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## J15 Contractor Advisory Committee (CAC) Meeting Regarding Electroretinography

<b>Meeting Date and Time:</b>	November 18, 2020 4:00 p.m. EST
<b>Facilitator:</b>	Dr. Meredith Loveless, CMD
<b>Location:</b>	Teleconference
<b>Attendees:</b>	Not to disclose

**Dr. Loveless:** Hello. Welcome to CGS's Contract Advisory Committee Meeting on electroretinography.

This is Meredith Loveless, Chief Medical Officer in the area of policy and I thank you for being on with us today and welcome our panel of experts to discuss electroretinography. This will be an evidence review on this topic.

It will be recorded and transcribed and the information we obtain today from our expert panel will help us in guiding future policymaking as well.

And, I want to introduce our panel. We have Dr. Favede, Dr. Kumar, Dr. Gaddie, Dr. Ohr, and Dr. Maldonado.

Dr. Favede and Dr Gaddie represent optometry and Dr. Kumar, Dr. Maldonado and Dr. Ohr represent ophthalmology. We have no significant conflicts of interest from our panelists.

The format of this meeting. We will go over the voting questions. I will read those out loud before each question.

And then our panelists will share their input on these questions with a focus on the clinical literature and evidence regarding this topic.

We have about 15 minutes or so for each question and then we'll have some time for any additional comments or discussion at the end.

We will vote on the question at the end, so that way if there's any additional discussion that can be considered.

So, thank you, and welcome to the panel.

The voting is on a scale of one to five. One means you have low confidence in the evidence to support the question, five being high confidence and 2.5 being intermediate confidence. So, we'll start with our first question.

What is your level of confidence there is robust clinical evidence that supports the use of patterned electroretinography also known as PER in the diagnosis and management of glaucoma?

And each panelist, I can turn this over to you to answer, and there's no particular order, so we'll just go ahead and get started.

Dr. Ohr: I guess anyone else wants to jump in, and I'll dive on that one. So, I think that my numerical answer to that would be a, 4. There's definitely robust evidence that used in conjunction with other testing that PER is a good additional tool to help in diagnosis and management of glaucoma.



Dr. Favede, I'll jump in, I'd say a 4.5. I also agree that use of conjunction with some other testing. I think it gives us another objective tool to measure the effects of glaucoma, that's my opinion.

**Dr. Gaddie:** I'll add if there is a 4.5, I would do that as well. I think that that is the value and that's what, of course, the literature showed that you provided. That there is value in equivocal cases where maybe the visual field and the OCT or not congruent or definitive in many times that the pattern ERG is. I would put it in that in that bucket and I think there are other papers that would discuss the value of it without as a stand-alone, but certainly, I use it combined.

**Dr. Kumar:** I would agree completely with Dr. Gaddi's comments and the previous commenters. I think, especially clinically speaking, this device, especially when it's bound to be normal and you have two other tests like the OCT and visual fields. I do think that it provides value in not over-treating the patients and being able to prevent misuse of medication and laser therapy when not really necessary. So, I would say I would give it a score of 4.5.

**Dr. Maldonado:** I agree with the previous comments, but I would like to maybe emphasize that the question is talking about patterned ERG without the mention of any specific system. So, there is evidence that the of the validity or the usefulness of the test that we have to recognize that the different ways to do patterned ERG. And one is special attention has to be placed on the type of electrodes that you use. It hasn't been shown that the signal coming from the patterned ERG is in the room of five Microvolts, so it is a very, very, very small signal. Because of that, the International Society for Clinical Electrophysiology of Vision has recommended and has placed standards only on patterned ERG done with corneal electrodes in different forms of the skin electrodes. But it has discouraged the use of the skin electrodes. So, the question only talks about the patterned ERG as a test, but it doesn't address the different forms of obtaining to test, so I just wanted to bring that to the attention of the discussion of the panelists. So, as a test, I agree that this is another tool to provide some sense of the diagnoses that the question is not addressing how to obtain the pattern ERG. Thank you.

**Dr. Loveless:** To expand on this, I'd like to seek some additional input. In terms of patterned ERG, in terms of management or diagnosis, and management of glaucoma, all of you mentioned this in combination with other tests. Does this test have any value as a free-standing test or is it necessary to be combined with the other test-, based on the evidence?

**Dr. Gaddie:** Yeah, I don't know whether we could. We could really put it as a standalone test at this point. Obviously, ideally, I would prefer another objective test. Like I said earlier, other than the visual field. So, it'd be great if we had one test that we were confident will give us the information that we needed. Especially since Glaucoma is such a nebulous disease that we're really not sure. But I will take, at this point, I wouldn't feel comfortable from everything I've read, usually, as a standalone test, without an OCT or visual field, alongside it, especially since visual field seems to be gold standard, as far as looking at vision loss. That's where I stand.

**Panelist:** I would add in that much like we wouldn't just use a visual field today because we have an OCT, so visual field as a measure of functional vision, and the OCT is of structural vision. Well, this is the electrical function in the retinal ganglion cells. So just like I wouldn't run an OCT without a field being done. I probably wouldn't do this without other test, if that, if that helps, put it in perspective.

**Dr. Loveless:** Yes, Thank you! And how does this test alter or change your management of glaucoma?

**Dr. Kumar:** I think I mentioned previously, where I find it most helpful in changing my management is for a patient, for example, who cannot do a very reliable visual field and there are instances where OCT may not be very reliable as well. Especially when the patient has high myopia or large area atrophy around the optic nerve. Those type of things can make the OCT less reliable. We're trying to, you know, to basically put the full picture together.

And if we have borderline eye pressure, optic nerves that are suspicious for glaucoma, then in this case where I may have started the patient on therapy previously now with basically a tiebreaker test. So, if we do the ERG and the test is normal, then I feel a lot more confident saying, why don't we just go ahead and observe at this point instead of starting therapy? Because once you start the therapy, in glaucoma, very much like blood pressure, they're usually on therapy for the rest of their lives are having no therapy like a laser procedure, which comes with the additional risks as well. So that's one instance.

**Dr. Maldonado:** I agree with the previous comments. And I think that it's very useful as an additional tool to diagnose glaucoma. As for follow up and for management it can be also a useful tool. Here we go again to the point that I was making. You do pattern ERG with the skin electrodes. The signal is so low that I think that it's going to be very difficult to know if this is worsening over time, even have signal in the room of three micro volts. I mean, it's going to be

very difficult to find worsening. As opposed if pair patterned ERG with a system that is using corneal electrodes, then the signal is tremendously amplified and then you can monitor patients over time again as an additional tool to the other tests that we have for glaucoma.

**Dr. Loveless:** Are you aware of any literature or papers that address the technique or concerns that you're educating us about? In the 21st Century Cures for policy, we need to be able to have literature to back-up everything we're doing. So, I'm going to ask, you know, in any of these areas that we're not sure if you know of any supporting papers or literature, and the same as far as any literature that helps to define the patients that would best benefit from the technology. What is the ideal patient for this particular technology? If anyone has comments to expand on that, that would be wonderful.

**Dr. Maldonado:** Yeah, regarding the best reference, I think that the best reference would be the ISCEV International Society for Clinical Electrophysiology and Vision. ISCEV have websites where they have the standards were electrophysiology. It's very easy to go to the website and you will find the guidelines and standards for every test and you will find standards for the patterned ERG. So, these are standards that are done, designed, or described by experts in the field and have been voted by all the members of the society. So, they're pretty comprehensive, and the documents are free downloads, and you can access them, and they are very detailed. And will explain and they will show you the techniques to do the tests and other considerations.

**Panelist:** I would note that in the United States unless you're in a, you know, a hospital system that does the type of testing that he's discussing, I think most of the commercially available systems to the practitioners out, you know, in the community are skin based test.

**Dr. Maldonado:** That is probably right that my point is essentially going back to the scientific part without trying to criticize any particular system. But the reality is the reality the skin electrodes they provide 25% of the signal over corneal electrodes. So, I agree that you know, most of the systems that use corneal electrodes are in the academic centers. I think that a skin electrode pattern ERG would be good for diagnoses. But I have serious doubt that it can be trusted for follow ups and for evaluating the response to treatment.

Because the signal is very low and, of course, as a clinician, you may not be aware of that because the system amplifies the signal and will show you amplified waveforms that, you know, it's very low signal that they can produce because the signal has to travel to all the tissue to get to the skin electrodes.

**Panelist:** I have references from the studies that talks about the reproducibility of some of those sensors. I'll send it just so you have it for your records and consideration.

**Dr. Loveless:** Excellent. That would be great. On the ISCEV protocols, we do have access to those. In some of the studies, they looked at whether or not the studies were compliant with these protocols. How are recognized as standard and practiced in the community? Or is it mostly varying in academia versus community based whether or not the ISCEV protocols are followed?

**Dr. Maldonado:** So, the ISCEV protocols are now the standards of practice within academic centers or any electrophysiology lab. They are a method to keep things standard between centers, specifically for clinical trials. It's not only that, it's the concept of the signal that you're getting. So, from all the standards that you can get, one little piece is the type of electrode that you, that you can use in the system. So, I think that that's a very important piece and again, I'm not arguing that the skin electrode is not valid.

Mainly, if there is evidence that can be used as another piece of diagnoses, it's only that I'm questioning that it can be used in the follow up and the monitoring of disease as corneal electrodes provide a better signal and is stronger in that way.

**Panelist:** I would agree with that to a certain extent. I don't in my practice use it more for diagnosis for glaucoma suspects, borderline cases, unusual cases of glaucoma, such as blood pressure glaucoma, normal tension glaucoma. From a clinical standpoint, do not use it to monitor the progression so much. Because once I have the diagnosis tonight, I do feel that I'm able to monitor the progression with either OCT or visual field in most cases.

Again, there are patients that you just can't you don't have anything else, you can't get a reliable visual field and the OTC is throwing back a lot of noise. So, you know, when you're left with that, then, sometimes you do have to try to get some type of marker surrogate, marker it, even if the signal is low, it still has some it's still a surrogate marker of something that might be giving you more information. On the patient's status.

**Dr. Loveless:** Thank you. In the American Academy of Ophthalmology-Open Angle Glaucoma Preferred Practice Pattern Guidelines, they don't mention ERG. In 2016 guidelines it states that it's not part of routine comprehensive medical eye evaluation, but acknowledges, it can be used

as an additional option for diagnostic testing. So, with your experience with this test and what the literature supports, who do you see as the patient that would best benefit from this test? I'm hearing that it plays a role in the diagnosis of glaucoma and can play a role in follow up if it is used with proper electrodes and modality, but is there a standard patient that this technology most benefits?

**Dr. Favede:** I would agree with whoever just recently spoke that, I don't think there's a perfect candidate this would apply to, other than the visual fields with unreliable OCT. It would be nice to have another objective tool in your toolbox to help you diagnose those patients. So, I don't know whether there's ever going to be one particular patient.

I would always say this is the one who's going to benefit most from the ERG. I hope that helps.

**Panelist:** I'll give you an example. There was a patient that came in just the other day. I see him all the time in the hospital and he came in for evaluation had strong family history, both parents with glaucoma and optic nerves, that were very suggestive of glaucoma and his eye pressures were borderline visual field and OCT were normal but definitely a lot of anxiety wanting to be treated as early as possible for glaucoma based on family history. That's the type of patient I would bring back in and perform an ERG on and if that were normal again, I feel more confident observing the patient as long as other has other glaucoma risk factors. But it takes those patients that are, you know you need a new diagnosis.

**Dr. Maldonado:** NRG is a newer technology newer in the field, so I think that the Academy updates in the practice recommendations every five years or so.

I think that we're going to find more use on the pattern ERG every time and the glaucoma field is going to sign them better use of pattern ERG in the upcoming years. But probably that's why it's not in the Academy recommendations yet, that's my best guess.

**Panelist:** Yeah, by the time that book is published, it's almost a little bit outdated. Because it's, a couple of years behind our current medical literature.

The other thing is that commercially available pattern ERG was not as widely available, I think, back then.

**Dr. Loveless:** Excellent. Thank you.

Do we have any other discussion on this question? We come back to it at the end if we have more.

Question 2, Do you feel there is robust clinical evidence that supports the role of other forms of electroretinography (ERG) in glaucoma management? And this is a yes or no question. And it's followed by, if yes, what form and what would be the supporting evidence? So basically, is it all pattern ERG, or are there other forms that play a role in glaucoma?

**Panelist:** I'll take a stab at that one again if you want me to do that. So, I think there is robust evidence to support to the role of ERG in glaucoma management. And the particular form that I think shows the most promise is a photopic negative response, PhNR. I have an article I can share with you, if that would helpful. Would you if that would be helpful?

**Dr. Loveless:** Yes, that would be great.

**Panelist:** I agree with that as well. I agree with the PhNR.

**Dr. Maldonado:** Yeah, I also agree with that. There have been papers to show when the negative tool to diagnose ganglion cell layer condition and so it would useful in glaucoma as well.

**Panelist:** I'll agree with that.

**Dr. Maldonado:** I would say that the photopic negative ERG and the pattern ERG are comparable in terms of the frequency as a test.

**Dr. Loveless:** Is this test largely a diagnosis or does it play a role in management?

**Dr. Maldonado:** If I can say something again, I go back to diagnoses. If it with skin electrodes, it can help also in the management and follow up if it's with corneal electrodes.

**Dr. Loveless:** Any other comments on question 2?

For question 3: What's your level of confidence? Is there robust clinical evidence to support the role of PERG and retinal disease diagnosis and/or management?

**Panelist:** I was going to say that for plaquenil screening, the multifocal ERG appears to have some utility as well as diabetes may have some opportunity with a pattern ERG retinopathy.

**Panelist:** I go with Dr. Gaddie as far as plaquenil goes, but the question was, was this specific to photopic negative multifocal ERG in there? I think there are some other ones that we know for sure.

**Dr. Loveless:** I think that the multifocal is pretty well established for the toxicity, so I was wondering more about the role of a PERG or other forms of ERG.

**Panelist:** The pattern ERG is being recognized in the diabetic retinopathy realm.

**Dr. Maldonado:** Also, in some cases of..... retinopathy, those ones is useful to get a pattern ERG to evaluate the ganglion cell layer. So, it could be another tool in that case.

**Panelist:** I think that any condition that has anti-retinal layers of the macula may be maybe some positivity, but I don't know how specific it is. They be sensitive, but not very specific to those retinal conditions.

**Panelist:** And so, going back, you want a number on this, right.

**Dr. Loveless:** I will ask for a voting number on it

**Panelist:** I'm a little bit more than an intermediate confidence level when it comes to the retinal role for this. I think there's still a lot to be determined has been, I think, a lot more evident than the glaucoma side of things. And then with the retina, of course, you know, using our tests per brings valuable information and diagnosis to management.

But in cases of retinal disease, you know, the standard ERG and multifocal ERG was mentioned, are typically prefer preferred and they bring more valuable information compared to PERG. That's that my personal opinion of how this plays a role in retinal disease anyway.

**Dr. Maldonado:** I agree with that. They full field ERG primarily is the main tool for diagnosis of especially the inherited retinal diseases.

Secondly, the multifocal and I would say that the PERG for retinal diseases perhaps as a minor role there.

**Panelist:** I give it a 1, just because it says it's not specific, so that really does aid you for diagnosis and management of retinal lesion.

**Dr. Maldonado:** Yeah, I agree with that.

**Dr. Loveless:** Thank you. In the future, we're hoping to be allowed to use webcam so that we can see when someone's wanting to talk. That's not really been something we've been able to do in Medicare, but given, the need to do everything by teleconference, we are working with our teams to help facilitate that for the future, just so you know.

I'm going to jump back up to the first question, and I know I keep asking about this, but I want to make sure that I'm gaining your expertise.

So, I'm understanding the role in the diagnosis of glaucoma and I'm hearing that there's a role for management with the corneal electrodes.

I'm trying to understand if there's a role in pattern ERG for glaucoma management for the skin electrodes of the commercially available device and if so, an understanding of what that role would be.

And, of course, based on the evidence because that's how we do things.

**Panelist:** Yeah. I'll take a shot at it. The commercially available ones with the skin electrodes is what most of us in clinical practice use and that's how the FDA approves these technologies as well. But what I think the utility is in the management of patients is that, you know, when you start therapy, whether that be medication, laser, or surgical intervention, there, are studies that show that the diminished amplitude of the pattern ERG can't be reversible with treatment or surgery.

So that's how I kind of look at it, if I make a diagnosis and a patient that's borderline and I start them on treatment and they don't have any change in there in the amplitude of their pattern ERG, then I question whether treatment was really indicated. I like to see a nice reversal or improvement not reversal, but improvement. So, I hope that helps.

**Dr. Loveless:** Yes, that's helpful.

**Panelist:** I also think it's important to delineate a lot of these studies, which, you know the clinical studies, especially which tests, were which device was used for those studies. And I also understand that the ISCEV, the standard is from back in 2013, I don't know if they've removed those standards and the sensors that the commercial devices use, I don't know if there's any evidence there. I'm just asking that question to the doctor that brought up in terms of the nice

to have some literature there. So, I think if we're basing on some of the literature that was the bibliography here.

**Dr. Maldonado:** The concept of the electrodes comes from the tremendous experience over the years. Multiple papers on doing full field ERGs.

In reality, these other tests are derivatives of the fulfilled ERG and so the concept tell you, acquires signal is essentially the same, you know, it's a stimulus that changes. And so, I'll be happy to share some references. I don't have them right now. But there are many papers showing how the signal with the skin electrodes is 25% of the signal that is coming from contact electrodes.

Now, let me just mention one more thing. This signal that you get in full field ERG is in the room of 200 to 400 micro volts. And so, what we used to amplify those micro volts, of course, we use an amplifier and we amplify the signal so it can be traced and that's 200 to 400 microvolts in the normal patient.

In the case of the patterned ERG, the amplitudes are in the room of 5 microvolts. So, the signal is a lot lower. And so, you're dealing with a very low signal.

And so that's why it's going to be difficult for anyone to gage responses from such a low signal there and so that is there are many papers showing the difference between the electrodes. So, it's a very well addressed concept in the world of electrophysiology.

Not particular to pattern ERG just the chapter of electrodes and how you connect signals. So just trying to translate the scientific concept not be particular to any system that it's out there.

**Panelist:** And I understand, I think what should be done this and making sure, you know, we send some studies that gave you the evidence of basically this skin electrode clinical studies.

**Panelist:** Yeah, I'll do that as well.

**Dr. Loveless:** Yes, if you could send those articles, and then also if there's any articles or evidence that that addresses how frequently, the tests would be used in management. Is this something that's done, you know, once or twice after their treatment has started? How frequently do they have this test done as part of the management role in glaucoma?

I'm going go ahead and ask everybody, I'm going go ahead and voting, ask each person to give me their numbers just to make sure I've got, got the correct number for each panelist. Going to question one, and I'll just read off your name. And if you can, give me your vote on a scale of, again, 1 to 5, 1 being low quality evidence, five being high quality evidence.

And if you could just commit to the whole number, that would be great, average together. So, we'll end up with a 4.5, if that's where you where you lie.

Let us start with doctor for question one, and this is regarding the role of ERG for diagnosis and/or management of glaucoma, and I'll start with Dr. Favede, I say 4. Dr. Gaddie, 4 Dr. Maldonado- 4, Dr. Ohr-4 Dr Kumar-4.

For question 2 this was on the role of other forms of ERG in glaucoma management and using the same scale. How would you rank the evidence to support the role of other forms of ERG in glaucoma management and the one that you all specifically brought up was the PHNR?

**Dr. Favede:** Other forms of scale I'd probably say it 4 that, also.

Unknown Speaker: The PHNR only, I would say four, but no other methods of this time.

**Dr. Loveless:** OK, that's very helpful. Thank you. We'll just make that the question since that seems to be the consensus. so that there's no confusion.

**Dr. Gaddie:** Yeah, I said 4. Thank you. Oh, sorry. This is where I need my video, Cam.

Dr. Maldonado for PHNR, 4.

Great Ohr? 4.

Dr. Kumar? 4.

And for our third question, this is the confidence in the clinical evidence to support PERG specifically in retinal disease diagnosis and management. Dr. Favede? Let's say 2. Dr. Gaddie? 1. Dr. Maldonado? 1. Dr. Ohr 1 and Dr. Kumar I'll stick with my initial 3.

Alright, and, is there any other?

I'm going to see if any of our other CMDs have any additional questions. I'm not hearing any.

Is there any other that you want, you want to share in terms of this topic? .

I want to thank you very much for your time and sharing your expertise with us and your participation in today's subject matter expert CAC meeting.

And if you could please share with me that literature that we've discussed that can help us to, to best understand the role of the electroretinography and glaucoma and retinal disease that would be much appreciated and helpful.

And if you have additional comments that you think of after the meeting, I welcome you to submit those as well. Thank you very much. We sure do appreciate it.

Thank you.

And thank you for all of our attendees for joining in on today's discussion.

And I hope everyone stays safe and has a great rest of their evening.