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# Electroretinography (for Louisiana Only)

Policy Number: CS370LA.AB  
Effective Date: June 1, 2024 TBD

[Instructions for Use](#)

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## Application

This Medical Policy only applies to the state of Louisiana.

## Coverage Rationale

### Multifocal Electroretinogram (mfERG)

Multifocal electroretinogram (mfERG) is proven and medically necessary for **chloroquine (CQ) and hydroxychloroquine (HCQ) retinopathy screening the following indications:**

- **To assess the health of the retina in patients following long term use of drugs known to cause retinal toxicity (e.g., chloroquine, hydroxychloroquine, vigabatrin, ethambutol)**
- **A need to differentiate retinal disease from optic nerve disease when visual field testing is inconclusive or cannot be performed reliably (e.g., advanced disease)**
- **Hereditary retinal dystrophies (e.g., birdshot chorioretinopathy or retinitis pigmentosa)**
- **Macular dystrophies (e.g., Stargardt disease, Best disease, pattern dystrophy)**

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Multifocal electroretinogram (mfERG) is unproven and not medically necessary for all other indications **(including but not limited to macular degeneration, macular edema, epiretinal membrane, and glaucoma)** due to insufficient evidence of safety and/or efficacy.

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### Pattern Electroretinogram (PERG)/Pattern Electroretinogram Optimized for Glaucoma Screening (PERGLA)

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Pattern electroretinogram (PERG) and pattern electroretinogram optimized for glaucoma screening (PERGLA) are unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

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## Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state, or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

CPT Code	Description
*0509T	Electroretinography (ERG) with interpretation and report, pattern (PERG)
92274	Electroretinography (ERG), with interpretation and report; multifocal (mfERG)

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Codes labeled with an asterisk (\*) are not on the State of Louisiana Medicaid Fee Schedule and therefore may not be covered by the State of Louisiana Medicaid Program.

## Description of Services

The electroretinogram (ERG) is a diagnostic test that measures the electrical activity of the retina in response to a light stimulus. ~~Multifocal electroretinogram (mfERG)~~ assesses many local ERG responses, typically 61 or 103, within the central 30 degrees. ~~Pattern electroretinogram (PERG)~~ is an electrophysiologic test that uses contrast reversing pattern stimuli to assess macular retinal ganglion cell (RGC) activity. When optimized for glaucoma screening (~~PERGLA~~), it is a fully automatic version of the PERG- (AAO 2022).

## Clinical Evidence

Hydroxychloroquine and Chloroquine Retinopathy Screening **Multifocal Electroretinography (mfERG)** In a 2024 prospective study, Li et al. assessed the changes in retinal function in patients with Type 2 diabetes mellitus (DM) without apparent retinopathy (Early Treatment of Diabetic Retinopathy Study [ETDRS] level < 20, diabetic retinopathy absent) via mfERG. Thirty six participants with type 2 DM (72 eyes) were the exposed group and 35 healthy subjects (70 eyes) served as the control. All subjects underwent slit lamp anterior segment examination, indirect ophthalmoscope fundus examination after pupil dilation, non-contact intraocular pressure exam and fundus photography. Participants with fundus abnormalities not related to retinal function (e.g., glaucoma, high myopia, macular disease and venous occlusion) were excluded. There was no statistically significant difference in the distribution of all subjects in terms of age and sex. In an analysis of implicit time (IT) and amplitude density (AD) of N1 and P1 waves from the first to fifth ring, the results showed no significant difference for the AD between the exposed and control groups. There was a significant difference in the IT of P1 waves of the first, third, fourth, and fifth rings in the exposed group which was delayed when compared with the control group. The IT of N1 waves of the fourth and fifth ring in the exposed group was also significantly delayed compared to the control group. In the analysis of implicit time and amplitude density of N1 wave and P1 wave in the nasal and temporal regions, the results showed delay in the temporal region of the exposed group, and no differences were shown in the nasal area. The implicit time analysis of the subjects working curve showed higher numbers in the exposed group, which indicates potential retinopathy. The authors concluded that that mfERG has the sensitivity to indicate early abnormal retinal function of patients with type 2 DM without visible retinopathy. This study is limited by a small number of participants and lack of assessment of the clinical utility of the test. Furthermore, no follow up was reported that would determine long term diagnosis utility.

In 2021, Huang et al. conducted a cross-sectional study to identify abnormalities in the retinal function in patients with type 2 DM without clinically apparent retinopathy by mf-ERG examination. Seventy-six eyes of patients with DM without clinically apparent retinopathy based on several ocular examinations, including slit-lamp, ophthalmoscopy, noncontact intraocular pressure and fundus photography, and sixty-four normal eyes from thirty-two healthy control (HC) participants, were examined using multifocal electroretinogram. The duration of diabetes ranged from 5 to 10 years. All eyes had a visual acuity above 16/20 without apparent microaneurysm or

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exudation in the retina. **Patients with glaucoma, hyper myopia, macular disease, and other fundus diseases were excluded from the study.** The results showed significantly prolonged implicit time of the P1 and N1 waves in participants with DM compared to the HC. Additionally, the function of the temporal retina was more frequently affected than the nasal retina suggesting that before clinically apparent retinopathy is diagnosed, there is a prolonged period of pathological changes. This study is limited by a small number of participants and lack of comparison to other diagnostic methods.

Senger et al. (2020) conducted a systematic review to review the result of studies regarding the clinical applicability of electrophysiological tests for glaucoma. Since 2013, there were nine published studies investigating mfERG for glaucoma. Most of the study protocols were modified from the traditional mfERG. The authors observed that currently, mfERG has not shown good correlation with visual field (VF) and is less effective than PERG for diagnosing glaucoma but might be useful for the detection of initial glaucoma. They also note that PERG may be of interest for examining patients with glaucoma and monitoring progression, as it showed accuracy in confirming localized defects. The authors concluded that clinical electrophysiological testing of the visual system reasonably matched with both the structural and functional analyses for glaucoma, but that no definitive indications of these tests have been established either at early detection or during follow-up of the disease, and that easier protocols and better topographical correspondence with current glaucoma tests are warranted for their routine use. (Studies by Cvenkel 2017, Preiser 2013, and Bannit 2013 previously cited in this policy are included in this systematic review)

Tsang et al. (2015) conducted a systematic review to determine the validity of mfERG as a screening tool for detecting CQ and HCQ retinal toxicity in patients using these medications. Individual patient data (449 eyes of 243 patients) identified in twenty-three studies published from 2000-2014 were analyzed. Multi-focal ERG had the greatest proportion of positive test results, followed by automated visual fields (AVF). The pooled sensitivity and specificity of mfERG were 90% and 52%, respectively. Specificity was variable when optical coherence tomography (OCT), fundus autofluorescence (FAF), and the positivity of 2 of 3 tests was used as the reference standard. When verified against AVF as the reference test, patients with a false-positive mfERG result received higher HCQ cumulative doses (1,068 g) than patients with true-negative (658 g,  $p < 0.01$ ) and false-negative (482 g,  $p < 0.01$ ) results. The authors concluded that mfERG was shown to have a high sensitivity but variable specificity when verified against AVF, OCT, FAF, and a combination of tests. The greater average cumulative dose in the false-positive group compared with the true-negative group when mfERG was verified against AVF suggested that mfERG may have the ability to detect cases of toxicity earlier than other modalities.

**Todorova et al. (2015) conducted a comparative study of 22 patients (43 eyes) diagnosed with typical retinitis pigmentosa (RP) and 13 age matched controls (26 eyes) to determine a relationship between the retinal vessel saturation via retinal vessel oximetry (RO) alterations and the residual retinal function measured with full-field electroretinography (ffERG), electrooculogram (EOG) and multifocal electroretinography (mfERG). The oxygen saturation in the first and second branch retinal arterioles and venules were measured, the difference was calculated, and ffERG amplitudes, EOG parameters and averaged mfERG response amplitudes were evaluated in relation to the RO measurements. The results showed that individuals with RP can be distinguished from controls when retinal vessel saturation, function or both are evaluated. In addition, within the RP group, retinal vessel saturation alterations corresponded to the severity of retinopathy, as measured by means of N1 and N1P1 amplitudes reduction of mfERG. The correlations between the V-SO<sub>2</sub> and the averaged responses of the mfERG reached statistically significant values in zone 1, 2 and 3.**

**In a 2015 review article, Tzekov et al. assessed the published literature on the use of electroretinography (full field ERG, PERG and mfERG) to assess changes in retinal function associated with the progression of birdshot chorioretinopathy (BRCS), a rare form of autoimmune posterior uveitis. The results showed that with regard to mfERG, only two studies have been published to date and they clearly demonstrate its potential as an objective test of central retinal function in BRCS, however more comprehensive studies are needed to compare how the mfERG changes that reflect macular function compare to extramacular changes. The authors concluded that since most of the observable changes in BRCS are located in the periphery, full field ERG is more sensitive to disease progression, and is important for evaluating, however wide field mfERG may provide more sensitivity and specificity either alone or in combination with full field ERG.**

**In a prospective study, Ambrosio et al. (2015) examined the role of mfERG for predicting visual acuity (VA) decline in early AMD with time. A total of 26 patients with early AMD (12 males and 14 females, mean age of 66.9 ± 9.8; range of 46 to 82 years) were included in the study. A complete ophthalmic examination and mfERG (Retiscan, Roland Germany,**

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ISCEV standard protocol) were performed at the study entry (baseline), after 20 and 24 months. The first-order kernel mfERG responses were analyzed by ring analysis. The amplitude density (AD) of the first positive peak (P1, nV/deg<sup>2</sup>), the P1 amplitude ( $\mu$ V) and P1 implicit time (ms) for Rings 1 (central) to 6 (most peripheral) were evaluated. Data were statistically analyzed by analysis of variance and receiver operating characteristic (ROC) curves. **The loss in the mfERG Ring 1 AD from normal control values, recorded at baseline, was correlated with the decrease in ETDRS VA with time ( $p = 0.004$ ); ROC analysis showed that, after 24 months, the average decline in VA was greater (3 letters versus 0.4 letters,  $p = 0.0021$ ) in patients whose Ring 1 P1 AD at baseline was equal to or less than 65.9 nV/deg<sup>2</sup>, compared to those with higher AD values. Both P1 amplitude and AD of Ring 1 had an area under the curve of 0.702 (95% CI: 0.50 to 0.92) with a sensitivity of 64.3% (35.14 to 87.24%) and a specificity of 91.7% (61.52 to 99.79%).** The authors concluded that these results indicate that mfERG P1 amplitude and AD of Ring 1 may be highly specific to predict visual acuity decline in early AMD. This was a nonrandomized study design without a control group, and small patient sample size.

**Yap et al. (2015) conducted a retrospective study to evaluate the clinical value of electrophysiology in identifying the cause of vision problems. Four hundred and ten subjects were included and divided by type of visual dysfunction (unexplained poor visions, visual field defects, or other visual symptoms including monitoring for drug toxicity). Subjects then underwent pattern, full-field and multifocal electroretinography (ERG) and pattern visual evoked potential (VEP) tests. The results showed that in approximately 158 subjects referred for poor vision, electrophysiology findings were suggestive of retinopathy (37%) or post-retinal pathology (34%). Those with poorer vision (worse than 6/24) were more likely to have abnormal recordings. Among the 102 subjects with unexplained visual field defects findings of retinopathy, post-retinal pathology and normal recordings were noted in 31, 24 and 28%, respectively. Most subjects with other visual symptoms had normal findings. The multifocal ERG was most sensitive for detecting retinopathy (96 %) and maculopathy (95%), while pattern VEP was most sensitive for post-retinal pathology (94%). The authors concluded that electrophysiology is effective in differentiating between retinopathy, post-retinal pathology and normality in 91 % of subjects. Pre-testing provisional diagnoses of retinopathy and post-retinal pathology were revised in 30 and 42 %, respectively, after electrophysiology.**

Gonzalez-Garcia et al. (2016) reported 2-years of follow-up data for electrophysiological and clinical tests in dry age-related macular degeneration (AMD) to determine the more sensitive technique between mfERG and OCT. Fundus photography, OCT (macular thickness and number of drusen), Pattern VEP (P100 wave), Pattern ERG (P50 wave) and mfERG (central rings) were carried out in 30 patients that were diagnosed with dry AMD in both eyes. The tests were repeated 1 and 2 years later. No statistically significant changes were observed in visual acuity or in the severity of the disease throughout the study. OCT showed an increase in the number of drusen, as well as in macular thickness. As for the electrophysiological techniques, no significant changes were observed throughout the study in Pattern VEP or Pattern ERG. mfERG showed significant alterations. The authors reported that the statistical analysis showed that mfERG is more efficient in detecting changes throughout the study period. The authors concluded that both OCT and mfERG are useful in the diagnosis and monitoring of patients with dry AMD, however mfERG is the most sensitive technique to study the progression of this disease in short periods of time. Study limitations include small patient population and short follow-up period.

In a prospective study, Kandel et al. (2012) evaluated the effects of ethambutol therapy in visual functions of both eyes in forty-four patients. Parameters evaluated included mfERG with Roland-RET1 scan. Based on the results of the study, the authors concluded that visual acuity, contrast sensitivity, and mfERG are sensitive tests to detect ethambutol toxicity in subclinical stages and hence especially useful tools for monitoring patients under ethambutol therapy for ocular toxicity. These findings require confirmation in a larger study and comparisons to other diagnostic methods.

Browning et al. (2014) conducted a retrospective case series analysis to determine the relative sensitivity and specificity of 10-2 visual fields (10-2 VFs), mfERG, and spectral domain optical coherence tomography (SD-OCT) in the detection HCQ retinopathy. A total of 121 patients taking HCQ ( $n = 119$ ) or chloroquine (CQ) ( $n = 2$ ) with 10-2 VF, mfERG, and SD-OCT test results were reviewed. Rates of test abnormality were determined. Retinopathy was present in 14 patients and absent in 107. Eleven of 14 (78.6%) patients with retinopathy were overdosed, defined as receiving HCQ and CQ doses  $> 6.5$  mg/kg/day and  $> 3.0$  mg/kg/day, respectively. Twelve (85.7%) had cumulative dosing greater than 1,000 g. The sensitivities of 10-2 VF, mfERG, and SD-OCT in detecting retinopathy were 85.7%, 92.9%, and 78.6%, respectively. The

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specificities of 10-2 VF, mfERG, and SD-OCT in detecting retinopathy were 92.5%, 86.9%, and 98.1%, respectively. Positive predictive values of 10-2 VF, mfERG, and SD-OCT in detecting retinopathy were less than 30% for all estimates of HCQ retinopathy prevalence. Negative predictive values were > 99% for all tests. The authors concluded that all three tests are most reliable when negative, allowing confident exclusion of retinopathy in patients taking  $\leq 6.5$  mg/kg/day. Each test is less useful in allowing a confident diagnosis of retinopathy when positive, particularly in patients taking  $\leq 6.5$  mg/kg/day. This study is limited by its retrospective case series design and the small number of HCQ and CQ retinopathy cases for which all three tests were available. Additional studies are needed with larger sample sizes to accurately determine the sensitivity and specificity of these tests.

Dale et al. (2010) compared the ability of the mfERG and frequency domain OCT (fdOCT) to detect retinal abnormalities. A total of 198 eyes (one hundred patients) were included in the study to rule out a retinal etiology of visual impairment. All patients were evaluated with static automated perimetry (SAP), mfERG, and fdOCT. Local mfERG and fdOCT abnormalities were compared to local regions of visual field sensitivity loss measured with SAP and categorized as normal/inconclusive or abnormal. 146 eyes were categorized as normal retina on both fdOCT and mfERG. The retina of fifty-two eyes (36 patients) was categorized as abnormal based upon mfERG and/or fdOCT. Of this group, twenty-five eyes (20 patients) were abnormal on both tests. However, twenty eyes (13 patients) were abnormal on mfERG, while the fdOCT was normal/inconclusive; and 7 eyes (7 patients) had normal or inconclusive mfERG, but abnormal fdOCT. According to the authors, considerable disagreement exists between these two methods for detection of retinal abnormalities. The authors stated that the mfERG tends to miss small local abnormalities that are detectable on the fdOCT. On the other hand, the fdOCT can appear normal in the face of clearly abnormal mfERG and SAP results. The authors indicated that while improved imaging and analysis may show fdOCT abnormalities in some cases, in others early damage may not appear on structural tests.

Lai et al.(2007) conducted a systematic review of the clinical applications of mfERG. It was concluded that analysis of mfERG response amplitudes and implicit times at different retinal locations, localized areas of retinal dysfunction caused by acquired or hereditary diseases can be identified. It is particularly useful for pathology limited to the central retina as a full field electroretinogram is often normal. Furthermore, mfERG enables the monitoring of toxic retinopathy resulting from systemic therapy, as well as monitoring efficacy of surgical and non-surgical treatments objectively.

## Clinical Practice Guidelines

### American Academy of Ophthalmology (AAO)

In a 2022 clinical statement on the guidelines for the clinical assessment of patients with inherited retinal degenerations, AAO states that the full-field electroretinogram is important for diagnosing and staging of diffuse photoreceptor disease to evaluate the retina-wide function of the rods and cones. Multifocal ERG testing can be useful for detecting and monitoring disease progression for those that primarily affect the macula, but its accuracy is uncertain in patients with significantly reduced central acuity and fixation is unstable.

The American Academy of Ophthalmology revised recommendations for chloroquine and hydroxychloroquine retinopathy screening state that mfERG is a useful screening tool and provides objective corroboration for visual fields (Marmor et al., 2016).

### Other Retinopathies-Screening **International Federation of Clinical Neurophysiology (IFCN)**

In the 2010 Recommendations for visual system testing, the IFCN states that mfERG is a powerful tool when used with appropriate technical considerations for diagnosing disturbances of macular function and to assess the degree of central retinal cone involvement in generalized retinal disease. The ability of a patient accurately to maintain good fixation throughout the recording session is a pre-requisite to obtaining clinically meaningful data.

### **PERG/PERGLA**

While the published evidence on PERG and PERGLA suggest that these exams can detect retinal manifestation of eye conditions, comparison with other diagnostic methods, and assessment of the clinical utility of the tests are lacking. Therefore, based on existing evidence, their non-inferiority or superiority to established methods cannot be determined.

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#### A 2020

In 2021, Huang et al. conducted a cross-sectional study to identify abnormalities in the retinal function in patients with type 2 diabetic mellitus (DM) without clinically apparent retinopathy by mf-ERG examination. Seventy-six eyes of patients with DM without clinically apparent retinopathy based on several ocular examinations, including slit lamp, ophthalmoscopy, noncontact intraocular pressure, and fundus photography, and sixty-four normal eyes from thirty-two healthy control (HC) participants, were examined using multifocal electroretinogram. The duration of diabetes ranged from 5 to 10 years. All eyes had a visual acuity above 16/20 without apparent microaneurysm or exudation in the retina. Patients with glaucoma, hypermyopia, macular disease, and other fundus diseases were excluded from the study. The results showed significantly prolonged implicit time of the P1 and N1 waves in participants with DM compared to the HC. Additionally, the function of the temporal retina was more frequently affected than the nasal retina suggesting that before clinically apparent retinography is diagnosed, there is a prolonged period of pathological changes. This study is limited by a small number of participants and lack of comparison to other diagnostic methods.

An ECRI report, Pattern Electoretinography for Detecting Central Retinal Damage from Diabetes, states that the evidence from four case control studies suggest that changes in PERG waveform amplitude and latency may indicate RGC damage in individuals with diabetes. However, no evidence is available to determine whether these findings enable earlier intervention that improves patient outcomes (2020).

Merchant et al. (2017) conducted a cross-sectional analysis of sixty patients using OCT and electroretinography (ERG), including flash ERG and PERG to determine the association of ocular manifestations in beta-thalassemia with patient's age, blood transfusion requirements, average serum ferritin and dose and duration of iron chelation therapy. Routine ophthalmic examination and B scan of the eye was also done. Flash ERG a-waves and b-waves were recorded, however, only a-wave amplitude was evaluated. PERG n35, n95 and p50 waves were recorded and p50 wave amplitude was evaluated. The a-wave on flash and p50 on pattern waves represent retinal photoreceptor epithelium (RPE) photoreceptor response, which is mainly affected in beta-thalassemia. Ocular changes were detected in 38.3% and a significant correlation was noted with increase in age ( $p = 0.045$ ) but not with serum ferritin, transfusion requirements or chelation therapy. Abnormalities were noted in a-wave amplitude on flash ERG in 20% of cases, while reduced p50 amplitude on PERG was noted in 15%. The authors concluded that ERG appears to be a promising tool for screening patients with beta-thalassemia and can serve as a follow-up test for evaluating retinal function. Randomized controlled trials with larger patient populations are needed to further evaluate this technology.

In a prospective study, Kandel et al. (2012) evaluated the effects of othambutol therapy in visual functions of both eyes in forty-four patients. Parameters evaluated included mfERG with Roland RETI scan. Based on the results of the study, the authors concluded that visual acuity, contrast sensitivity, and mfERG are sensitive tests to detect othambutol toxicity in subclinical stages and hence especially useful tools for monitoring patients under othambutol therapy for ocular toxicity. These findings require confirmation in a larger study and comparisons to other diagnostic methods.

Dale et al. (2010) compared the ability of the mfERG and frequency domain-OCT (fdOCT) to detect retinal abnormalities. A total of 198 eyes (one hundred patients) were included in the study to rule out a retinal etiology of visual impairment. All patients were evaluated with static automated perimetry (SAP), mfERG, and fdOCT. Local mfERG and fdOCT abnormalities were compared to local regions of visual field sensitivity loss measured with SAP and categorized as normal/inconclusive or abnormal. 146 eyes were categorized as normal retina on both fdOCT and mfERG. The retina of fifty-two eyes (36 patients) was categorized as abnormal based upon mfERG and/or fdOCT. Of this group, twenty-five eyes (20 patients) were abnormal on both tests. However, twenty eyes (13 patients) were abnormal on mfERG, while the fdOCT was normal/inconclusive; and 7 eyes (7 patients) had normal or inconclusive mfERG, but abnormal fdOCT. According to the authors, considerable disagreement exists between these two methods for detection of retinal abnormalities. The authors stated that the mfERG tends to miss small local abnormalities that are detectable on the fdOCT. On the other hand, the fdOCT can appear normal in the face of clearly abnormal mfERG and SAP results. The authors indicated that while improved imaging and analysis may show fdOCT abnormalities in some cases, in others early damage may not appear on structural tests.

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### **Clinical Practice Guidelines**

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### **Glaucoma**

A 2021 Hayes health technology assessment, updated in 2022~~2024~~, Pattern Electrorretinography for Diagnosis of Glaucoma, concluded that based on an evidence base of seven studies (including 1 prospective cohort, and 6 case-control studies), low quality evidence that the accuracy of PERG is similar to or greater than other available methods for diagnosing glaucoma or ocular hypertension (OHT). There is a lack of evidence of clinical utility for PERG in the management of patients who have or are at risk for glaucoma and for long-term health outcomes.

A 2020 ECRI report, Pattern Electrorretinography for Detecting Central Retinal Damage from Glaucoma, states that evidence from one systematic review and 5 case-control studies (comprising 930 patients) suggests that changes in PERG waveform amplitude and latency may indicate retinal ganglion cell (RGC) damage in individuals with glaucoma. However, the evidence does not demonstrate that early detection of RGC damage would enable early therapeutic intervention, which would improve patient outcomes.

~~Senger et al. (2020) conducted a systematic review to review the result of studies regarding the clinical applicability of electrophysiological tests for glaucoma. Since 2013, there were nine published studies investigating mfERG for glaucoma. Most of the study protocols were modified from the traditional mfERG. The authors observed that currently, mfERG has not shown good correlation with visual field (VF) and is less effective than PERG for diagnosing glaucoma but might be useful for the detection of initial glaucoma. They also note that PERG may be of interest for examining patients with glaucoma and monitoring progression, as it showed accuracy in confirming localized defects. The authors concluded that clinical electrophysiological testing of the visual system reasonably matched with both the structural and functional analyses for glaucoma, but that no definitive indications of these tests have been established either at early detection or during follow-up of the disease, and that easier protocols and better topographical correspondence with current glaucoma tests are warranted for their routine use. (Studies by Cvenkel 2017, Proiser 2013, and Bannit 2013 previously cited in this policy are included in this systematic review)~~

Park et al. (2017- included in ECRI report regarding glaucoma above) conducted a retrospective cohort study of seventy-four patients with glaucoma (44 early stage and 30 advanced stage cases) and 66 control subjects to determine possible relationships between the N95 amplitude of PERG (PERGamp) and macular ganglion cell/inner plexiform layer thickness (GCIPLT). Macular GCIPLT was measured using Cirrus spectral domain-optical coherence tomography. Standard automated perimetry and pattern ERGs were used in all patient examinations. Three types of regression analysis (broken stick, linear regression, and quadratic regression) were used to evaluate possible relationships between PERGamp and GCIPLT. Correlations between visual field parameters and GCIPLT were evaluated according to glaucoma severity. The best fit model for the relationship between PERGamp and GCIPLT was the linear regression model ( $R^2 = 0.22$ ;  $p < p 0.001$ ). The best-fit model for the relationship between visual field parameters and GCIPLT was the broken stick model. During early glaucoma, macular GCIPLT was positively correlated with PERGamp, but not with visual field loss. In advanced glaucoma, macular GCIPLT was positively correlated with both PERGamp and visual field loss. The authors concluded that based on the results of this study, PERGamp is a method to assist clinicians in making an early decision regarding the most suitable treatment plan, especially when GCIPLT is thinning with no change in visual field performance. Study limitations include its retrospective nature, and lack of a standard international reference range for PERG measurements. The clinical utility of this method needs to be confirmed in comparison to other methods.

Jafarzadehpour et al. (2013) evaluated RGC dysfunction in participants with suspicion of glaucoma and patients with early primary open angle glaucoma (POAG) using PERG. Transient PERG was recorded in response to 0.8° and 16° black and white checkerboard stimuli. Amplitude and peak time (latency) of the P50 and N95 components of the PERG response, and the ratio of N95 amplitude in response to 0.8° and 16° checks were measured. Twenty participants with suspicion of glaucoma, 15 early POAG and 16 normal controls were enrolled. N95 peak time (latency) was significantly increased in both early manifest POAG and participants with suspicion of glaucoma as compared to normal controls. In early POAG, N95 amplitude in response to small (0.8°) checks and the small/large check ratio were reduced in comparison to normal

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eyes. However, in participants with suspicion of glaucoma, no significant N95 amplitude reduction was observed. No significant difference was observed among the study groups in terms of P50 amplitude or peak time. According to the authors, PERG may detect RGC dysfunction (increased latency) before cell death (decreased amplitude) occurs. The design and sample size in this study limits the conclusions that can be drawn from it for the usefulness of PERG as a diagnostic tool.

## Clinical Practice Guidelines

### American Academy of Ophthalmology (AAO)

The AAO preferred practice pattern for primary open-angle glaucoma (POAG) does not specifically mention ERG as a diagnostic tool. (Gedde et al., 2021).

A 2016 AAO ophthalmic technology assessment, reviewed for updates in 2016, on the assessment of visual function in glaucoma states that other testing that provides objective measures of visual function, including electroretinography have issues that prevent their adoption for glaucoma. (Prum et al. 2016).

### Macular Degeneration

Genzalez Garcia et al. (2016) reported 2 years of follow up data for electrophysiological and clinical tests in dry age-related macular degeneration (AMD) to determine the more sensitive technique between mfERG and OCT. Fundus photography, OCT (macular thickness and number of drusen), Pattern VEP (P100 wave), Pattern ERG (P50 wave) and mfERG (central rings) were carried out in 30 patients that were diagnosed with dry AMD in both eyes. The tests were repeated 1 and 2 years later. No statistically significant changes were observed in visual acuity or in the severity of the disease throughout the study. OCT showed an increase in the number of drusen, as well as in macular thickness. As for the electrophysiological techniques, no significant changes were observed throughout the study in Pattern VEP or Pattern ERG. mfERG showed significant alterations. The authors reported that the statistical analysis showed that mfERG is more efficient in detecting changes throughout the study period. The authors concluded that both OCT and mfERG are useful in the diagnosis and monitoring of patients with dry AMD, however mfERG is the most sensitive technique to study the progression of this disease in short periods of time. Study limitations include small patient population and short follow up period.

In a prospective study, Ambrosio et al. (2015) examined the role of mfERG for predicting visual acuity (VA) decline in early AMD with time. A total of 26 patients with early AMD (12 males and 14 females, mean age of 66.9 ± 0.8; range of 46 to 82 years) were included in the study. A complete ophthalmic examination and mfERG (Rotiscan, Roland Germany, ISCEV standard protocol) were performed at the study entry (baseline), after 20 and 24 months. The first order kernel mfERG responses were analyzed by ring analysis. The amplitude density (AD) of the first positive peak (P1, nV/deg<sup>2</sup>), the P1 amplitude (µV) and P1 implicit time (ms) for Rings 1 (central) to 6 (most peripheral) were evaluated. Data were statistically analyzed by analysis of variance and receiver operating characteristic (ROC) curves. The loss in the mfERG Ring 1 AD from normal control values, recorded at baseline, was correlated with the decrease in ETDRS VA with time (p = 0.004); ROC analysis showed that, after 24 months, the average decline in VA was greater (3 letters versus 0.4 letters, p = 0.0021) in patients whose Ring 1 P1 AD at baseline was equal to or less than 65.9 nV/deg<sup>2</sup>, compared to those with higher AD values. Both P1 amplitude and AD of Ring 1 had an area under the curve of 0.702 (95% CI: 0.50 to 0.92) with a sensitivity of 64.3% (35.14 to 87.24%) and a specificity of 91.7% (61.52 to 99.79%). The authors concluded that these results indicate that mfERG P1 amplitude and AD of Ring 1 may be highly specific to predict visual acuity decline in early AMD. This was a nonrandomized study design without a control group, and small patient sample size.

### International Society for Clinical Electrophysiology of Vision (ISCEV) Clinical Practice Guidelines

In a 2018 guide to visual electrodiagnostic procedures, updated in 2022, the ISCEV International Society for Clinical Electrophysiology of Vision (ISCEV) states that the pattern ERG and mfERG may be used to assess the severity of macular dysfunction in the presences of fundus abnormality or detection of dysfunction in occult cases of maculopathy or macular dystrophy (Robson, et al. 2018).

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## U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Electroretinography devices receive FDA 501(k) as Class II medical devices. For specific devices, refer to the following website and search using code GWE: <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm>. (Accessed ~~May 10, 2023~~ **June 4, 2024**)

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**Policy History/Revision Information**

Date	Summary of Changes
<b>TBD</b>	<p><b>Coverage Rationale</b>  <b>Multifocal Electroretinogram (mfERG)</b></p> <ul style="list-style-type: none"> <li>• <b>Added language to indicate:</b> <ul style="list-style-type: none"> <li>○ <b>Multifocal electroretinogram (mfERG) is proven and medically necessary for the following indications:</b> <ul style="list-style-type: none"> <li>▪ <b>A need to differentiate retinal disease from optic nerve disease when visual field testing is inconclusive or cannot be performed reliably (e.g., advanced disease)</b></li> <li>▪ <b>Hereditary retinal dystrophies (e.g., birdshot chorioretinopathy or retinitis pigmentosa)</b></li> <li>▪ <b>Macular dystrophies (e.g., Stargardt disease, Best disease, pattern dystrophy)</b></li> </ul> </li> <li>○ <b>Unproven and not medically necessary indications include but are not limited to macular degeneration, macular edema, epiretinal membrane, and glaucoma</b></li> </ul> </li> <li>• <b>Replaced language indicating “multifocal electroretinogram (mfERG) is proven and medically necessary for chloroquine (CQ) and hydroxychloroquine (HCQ) retinopathy screening” with “multifocal electroretinogram (mfERG) is proven and medically necessary to assess the health of the retina in patients following long term use of drugs known to cause retinal toxicity (e.g., chloroquine, hydroxychloroquine, vigabatrin, ethambutol)”</b></li> </ul> <p><b>Supporting Information</b></p> <ul style="list-style-type: none"> <li>• <b>Updated Clinical Evidence and References sections to reflect the most current information</b></li> <li>• <b>Archived previous policy version CS370L.A.A</b></li> </ul>

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