their outcome, their conclusion and outcomes was that amniotic fluid, epidural injections are the most effective for patients with lumbar HNP and moderately effective for those that stenosis and inconsistent results were found in those with degenerative disk disease.

Now, interestingly, you know, it's important to note that this methodology, again, not having a control, not come from a comparison group. You know, there is data out there and to supply.

So that steroid paper we just discussed as well, where the injection of just lidocaine into the space is published in the New England Journal of Medicine in an epidural injection can result in significant relief for these patients. Also, of note, for this particular paper was that the HNP group was on the younger side, 30 years plus minus and that their symptoms, the inclusion criteria required that they have pain for at least three months. But, again, that is a population in a time period that has been shown to have more resolution than others, as well. So, that might be, for it noting, as well as we look at this particular paper.

I did have paper 12 included in my list, the micronized dehydrated use of amniotic allograft, for treatment of tendinopathy, but that was all discussed in under Condition two, and so I won't include that in the summary here.

With that, again, I will summarize with what I started with, which is, that I do believe that these studies are inadequately powered. And for us to come to any real conclusion on the safety signals or efficacy.

And, as one of our, speakers has just pointed out, again, the actual products being used, and, you know, from both the safety and efficacy, and, honestly, content perspective, seem to leave a lot to be desired in terms of further investigation and standardization.

The involvement of a more stringent and standardized process is significantly wanting, before we can truly assess the safety and efficacy of these products in treatment, for low back pain, and cervical facet joint disease. So, with that, I will end, and open to any discussion.

Dr. Janet Lawrence

Thank you so much for that Dr. Gulur and again, addressing the back pain and facet injections, which is also an area where we're seeing use. I just want to make one overall comment and perhaps get comments from the panel.

And I think there is a general consensus that the evidence is sparse. And the evidence is sparse in all populations. As you know, we are particularly interested in our population, the Medicare population, most patients over the age of 65 or below 65 with significant usually disability, and I'm not, I would just like some of the panel, again, to comment on the safety, because this particular vulnerable population is more subject to comorbidities and, possibly more sensitive to complications. Should there be some so if someone could just comment on that because I think I saw, throughout all of the papers, they mentioned, I think I got the age of one 81 year old person as the oldest, and in general, I would get, I read about median population ages of say mid 50’s give or take with the standard deviation of 10 or 12, or so. So, if someone, could just to make a brief comment on that, I would appreciate it.

Dr. James Gajewski

Dr. Lawrence, this is Jim Gajewski again. I will make a little bit of a comment for the bone marrow transplant field. We had over the course of about six years, extensive discussions with CMS over there, where CMS was silence on coverage such as allogeneic stem cell transplants from mild dysplasia. They would wait till they progressed to acute leukemia where we really couldn't treat them. But, part of our discussions at that time with CMS is, you know there were people disabled with MDS who were below age 65 to qualify for Medicare for Disability.

We were told we could not look at those separately. That we had, we did have some registry data on the over 65, but when you had a very expensive procedure where coverage was not, where payment was not assured, we didn't, we had several, we had outcomes in the 2 to 3 hundreds. CMS came back to us and demanded that, we do a coverage for evidence development that with five-year follow-up, and so we are still in the process of doing that. The difficulty is those type of coverage for evidence development. With CMS, they don't fund the data management, the data collection. It becomes an unfunded mandate. And you have to hope you'll have an operational registry that has other source of funding so that it can withstand this and this constant reporting to CMS. I don't see how these products could be treated any differently than we were treated.

Dr. Janet Lawrence

Thank you Dr. Gajewski. Any other comments regarding their use in our population?

Dr. Padma Gulur

This is Dr. Gulur. I would, I would agree that there is not adequate for the conditions I reviewed particularly back pain, and cervical facet joint. Not adequate study in the elderly and the older population, which would be important and from a safety perspective, you know, a product that we don't know how it's being stored, how it's being processed, how it's being, you know, where it's being injected et cetera. Which is, where the treatment for back pain, and cervical facet joint will be done is a, particularly, a wonderful site, the fungal meningitis, you know, issues that we we saw with even the steroids that weren't not appropriately stored et cetera and the honestly devastating consequences of infection in the neuraxis should warrant more stringent understanding and process as far as storage and use of these these products.

Dr. Janet Lawrence

Thank you. Any other comments from any of the panelists about any of the topics today? Any last-minute thoughts or anything anyone would like to add at this time?

Dr. Nick Beatty

This is a Dr. Beatty I just wanted to mention the back presentation was excellent. I just wanted to confirm that that first paper was a chapter, so that was not a peer reviewed document.

And the third paper, I believe, was an abstract and not a full publication as well, but I think that was well communicated.

But to your question, I don't want to bring up a big can of worms, but if you had a 65 year old new Medicare patient who had a degenerative meniscal tear, you know, we always think and what we hear today is about do no harm and safety. You could argue, or one might argue that an injection ultrasound guided with growth factors plus and by growth factors I mean in acellular, reconstituted, embryonic injection that we're talking about. Plus, physical therapy and weight loss and not smoking would probably at 10 years be safer perhaps than a partial mastectomy, which between 3 to 3.4 and about 8.8 years is shown to develop osteoarthritis.

So, I guess I'm just saying that this field is probably not alone in the evidence, department in terms of evidence. I think there's an editorial on the front of the Arthroscopy journals saying to the whole entire orthopedic community that, we need more evidence. We need better evidence for what we do. And I think what we're saying today is that there is a lack of evidence that we want more of it, but not necessarily that the lack of evidence directly implies that none of these treatments work, if that makes sense.

Dr. Janet Lawrence

It makes a lot of sense. It goes back to it may all be promising, but we need more evidence to confirm that before standardizing of this treatment. Any other comments?

Dr. James Gajewski

This is Jim Gajewski. I will partly echo what the prior speaker said. There is a distinction between internal medicine and pediatric journals and evidence and standards are what studies we do versus our surgical colleagues. And part of that is the nuances of surgery, surgery itself.

It's hard to measure, hard to study, and hard to get good randomized controlled trials, the type to which we are held the standards of in cancer therapy. I don't have a good solution for that. That also became a frequent discussion at CPT and RUC that we in internal medicine were held to a higher standard because our literature demands it.

Dr. Janet Lawrence

Well said. If there are no further comments, then we will proceed to our fourth and final poll.

Linda?

Linda Meyer

Thanks, Janet.

And the final polling questions, again, we will be answering the four questions, this time, specific to back pain and cervical facet joints.

The first two questions regarding safety, the next two, for efficacy, and the final two for post-operative outcome.

We'll give our panel members a few moments, to vote, and then we will conclude our meeting for the day.

Dr. Lawrence are you there?

Dr. Janet Lawrence

Yes I am, are we ready?

Linda Meyer

Yeah go ahead. Sorry maybe I was talking on mute a second ago.

Dr. Janet Lawrence

Okay, then to everyone, again, we want to thank our outstanding panel for their detail, and very comprehensive discussion regarding the evidence of this topic.

It's obvious that we pick and assemble the right group of people, So the, and it's obvious, as well, how much time and attention to detail you took, and for that, we are appreciative.

The MAC CMDs will take the information from today's meeting and continue discussions on this topic. Please monitor the MAC websites and listserv's where the publishing of a proposed LCD for public comment will be communicated.

We thank you for all for your time today.

So, everyone have a wonderful day and stay safe.