

Policy	MM-051
Effective Date	09/01/2024
Reviewed/Revised Date	04/27/2026
Next Review Date	04/27/2027
Origination Date	07/09/2024
Originated Department	Clinical Operations

Electroretinography

Audience
Providers, Members, Brokers, MHC

Purpose
<p>Medical policies provide general support for applying Mountain Health Co-Op member policy document coverage decisions and must reference the member-specific benefit plan document. The terms of the member-specific Policy document may differ from the standard benefit plan on which this medical policy is based. If there is a conflict between a member-specific policy document and the Mountain Health Co-Op medical policy, the member-specific policy document supersedes this medical policy. Any person(s) applying this medical policy must identify member eligibility, the member-specific policy document, and related policies or guidelines before applying this medical policy, including the existence of any state or federal guidance. Mountain Health Co-Op medical policies are designed for informational purposes only and are not an authorization, explanation of benefits, or contract. Receipt of benefits is subject to satisfaction of all terms and conditions of the member-specific policy document coverage. Mountain Health Co-Op reserves the sole discretionary right to modify all policies and guidelines at any time.</p>

Definition
<p>Electroretinography (ERG) is a diagnostic test used to measure electrical activity generated by neural and non-neuronal cells in the retina in response to a light stimulus. ERGs are obtained by using electrodes embedded in a corneal contact lens, or a thin wire inside the lower eyelid, which measures retinal electrical activity at the corneal surface. A standard ERG measures five retinal responses by isolating rod (scotopic) and cone (photopic) circuits following dark and light adaptation. Currently, ERGs are used to detect loss of retinal function or to distinguish between retinal and optic nerve lesions.</p>

Multi-focal electroretinography (mfERG) is a higher resolution form of ERG, enabling assessment of ERG activity in small areas of the retina. Electrical responses from the retina are recorded with a corneal electrode as in conventional ERG recording. However, the nature of the stimulus and the form of the analysis differ. These differences allow a topographic map of the local ERG activity to be measured. mfERG also allows the stimulation of multiple spots simultaneously, producing a changing pattern that is supposed to provide more diagnostic information.

Pattern electroretinogram (PERG) is a retinal bio-potential test evoked by a temporally modulated patterned stimulus (e.g. checkerboard or grating) of constant mean luminance. The standard PERG is recorded to abrupt contrast reversal of a black and white checkerboard pattern with central fixation. The PERG arises largely in the ganglion cells, driven by the photoreceptors and corresponding retinal cells. Since the PERG (in contrast to the flash ERG) is a local response from the area covered by the retinal stimulus image, it can be used as a sensitive indicator of dysfunction within the macular region and it reflects the integrity of the optics, photoreceptors, bipolar cells and retinal ganglion cells (RGC). PERG is currently being investigated to assess RGC function in patients with glaucoma.

Policy/Procedure

Commercial Plans/CHIP

Mountain Health Co-Op considers electroretinography (ERG) medically necessary as an acceptable alternative adjunctive modality to establish loss of retinal function or to distinguish between retinal lesions and optic nerve lesions.

Mountain Health Co-Op considers ERG experimental, investigational and/or unproven for all other indications, including but not limited to the diagnosis and evaluation of glaucoma and the evaluation of childhood brain tumor(s).

Mountain Health Co-Op considers multi-focal Electroretinography (mfERG) medically necessary for detecting chloroquine (Aralen) and hydroxychloroquine (Plaquenil) toxicity.

Mountain Health Co-Op considers mfERG experimental, investigational and/or unproven for all other indications, including but not limited to the diagnosis and evaluation of glaucoma and the prediction of visual acuity decline in age-related macular degeneration.

Mountain Health Co-Op considers pattern electroretinography (PERG) experimental, investigational and/or unproven for all indications.

1. Clinical Rationale

1.1 A fair body of evidence has been published related to electroretinography (ERG). An assessment conducted by the Australian Medical Services Advisory Committee (MSAC, 2001; Johnston et al, 2003) concluded that mfERG is experimental. The

report reached the following conclusions regarding mfERG: “All the studies of multifocal ERG were classified as level IV evidence. They did not present diagnostic characteristics or sufficient data to compute them. Although the studies showed that the multifocal ERG was able to discriminate between some visual parameters of patients with disease and controls with normal vision, they had little consistency and comparability. It is apparent from the available studies that much of the attention is focused on the mechanics of the technique and issues concerned with averaging signals and presentation of results. Thus, the clinical benefits of this technique are not yet apparent”.

- 1.2** Feigl et al (2005) investigated the cone- and rod-mediated mfERG in early age-related maculopathy (early ARM). A total of 17 eyes of 17 subjects with early ARM and 16 eyes of 16 age-matched control subjects with normal fundi were examined. These researchers concluded that their findings show a functional impairment of the rods in early ARM subjects. As there is histopathological evidence showing earlier rod than cone impairment in early ARM, following the rod function with the mfERG might be helpful in diagnosis or for monitoring the progression of early ARM.
- 1.3** In a prospective cohort study, Lai and colleagues (2005) assessed the longitudinal changes in mfERG in patients receiving hydroxychloroquine (HCQ) and examined the effects of cumulative HCQ dose on mfERG. A total of 24 eyes in 12 patients receiving HCQ underwent mfERG recordings at baseline and 1 to 2 years later. The first negative (N1) and first positive (P1) response amplitudes and peak latencies were compared with normal controls. Serial changes in the pattern of mfERG abnormalities and in response amplitudes and peak latencies were also compared between eyes in which HCQ therapy was continued or stopped. Correlation analyses were performed to assess the effects of a cumulative dose of HCQ on mfERG. These investigators concluded that patients receiving HCQ showed a longitudinal decline in retinal function; patients who stopped HCQ therapy showed improvement. Although these data are insufficient to demonstrate the sensitivity of mfERG for evaluating early HCQ toxicity, the results suggested that serial mfERG assessment may help detect early retinal changes associated with HCQ therapy. Therefore, further studies with long-term results will be useful in clarifying the value of mfERG in evaluating early retinal toxicity due to HCQ. Lai et al (2007) stated that mfERG is an investigation that can simultaneously measure multiple electroretinographic responses at different retinal locations by cross-correlation techniques. Thus, mfERG allows topographic mapping of retinal function in the central 40 to 50 degrees of the retina. The strength of mfERG lies in its ability to provide objective assessment of the central retinal function at different retinal areas within a short duration of time. Since the introduction of mfERG in 1992, mfERG has been applied in a large variety of clinical settings. Multi-focal ERG has been found to be useful in the assessment of localized retinal dysfunction caused by various acquired or hereditary retinal disorders.
- 1.4** The use of mfERG also enabled clinicians to objectively monitor the treatment outcomes as the changes in visual functions might not be reflected by subjective methods of assessment. By changing the stimulus, recording, and analysis parameters, investigation of specific retinal electrophysiological components can be performed topographically. Further developments and consolidations of these

parameters will likely broaden the use of mfERG in the clinical setting. Moon et al (2012) conducted a study to investigate the association between automated perimetry, mfERG, and optical coherence tomography (OCT) measurements in patients with advanced retinitis pigmentosa (RP). In 25 patients with advanced RP central visual field sensitivity (VFS) was evaluated using an average of visual sensitivity value at central four test points during central 30-2 static automated perimetry. When OCT imaging was conducted the inner and outer segment (IS/OS) line was classified into three groups: Group 1, absence; Group 2, partially intact; and Group 3, intact. Central retinal thickness (CRT), defined as the retinal thickness of central 3.0 mm, was also evaluated. Average amplitude and implicit time of N1 and P1 in ring 1 and 2 were measured on mfERG and comparisons of VFS, mfERG and OCT among the three subgroups were performed following IS/OS integrity. The relationship between VFS, mfERG and CRT was evaluated by regression analysis. The study found that group 3 patients with an intact IS/OS line showed a better VFS, and amplitude of mfERG response than those of Group 1 and 2. VFS and amplitudes of mfERG were correlated significantly with CRT in linear regression analysis. In conclusion, disrupted IS/OS integrity was associated with visual dysfunction which was shown by decreased amplitude of mfERG response and reduced central VFS. CRT was significantly correlated with amplitude of mfERG response and central VFS and an eye with the more reduced CRT was associated with the worse amplitude of mfERG response and central VFS.

- 1.5** Narayanan et al (2013) conducted a prospective study of mfERG in patients with type 2 MacTel to characterize the electroretinography response of the macula by mfERG. The study was conducted from April 2009 to November 2009 and mfERGs were recorded using a visual evoked response imaging system (MonElec2, Metrovision, Perenchies, France). The International Society for Clinical Electrophysiology of Vision (ISCEV) guidelines were followed and the study included patients with type 2 MacTel confirmed by fundus fluorescein angiography without subretinal neovascularization. Individual mfERG responses for the hexagons were grouped into concentric rings centered on the fovea for analysis (less than 2°, 5 to 10°, 10 to 15° and greater than 15°). A total of 28 eyes of 14 patients and 20 eyes of 10 normal controls were included in the study. The authors reported that the mean logMAR visual acuity of the patients was 0.51 (Snellen equivalent 20/63) and the mean N1 amplitude (nv/deg²) of patients were significantly reduced compared to controls as follows: 8.91 ± 14.00 versus 43.44 ± 9.55 ($p < 0.0001$) in less than 2°, 9.24 ± 10.47 versus 22.00 ± 3.87 ($p < 0.0001$) in 5-10°, 8.57 ± 10.02 versus 15.24 ± 1.89 ($p < 0.0001$) in 10-15°, and 7.03 ± 6.52 versus 12.47 ± 2.62 in $> 15^\circ$ ($p < 0.001$). The mean P1 amplitude (nv/deg²) was also significantly reduced in patients compared to controls. The results specified 27.66 ± 37.44 versus 96.20 ± 12.41 ($p < 0.0001$) in less than 2°, 22.61 ± 19.38 versus 53.78 ± 9.79 ($p < 0.0001$) in 5-10°, 18.75 ± 20.21 versus 35.22 ± 4.16 ($p < 0.001$) in 10-15°, and 17.10 ± 12.54 versus 25.71 ± 3.93 ($p < 0.001$). The implicit time of N1 and P1 were also delayed significantly in all the rings. The mean central foveal thickness assessed by OCT scan was 84.78 ± 45.12 μm . There was poor correlation between mfERG amplitudes or implicit times with either the visual acuity or OCT central thickness. In conclusion, mfERG showed significant reduction in amplitudes and implicit times of the waveforms in patients

with type 2 MacTel in all the rings, suggesting a more generalized affection of the macula. The maximum reductions were seen in the <2 (o) rings. Although there was poor correlation between the visual acuity and the amplitudes of the waveforms, mfERG is a useful investigative modality for functional assessment of macula in type 2 MacTel patients. However, this study was limited by the sample size of 28 eyes in 14 patients. In a review on “Hydroxychloroquine-induced retinal toxicity”, Hansen and Schuman (2011) stated that at the initiation of treatment with HCQ, the prescribing physician should refer the patient to an ophthalmologist. During the initial examination, it is recommended that the patient receive:

- a)** A thorough ocular examination documenting any pre-existing conditions; and
- b)** A Humphrey visual field central 10-2 white-on-white pattern; and
- c)** At least 1 of the following objective tests, if available:
 - i.** fundus auto-fluorescence (FAF) test; or
 - ii.** mfERG; or
 - iii.** Spectral domain OCT (SD-OCT).

1.6 Moreover, these investigators noted that mfERG, a test that is typically available in large clinical centers, objectively evaluates function and can be used in place of visual fields. They also stated that it is also worth considering the use of color fundus photographs to assist in documenting changes over time, especially if there is pre-existing retinal pathology. However, the dilated fundus examination should not be considered a screening tool, as it only picks up relatively late toxic changes.

1.7 Costedoat-Chalumeau et al (2012) stated that new recommendations for screening of HCQ retinopathy, updating those of 2002, have been recently published by the American Academy of Ophthalmology (AAO). These recommendations have been necessary because of new knowledge about the prevalence of toxicity and because of improved screening tools. Amsler grid testing, color vision testing, fluorescein angiography, full-field ERG, and electro-oculogram are no longer recommended. It is now recommended to perform fundus examinations with 10-2 automated fields, and whenever possible, at least 1 objective test including mfERG, FAF or SD-OCT. A baseline examination is advised as a reference and then, annual screening should be initiated no later than 5 years after starting HCQ therapy.

1.8 An eMedicine review on “Chloroquine and Hydroxychloroquine Toxicity” (Roque, 2019) listed full-field ERG or electro-oculogram as one of the ancillary tests, although not recommended for toxicity screening because of sensitivity, specificity and reliability issues, may also be used in diagnosing toxicity. Moreover, the author also indicated that the ophthalmic examination should also include a Humphrey visual field central 10-2 white-on-white pattern, and at least one of the following objective tests, if available: SD-OCT, FAF test, or mfERG.

1.9 Browning and Lee (2014) determined the relative sensitivity and specificity of 10-2 visual fields (10-2 VFs), mfERG, and SD-OCT in detecting HCQ retinopathy. A total of 121 patients taking HCQ (n = 119) or chloroquine (CQ; n = 2) with 10-2 VF, mfERG, and SD-OCT tests were retrospectively reviewed. Rates of test abnormality were determined. Retinopathy was present in 14 and absent in 107; 11 of 14 (78.6%) patients with retinopathy were over-dosed; 12 (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 (PPVs) 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 (NPVs) were greater than 99% for all tests. The study concluded that based on published estimates of HCQ retinopathy prevalence, all 3 tests are most reliable when negative, allowing confident exclusion of retinopathy in patients taking less than or equal to 6.5 mg/kg/day. Each test is less useful in allowing a confident diagnosis of retinopathy when positive, especially in patients taking less than or equal to 6.5 mg/kg/day.

- 1.10** Guidelines from the AAO (Marmor et al, 2011) on screening for CQ and HCQ toxicity stated that newer objective tests, such as mfERG, SD-OCT, and FAF, can be more sensitive than visual fields. The guidelines recommended that along with 10-2 automated fields, at least 1 of these procedures be used for routine screening where available. Also, because mfERG testing is an objective test that evaluates function, it may be used in place of visual fields.
- 1.11** Tsang et al (2015) determined the validity of mfERG as a screening tool for detecting CQ and HCQ retinal toxicity in patients using these medications. To evaluate the sensitivity and specificity of mfERG when compared with automated visual fields (AVFs), FAF, and OCT. The 2011 AAO recommendations on screening for CQ/HCQ retinopathy recommended a shift toward more objective testing modalities.
- 1.12** Multi-focal ERG may be effective in detecting functional change before irreversible structural damage from CQ/HCQ toxicity. These investigators performed a search for records reporting the use of mfERG for screening CQ/HCQ retinopathy in MEDLINE (PubMed and OVID), EMBASE, and Web of Science, and assessed these using the QUADAS-2 risk of bias tool. They conducted an analysis of 23 individual studies and their reported individual patient data (449 eyes of 243 patients) published from January 2000 to December 2014. Multi-focal ERG had the greatest proportion of positive test results, followed by AVF. The pooled sensitivity and specificity of mfERG were 90% (95% confidence interval [CI]: 0.62 to 0.98) and 52% (CI: 0.29 to 0.74), respectively, with AVF as reference standard (13 studies). Sensitivity was high, but specificity was variable when OCT, 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. In conclusion, 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. Moreover, they state that there is an unclear risk of bias in the available evidence, and future studies should adhere to Standards for Reporting of Diagnostic Accuracy reporting guidelines.
- 1.13** Several studies have looked at multi-focal electroretinography (mfERG) for prediction of visual acuity decline in age-related macular degeneration. In a prospective study, Ambrosio et al (2015) examined the role of mfERG for predicting

visual acuity (VA) decline in early age-related macular degeneration (ARMD) with time. A total of 26 early ARMD patients (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), then 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 findings indicated that mfERG P1 amplitude and AD of Ring 1 may be highly specific to predict VA decline in early ARMD. However, these preliminary findings need to be validated by well-designed studies. Guidelines from the American Academy of Ophthalmology (AAO, 2015) on age-related macular degeneration have no recommendation for mfERG.

1.14 As it relates to the use of ERG or mfERG for diagnosis/evaluation of glaucoma, in a report by the AAO on “Assessment of visual function in glaucoma”, Jampel and colleagues (2015) reviewed the published literature to summarize and evaluate the effectiveness of visual function tests in diagnosing glaucoma and in monitoring progression. The authors concluded that advances in technology and analytic tools over the past decade had provided them with more rapid and varied ways of assessing visual function in glaucoma, but they have yet to produce definitive guidance on the diagnosis of glaucoma or its progression over time. Therefore, further research on an objective measure of visual function is needed.

1.15 Nouri-Mahdavi (2014) stated that testing the peripheral field of vision is the mainstay for detection of glaucoma deterioration. Various methods and algorithms are currently available for detection of early glaucoma or establishing disease progression. Alternative testing strategies such as frequency doubling technology perimetry or short-wavelength automated perimetry have been extensively explored over the last 2 decades. The former has been found most promising for detection of earliest evidence of functional glaucoma damage when the standard achromatic perimetry results are still within the normal range. However, standard achromatic perimetry remains the standard technique for establishing deterioration of the disease. Both trend and event analyses were used for establishing change within series of visual fields. Trend analyses provided the clinician with rates of progression, putting the speed of glaucoma progression in the context of patient longevity, whereas event analyses demonstrated a "step" change regardless of the length of time it took for this amount of change to occur. The 2 techniques are

complementary and should be used concurrently; ERG/mfERG was not mentioned as a management tool.

1.16 Furthermore, guidelines from the American Academy of Ophthalmology (2015) and UpToDate reviews on “Open-angle glaucoma: Epidemiology, clinical presentation, and diagnosis” (Jacobs, 2019), “Angle-closure glaucoma” (Weizer, 2019), and “Overview of glaucoma in infants and children” (Olitsky and Reynolds, 2019) do not mention ERG/mfERG as diagnostic tools.

1.17 Recently published updates to the ISCEV standard for clinical multifocal electroretinography (Hoffman et al, 2021) affirm the use of mfERG for the detection of CQ and HCQ toxicity. In a prospective, case-series study, Gupta and colleagues (2015) evaluated the use of mfERG in diagnosing retinal toxicity from siderosis with normal ERG. A total of 6 patients with retained intra-ocular foreign body were recruited. The affected eye of the patients had no clinical evidence of siderosis, had similar full-field photopic 3.0 ERG compared with the fellow eye, and had subnormal VA. Group averages in each mfERG ring for implicit time and amplitude at P1 wave were compared between affected and fellow eye to look for latent siderosis. On mfERG, no statistical difference in group averaged amplitude was observed; however, a significant difference ($p < 0.05$) was found in group averaged latency between fellow and affected eye at most tested rings (less than 2 degree, 2 to 5 degree, and greater than 15 degree rings). Average latency for overall retinal area mapped also showed significant difference ($p = 0.010$). The authors concluded that increased mfERG latency may serve as an early predictor of retinal damage from siderosis when full-field ERG is normal.

1.18 Senger and colleagues (2020) also concurred with the nonuse of ERG/mfERG for glaucoma noting that no definitive indications of these tests have been established either at early detection or during followup of the disease. Does not mention ERG/mfERG as diagnostic tools.

1.19 Wilsey and colleagues (2017) compared diagnostic performance and structure-function correlations of mfERG, full-field flash ERG (ffERG) photopic negative response (PhNR) and transient pattern-reversal ERG (PERG) in a non-human primate (NHP) model of experimental glaucoma (EG). Study duration was 15 ± 8 months. Among the ERG modes evaluated in this study, the mfERG HFC had the highest diagnostic sensitivity and strongest correlation to structure in this cohort of NHP with experimental glaucoma. Consistent with numerous other reports, accounting for inter-eye differences by normalization to baseline amplitudes and/or by normalization to other features of the same ERG response less sensitive to glaucomatous damage improved both diagnostic performance and correlation to a structural measure of damage severity for the best parameters of all 3 ERG modes. After normalization, the mfERG HFC had the highest diagnostic sensitivity and strongest correlation to RNFL thickness and missed only a few EG eyes flagged by PhNR or PERG. The mfERG also offered an opportunity to evaluate focal loss, unlike the ffERG; future studies are planned to evaluate whether any benefit can be realized from this potential advantage, even in this EG model, which tends to manifest as more diffuse progressive damage rather than as sequential focal loss. Moreover, the authors stated that further research is needed to examine if these

observations will successfully translate to clinical management of human glaucoma.

- 1.20** ERG has also been studied for the diagnosis of Birdshot Chorioretinopathy (BSCR), a rare form of autoimmune posterior uveitis that can affect the visual function and, if left untreated, can lead to sight-threatening complications and loss of central vision. Tzekov and Madow (2015) performed a systematic search of the literature focused on visual electrophysiology studies, including ERG, electrooculography (EOG), and VEP, used to monitor the progression of BSCR and estimate treatment effectiveness. The authors concluded that despite its wide use, a well-designed longitudinal multi-center study to systematically evaluate and compare different electrophysiological methods or parameters in BSCR is still lacking; but would benefit both diagnostic and therapeutic decisions. The authors stated that, "until then, there is enough evidence to recommend the use of photopic 30 Hz flicker in the clinical management of BSCR.
- 1.21** When applied for evaluation of childhood brain tumor survivors Pietila and colleagues (2016) evaluated the clinical value of ERG and VEP in a population-based, cross-sectional study, in childhood brain tumor survivors. Abnormal ERGs are rarely observed, but abnormal VEPs are common even without evident anatomic lesions in the visual pathway. Bilateral changes suggested a general and possibly multifactorial toxic/adverse effect on the visual pathway. The authors concluded that ERG and VEP may have clinical and scientific value while evaluating long-term effects of childhood brain tumors and tumor treatment.
- 1.22** ERG has also been assessed for evaluation of achromatopsia. Schallhorn and colleagues (2018) reported novel ERG findings in a genetically confirmed case of achromatopsia. This single case study assessed a patient with a history of childhood nystagmus, photo-aversion, and absent color vision. Electroretinography and fundus examination were performed under anesthesia at the time of corrective surgery for nystagmus. Genomic DNA isolated from peripheral blood was directly sequenced for variations in the CNGA3 and CNGB3 genes. In conclusion, novel ERG findings in a patient with genetically confirmed achromatopsia were reported; the electro-negative configuration in this clinical setting is of unclear etiology; however, it may suggest some component of inner retinal dysfunction. Further studies investigating the clinical value of ERG in the evaluation of achromatopsia are needed.
- 1.23** The evaluation of autism spectrum disorder has been another condition for which ERG has been assessed. Constable and colleagues (2016) explored early findings that individuals with autism spectrum disorder (ASD) have reduced scotopic ERG b-wave amplitudes. No group differences were observed for the distributions of the time to peaks of LA a-wave, b-wave or the photopic negative responses (phNR) ($p > 0.08$) to the single flash stimuli, but there was a significant difference in the distribution for the LA b-wave amplitudes (corrected $p = 0.006$). Under LA conditions, the b-wave was reduced across the ASD group, along with the ON response of the prolonged flash ERG and some ASD individuals also showed subnormal DA ERG b-wave amplitudes. The authors concluded that these exploratory findings suggested there is altered cone-ON bipolar signaling in ASD.

Furthermore, an UpToDate review on “Autism spectrum disorder: Diagnosis” (Augustyn, 2019) does not mention electroretinography as a diagnostic tool.

- 1.24** As it relates to the evaluation of non-glaucomatous optic neuropathies Bach and Kay (2017) presented a case study of 3 cases of inflammatory optic neuritis that was followed to resolution using PERG. They noted that these cases represented the first report in which a relatively new office-based PERG technology has been demonstrated to be useful in monitoring recovery of visual function in the setting of inflammatory optic neuropathies. Two patients demonstrated normalization of their PERG paralleling their full recovery of optic nerve function as assessed via other standard measures such as VA and Humphrey visual field (HVF), while the third demonstrated improvement, albeit still reduced in amplitude, consistent with the incomplete recovery of optic nerve function, at most recent follow-up.
- 1.25** Furthermore, in one of the patients, use of this technology provided an objective means of following recovery of ganglion cell function in an individual who could not be reliably monitored with serial HVFs secondary to poor field testing technique. The authors concluded that the PERG technique may prove useful as an adjunctive objective measure for monitoring progression and/or resolution of glaucoma and other optic neuropathies in patients who are consistently unreliable when performing HVF. They stated that further studies are needed to determine if this new testing paradigm will be of benefit in monitoring for progression or recovery of ganglion cell function in other non-glaucomatous optic neuropathies including compressive lesions of the optic apparatus, ischemic optic neuropathy, papilledema, and toxic optic neuropathies.
- 1.26** Sickle Cell Retinopathy has been another area of study for ERG. In a mono-centric, retrospective, observational study, Bottin and colleagues (2017) discussed full-field ERG (ffERG) findings in patients with early sickle cell (SC) retinopathy according to the following hemoglobin types: HbSS or HbSC (homozygous or heterozygous mutations, respectively). All groups underwent full ophthalmologic examination (fundus examination) and ffERG. For SC patients, additional imaging testing was also performed (fluorescein angiography and spectral domain OCT). In this small study, a total of 24 eyes from 12 patients (6 HbSS and 6 HbSC) and 12 eyes from 6 controls were included. The HbSS group exhibited a dramatic decrease of the b-wave amplitudes for all DA ffERG responses when compared with the control group ($p = 0.02$, $p = 0.003$, $p = 0.005$, respectively, after DA 0.01, DA 3.0, and DA 10.0 cd.s.m² stimulations) and decreased a-wave amplitudes for LA responses ($p = 0.03$ after LA 3.0 cd.s.m⁻² stimulations). The a-wave amplitudes were significantly reduced for all DA and LA responses in the HbSC group compared to the control group ($p = 0.03$, $p = 0.01$, $p = 0.03$, respectively, after DA 3.0, DA 10.0, and LA 3.0 cd.s.m⁻² stimulations). The HbSS and HbSC groups presented decreased a-wave amplitudes for DA and LA responses and decreased b-wave amplitude after DA 0.01 and 10.0 cd.s.m⁻² stimulations when compared to the control group. These findings could suggest an early involvement of the inner retinal cells in the disease process in HbSS patients and of the outer retinal cells in HbSC patients. This could also provide new insights on the pathophysiology of the retinal affection in HbSS/HbSC SC disease. The authors stated that it would also be of interest to compare ffERG data to OCT-angiography findings; however, current

systems mostly cover the area of the central retina, whereas ffERG collects responses from the whole retina. Moreover, the main drawback of this study was its small sample size ($n = 12$ for the experimental group); larger studies are needed to support this hypothesis. Reinforcing the need for further assessment, an UpToDate review on “Overview of the clinical manifestations of sickle cell disease” (Vichinsky, 2019) does not mention electroretinography as a diagnostic tool.

1.27 An additional area in which ERG has been assessed is in rhegmatogenous retinal detachment. Parvaresh (2018) noted that few studies have evaluated the role of retinal electrophysiology testing in patients with retinal detachment and after retinal re-attachment surgery using ffERG and mfERG. Both animal as well as human studies have shown that retinal detachment causes the loss of the outer segments of photoreceptor cells. Both cone and rod photoreceptors are affected in retinal detachment. However, the magnitude of the damage and its likely location in the retina are not clearly known. This investigator stated that current knowledge of electrophysiological changes in rhegmatogenous retinal detachment (RRD) is limited and future studies regarding the application of ERG studies in eyes with RRD are needed; and that although some studies have reported the prognostic value of ERG testing in eyes with RRD, the potential clinical applications of this technique are not clear. It was concluded future large-scale studies may be helpful to examine the use of ERG testing for various aspects of retinal detachment, such as determination of the optimal time of intervention, the outcomes of different types of surgery, and effects of pharmacotherapies on surgery.

1.28 One last area in which mfERG has been assessed is for the evaluation of idiopathic epiretinal membrane/ Poppers Maculopathy. Gao and colleagues (2017) evaluated the macular function changes in patients with idiopathic macular epiretinal membrane (ERM) by mfERG and their correlations with VA and central macular thickness (CMT) by OCT. A total of 20 eyes of 20 patients with ERM underwent OCT and mfERG examinations. The response amplitude densities and implicit times of mfERG were compared to the control fellow eyes. Correlation analyses among VA, CMT and mfERG values in the central 2 concentric rings were performed. The mfERG P1 response amplitude densities in ring 1 to 2 and P1 implicit time in ring 1 were significantly changed in epiretinal membrane eyes compared with controls ($p < 0.05$). Multivariate step-wise linear regression analyses showed LogMAR VA was significantly correlated with CMT ($p = 0.004$), and also with the P1 amplitude density in ring 1 ($p = 0.002$); CMT showed significant correlation with P1 implicit time in ring 2 ($p = 0.013$). These findings showed mfERG abnormalities appeared to demonstrate subtle macular function changes and correlated with VA and CMT in eyes with ERM. Also in first-order mfERG responses, P1 wave changes may be a sensitive functional measurement for ERM patients. However, the small sample size ($n = 20$) is a significant drawback to this study and this might have limited the power in detecting photoreceptor statues and other influence factors, which may have an impact on ERG values and statistical analysis. These researchers noted that the mechanism of mfERG impairment related to ERM may not be straight-forward; the mfERG abnormalities as described in this report need further investigation.

1.29 Pahlitzsch and associates (2018) noted that maculopathy is a potential side effect of amyl nitrite or "poppers" abuse. It is characterized by a sudden, painless decrease in VA. While the fundusoscopic changes are subtle, OCT showed alterations of the outer retinal layers in the fovea. However, the extent of retinal dysfunction remains poorly understood. These investigators compared the mfERG of 6 patients with poppers maculopathy to that of a control group consisting of 6 healthy subjects. Response densities and implicit times of N1 and P1 were analyzed. Both N1 and P1 were lower in the patients with poppers maculopathy than in the control group, particularly in ring 1 and rings 4 and 5. The only statistically significant finding, however, was a reduced N1 response density of 1 hexagon in the patient group. No significant differences were found considering the sum response or the averaged rings 1 to 5. The authors concluded that compared to a healthy control group, mfERG of patients with poppers maculopathy showed no relevant impairment contrasting the marked effect of the disease on VA. These investigators also stated that in clinical practice, poppers maculopathy could not be diagnosed by mfERG.

Applicable Coding

CPT Codes

- 0509T** Electroretinography (ERG) with interpretation and report, pattern (PERG)
92273 Electroretinography (ERG), with interpretation and report; full field (ie, ffERG, flash ERG, Ganzfeld ERG)
92274 Electroretinography (ERG), with interpretation and report; multifocal (mfERG)

HCPCS Codes

No applicable HCPCS codes

Vendors

- **Personify**
- **HPS**

References

1. Al-Nosairy KO, Prabhakaran GT, Pappelis K, Thieme H, Hoffmann MB. Combined multi-modal assessment of glaucomatous damage with electroretinography and optical coherence tomography/angiography. *Translational vision science & technology*. 2020 Nov 2;9(12):7-.
2. Ambrosio L, Ambrosio G, Nicoletti G, et al. The value of multifocal electroretinography to predict progressive visual acuity loss in early AMD. *Doc Ophthalmol*. 2015;131(2):125-135.
3. American Academy of Ophthalmology (AAO), Glaucoma Panel. Primary Open-Angle Glaucoma. Preferred Practice Pattern. San Francisco, CA: AAO; 2015.
4. American Academy of Ophthalmology (AAO), Glaucoma Panel. Primary Open-Angle Glaucoma Suspect. Preferred Practice Pattern. San Francisco, CA: AAO; 2015.
5. American Academy of Ophthalmology (AAO), Glaucoma Panel. Primary Angle Closure. Preferred Practice Pattern. San Francisco, CA: AAO; 2015

6. American Academy of Ophthalmology (AAO), Retina/Vitreous Panel. Age-related macular degeneration. Preferred Practice Pattern. San Francisco, CA: AAO; 2015.
7. Augustyn M. Autism spectrum disorder: Diagnosis. . UpToDate Inc., Waltham, MA. Last reviewed November 2019.
8. Bach A, Kay MD. Demonstration of reversible retinal ganglion cell dysfunction in inflammatory optic neuropathies utilizing pattern electroretinography. *Int J Ophthalmol.* 2017;10(2):321-324.
9. Bottin C, Racine J, Robert MP, et al. Electroretinogram findings in early-stage sickle cell retinopathy according to hemoglobin type. *Invest Ophthalmol Vis Sci.* 2017;58(7):3262-3267.
10. Browning DJ, Lee C. Relative sensitivity and specificity of 10-2 visual fields, multifocal electroretinography, and spectral domain optical coherence tomography in detecting
11. hydroxychloroquine and chloroquine retinopathy. *Clin Ophthalmol.* 2014;8:1389-1399.
12. Constable PA, Gaigg SB, Bowler DM, et al. Full-field electroretinogram in autism spectrum disorder. *Doc Ophthalmol.* 2016;132(2):83-99.
13. Costedoat-Chalumeau N, Ingster-Moati I, Leroux G, et al. Critical review of the new
14. recommendations on screening for hydroxychloroquine retinopathy. *Rev Med Interne.* 2012;33(5):265-267.
15. Feigl B, Brown B, Lovie-Kitchin J, et al. Cone- and rod-mediated multifocal electroretinogram in early age-related maculopathy. *Eye.* 2005;19(4):431-441.
16. Gao M, Wang Y, Liu W, et al. Assessment of macular function in patients with idiopathic
17. epiretinal membrane by multifocal electroretinography: Correlation with visual acuity and optical coherence tomography. *BMC Ophthalmol.* 2017;17(1):221.
18. Gupta S, Midha N, Gogia V, et al. Sensitivity of multifocal electroretinography (mfERG) in detecting siderosis. *Can J Ophthalmol.* 2015;50(6):485-490.
19. Hansen MS, Schuman SG. Hydroxychloroquine-induced retinal toxicity. *EyeNet Magazine.* June 2011. Available at: <https://www.aao.org/eyenet/article/hydroxychloroquine-induced-retinal-toxicity?june-2011>. Accessed August 22, 2017.
20. Hoffmann MB, Bach M, Kondo M, Li S, Walker S, Holopigian K, Viswanathan S, Robson AG. ISCEV standard for clinical multifocal electroretinography (mfERG) (2021 update). *Doc Ophthalmol.* 2021 Feb;142(1):5-16. doi: 10.1007/s10633-020-09812-w. Epub 2021 Jan 25. PMID: 33492495; PMCID: PMC7906932.
21. Jampel HD, Singh K, Lin SC, et al. Assessment of visual function in glaucoma: A report by the American Academy of Ophthalmology. *Ophthalmology.* 2011;118(5):986-1002
22. Johnston RV, Burrows E, Rauli A. Assessment of diagnostic tests to inform policy decisions--visual electrodiagnosis. *Int J Technol Assess Health Care.* 2003;19(2):373-383.
23. Lai TY, Chan WM, Lai RY, et al. The clinical applications of multifocal electroretinography: A systematic review. *Surv Ophthalmology.* 2007;52(1):61-96.

24. Lai TY, Chan WM, Li H, et al. Multifocal electroretinographic changes in patients receiving hydroxychloroquine therapy. *Am J Ophthalmology*. 2005;140(5):794-807.
25. Marmor MF, Kellner U, Lai TY, et al.; American Academy of Ophthalmology. Revised recommendations on screening for chloroquine and hydroxychloroquine retinopathy. *Ophthalmology*. 2011;118(2):415-422.
26. Marmor MF, Kellner U, Lai TY, et al; American Academy of Ophthalmology. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 Revision). *Ophthalmology*. 2016;123(6):1386-1394.
27. Medical Services Advisory Committee (MSAC). Visual electrodiagnosis. Assessment Report. MSAC Application 1005. Canberra, ACT: MSAC; April 2001. Available at: <http://www.msac.gov.au/reports.htm>. Accessed July 21, 2012.
28. Moon CH, Park TK, Ohn YH. Association between multifocal electroretinograms, optical coherence tomography and central visual sensitivity in advanced retinitis pigmentosa. *Doc Ophthalmology*. 2012;125(2):113-122.
29. Narayanan R, Dave V, Rani PK, et al. Multifocal electroretinography in type 2 idiopathic macular telangiectasia. *Graefes Arch Clin Exp Ophthalmology*. 2013;251(5):1311-1318.
30. Nouri-Mahdavi K. Selecting visual field tests and assessing visual field deterioration in glaucoma. *Can J Ophthalmol*. 2014;49(6):497-505
31. Olitsky SE, Reynolds JD. Overview of glaucoma in infants and children. UpToDate Inc., Waltham, MA. Last reviewed August 2015
32. Pahlitzsch M, Salchow D, Rossel M, Bergholz R. Multifocal electroretinography in patients with poppers maculopathy. *Klin Monbl Augenheilkd*. 2017 Oct 12 [Epub ahead of print].
33. Parvaresh MM. Electroretinography and rhegmatogenous retinal detachment. *J Ophthalmic Vis Res*. 2018;13(3):217-218.
34. Pietila S, Lenko HL, Oja S, et al. Electroretinography and visual evoked potentials in childhood brain tumor survivors. *J Child Neurol*. 2016;31(8):998-1004.
35. Roque MR. Chloroquine and hydroxychloroquine toxicity workup. Medscape. Last updated: March 15, 2019. Available at: <http://emedicine.medscape.com/article/1229016-workup>. Accessed November 9, 2019.
36. Schallhorn CS, Granet DB, Ferreyra HA. Electronegative electroretinography in achromatopsia. *Retin Cases Brief Rep*. 2018;12(2):143-148.
37. Senger C, Moreto R, Watanabe SES, Matos AG, Paula JS. Electrophysiology in Glaucoma. *J Glaucoma*. 2020 Feb;29(2):147- 153. doi: 10.1097/IJG.0000000000001422. PMID: 31809397
38. Tsang AC, Ahmadi Pirshahid S, Virgili G, et al. Hydroxychloroquine and chloroquine retinopathy: A systematic review evaluating the multifocal electroretinogram as a screening test. *Ophthalmology*. 2015;122(6):1239-1251
39. Tzekov R, Madow B. Visual electrodiagnostic testing in birdshot chorioretinopathy. *J Ophthalmol*. 2015;2015:680215.
40. Vichinsky EP, Field JL, Overview of the clinical manifestations of sickle cell disease. UpToDate Inc., Waltham, MA. Last reviewed November 2019.

41. Weizer JS. Angle-closure glaucoma. UpToDate Inc., Waltham, MA. Last reviewed August 2015
42. Wilsey L, Gowrisankaran S, Cull G, et al. Comparing three different modes of electroretinography in experimental glaucoma: diagnostic performance and correlation to structure. Doc Ophthalmol. 2017;134(2):111-128.

Review/Revision/Approval History	
Date	Description
07/09/2024	New Policy
04/27/2026	Reviewed and approved by Mountain Health CO-OP Policy Committee

Disclaimer

This document is for informational purposes only and should not be relied on in the diagnosis and care of individual patients. Medical and Coding/Reimbursement policies do not constitute medical advice, plan preauthorization, certification, an explanation of benefits, or a contract. Members should consult appropriate healthcare providers for medical advice, care, and treatment. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the member’s benefit plan, effective when services are rendered.

The codes for treatments and procedures applicable to this policy are included for informational purposes. Including or excluding a procedure, diagnosis, or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as they apply to an individual member.

Mountain Health Co-Op makes no representations and accepts no liability regarding the content of any external information cited or relied upon in this policy. Mountain Health Co-Op updates its Coverage Policies regularly and reserves the right to amend these policies and give notice per State and Federal requirements. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Mountain Health Co-Op.

”Mountain Health Co-Op” and its accompanying logo and marks are protected and registered trademarks of Mountain Health Co-Op. The content of this Service is proprietary and protected by copyright. You may access the copyrighted content of this Service only for purposes outlined in these Conditions of Use.

© CPT Only – American Medical Association