Electroretinography

Guideline Number: MMG205.A
Effective Date: January 1, 2024

Instructions for Use

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Related Medical Management Guidelines
None

Related Benefit Interpretation Policies
None

Coverage Rationale

Multifocal Electroretinogram (mfERG)

Multifocal electroretinogram (mfERG) is proven and medically necessary for chloroquine (CQ) and hydroxychloroquine (HCQ) retinopathy screening.

Multifocal electroretinogram (mfERG) is unproven and not medically necessary for all other indications due to insufficient evidence of safety and/or efficacy.

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

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

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 guideline 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 the member specific benefit plan document 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)

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

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.

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 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 ≤ 6.5 mg/kg/day. Each test is less useful in allowing a confident diagnosis of retinopathy when positive, particularly in patients taking ≤ 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.

Clinical Practice Guidelines

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

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 Electroretinography 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 ethambutol 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 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.

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.

Clinical Practice Guidelines

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.

Glaucoma

A 2021 Hayes health technology assessment, updated in 2022, Pattern Electroretinography 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 Electroretinography 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, Preiser 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 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

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 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

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, 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, 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/deg2), 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/deg2, 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.

Clinical Practice Guidelines

In a 2018 guide to visual electrodiagnostic procedures, updated in 2022, the 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)

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.

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Guideline History/Revision Information

Date	Summary of Changes
01/01/2024	**Title Change/Template Update** • Relocated and reformatted content previously included in the Medical Policy titled *Omnibus Codes* **Supporting Information** • Added *Description of Services* and *FDA* sections • Updated *Clinical Evidence* and *References* sections to reflect the most current information • Archived previous policy version MMG093.QQ

Instructions for Use

This Medical Management Guideline provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this guideline, please check the member specific benefit plan document and any applicable federal or state

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