Visual electrodiagnostic tests provide objective functional evaluation of the primary visual pathway in patients with ocular diseases and vision loss.

- Evaluate the functions of RPE, outer retina (photoreceptors, bipolar cells), ganglion cells, optic nerve and beyond
- Evaluate the functions of the rod and cone systems
- Evaluate the functions of the entire retina, topographic map the macular area
Clinical indications of visual electrodiagnostic tests include:

1. Establish the diagnosis of diseases with various etiologies (maldevelopment, hereditary, inflammatory and autoimmune, degenerative, toxic, vascular, tumor-associated, and traumatic causes etc.)
2. Visual function evaluation at various stages of disease process:
   - Early detection
   - Monitoring disease progression
   - Evaluating therapeutic effects
   - Functional assessment at advanced stage
3. Assessing visual pathway function in patients with ocular media opacity
   - patients with functional vision loss
Overview of Visual electrodiagnostic tests

ELECTRORETINOGRAM (ERG)
  ffERG, mfERG, pERG

VISUAL EVOKED POTENTIAL (VEP)
  fVEP, pattern reversal VEP, pattern onset/offset VEP, mfVEP

ELECTRO-OCULOGRAM (EOG)
Electrodiagnostic systems

Common systems used in USA:

Electro-Diagnostic Imaging → VERIS system
Diagnosys → E³ and profile systems
LKC Technologies → RETeval and UTAS systems
Diopsys → NOVA and ARGOS systems
Konan Medical → EvokeDX
1. ffERG (full-field ERG)

Evaluate the gross response of the retina for both the rod and cone systems

**Recording setting:**
**Active electrode:** Burian-Allen contact lens electrode or DTL microfiber electrode
**Patient:** needs dilation
**Stimuli:** single flashes and flickers
- rod system is evaluated with dim flash light when patient is dark-adapted
- rod and cone systems together are evaluated with bright flash light when patient is dark-adapted
- cone system is evaluated with bright single flash and flicker light when patient is light-adapted
ffERG waveforms
Major ffERG waveform components:

**a-wave**
- reflects photoreceptors function

**b-wave**
- reflects bipolar cell & Müller cell function
- oscillatory potentials (OPs)
- reflects amacrine cell function
2. mfERG (multifocal ERG)

Topographic mapping of the retina function for the cone system in the central retina with a diameter of 40-50 degrees.

Recording setting:
Active electrode: Burian-Allen contact lens electrode or DTL microfiber electrode
Patient: needs dilation
Stimuli: 103 hexgonal elements, with the luminance of each hexagon independently modulated according to a pseudorandom m-sequence.
mfERG typical waveforms:

- Local response is extracted by correlating the recorded continuous ERG signal with the stimulus sequence.
- Each local response is associated with one of the scaled hexagonal elements of the display.
  - 1st order kernel reflects the retinal response to the flash.
  - 2nd order kernel reflects the influence of the preceding flash.
Ring/Group Averages
42 year old female
Noticed decreasing night vision since young adulthood; fundus exam shows bone spicule pigmentation and vitreal degeneration of the right and left eyes
39 year-old female
Noticed peripheral and night vision loss for approximately twenty years and she also reported seeing “sparks of light” for approximately ten years in both eyes.
VA: 20/20 OD and 20/20 OS
mfERG

Right Eye

Retinal view

Left Eye

Retinal view

- 500 nV
- 100 ms
Retinitis pigmentosa

A heterogeneous group of hereditary retinal diseases characterized by dysfunction and loss of rod and cone photoreceptors, with loss of rods followed by loss of cones in most forms of typical RP.

Patients usually report night vision loss in adolescence, peripheral vision loss in young adulthood, and central vision loss later in their life.

Typical fundus findings include retinal vessel attenuation, bone-spicule intraretinal pigmentation in the mid-periphery or far periphery, & optic nerve head pallor.

ERG is used for diagnosis of the disease, assessment of severity, monitoring the progress, providing visual prognosis, and measurement of therapeutic effects. ffERG shows reduced rod and cone response amplitudes and delay in implicit time, with rod responses more severely affected than the cone responses. mfERG is used to further map the residual cone function in the central retina.
7 year-old boy
Noticed central “blurry” vision for approximately four weeks OD & OS
BVA: 20/30 OD, 20/30 OS
Full-field ERG

Right Eye

A
Dark-adapted 0.01

B
Dark-adapted 3.0

C
Dark-adapted 3.0 Oscillatory Potentials

D
Light-adapted 3.0

E
Light-adapted 3.0 Flicker

Left Eye
mfERG

Right Eye

Traces

Field View

Ring Averages

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50 mV/deg²

0 10 20 30 40 50 60 70 80 90 100 ms

P1 Response Density

Field View

Patient-Normal Comparison

Field View

Patient-Normal Comparison
Progressive cone and cone-rod dystrophies

A heterogeneous group of retinal dystrophies with cone loss and subsequent rod loss later in the disease process.

Fundus appearance:
- Macular atrophy or a bull’s-eye maculopathy in the early stages
- Peripheral RPE atrophy, retinal pigmentation, arteriolar attenuation, and optic disc pallor can be seen in later stages

ffERG shows substantially impaired cone function at the early stage and then additional rod dysfunction.
39 year-old male
Noticed central vision loss OD & OS for nine years
Twin brother has Stargardt disease
BVA: 20/80 OD, 20/200 OS
mfERG

Right Eye

Traces

Left Eye

PI Response Density
Stargardt disease

Stargardt disease (STGD) is a juvenile macular dystrophy characterized by the presence of bilateral atrophie-appearing lesions affecting predominantly the macula. Typical onset is in early childhood or adolescence, however, later onset has also been observed.

For most cases of STGD, the inheritance pattern is autosomal recessive. ABCA4 (ATP-binding cassette, sub-family A) is the current known gene to cause autosomal recessive STGD.
Stargardt disease

Fundus appearance:
In the very early stage, ophthalmoscopy may show no abnormal appearance. With progression of the disease, funduscopic findings reveal yellow-white pisciform retinal flecks, a beaten bronze appearance, RPE mottling to atrophy, or a bull’s eye lesion.

Fluorescein angiography (FA):
Lipofuscin-like deposits in the RPE cells likely block choroidal hyperfluorescence during FA resulting in choroidal silence (dark choroid). In the later stages of the disease, RPE atrophy may reveal the underlying large choroidal vessels demonstrating hyperfluorescence.

ERG:
Typically show abnormal mfERG results in the macular area, normal ffERG in the early stages and can show abnormal ffERG in the later stages. However, various ERG functional phenotypic subtypes have been identified involving both the cone and rod populations.
AIR case

(Woods, A., Bi, H. & Caputo M. Rod Loss with 43-kDa and 52-kDa Protein Anti-Retinal Autoantibodies in Autoimmune Retinopathy. 2012 American Academy of Optometry meeting)

55 year-old female
Noticed decreased central vision for one year OD & OS, peripheral vision loss in the OS, and nyctalopia OU. Her medical history was significant for a weight loss of around 40 lb over the past year. “Abnormal” breast cells and small lung nodules were noted with imaging, but follow-up with surgical biopsies did not reveal any malignancy. Brain MRI was negative. There is no family history of retinitis pigmentosa.
VA: 20/30 OD and 20/40 OS. Goldman visual field test showed field constriction for both eyes.
Full-field ERG

Right Eye

A

Dark-adapted 0.01

Latencies [ms]  Values [$\mu V$

0.000  0.000  12.5 [X]

100 $\mu V$

0  50  100  150  200  250 [ms]

B

Dark-adapted 3.0

Latencies [ms]  Values [$\mu V$

0.000  2.335  128.5 [X]

200 $\mu V$

0  20  40  60  80  100  120  140 [ms]

C

Dark-adapted 3.0 Oscillatory Potentials

D

Light-adapted 3.0

Latencies [ms]  Values [$\mu V$

0.000  -0.553
15.617  51.667
52.917  45.000

50 $\mu V$

0  20  40  60  80  90  100 [ms]

E

Light-adapted 3.0 Flicker

Latencies [ms]  Values [$\mu V$

20.000  50.000
41.190  49.000
61.190  59.000

50 $\mu V$

0  10  20  30  40  50  60  70  80  90  100 [ms]

Left Eye

Latencies [ms]  Values [$\mu V$

0.000  0.000  21.8 [X]

100 $\mu V$

0  50  100  150  200  250 [ms]

Latencies [ms]  Values [$\mu V$

0.000  0.000  25.0 [X]

Latencies [ms]  Values [$\mu V$

0.000  5.000  15.0 [X]

200 $\mu V$

0  20  40  60  80  100  120  140 [ms]

Latencies [ms]  Values [$\mu V$

0.000  0.000  25.0 [X]

Latencies [ms]  Values [$\mu V$

0.000  0.000  25.0 [X]
RESULTS:
Test results must be interpreted in the context of clinical presentation

**WB:** POSITIVE for anti-retinal autoantibodies against 43-kDa and 52-kDa proteins

**IHC:** POSITIVE—moderate cytoplasmic staining of the outer nuclear layer in human retina

INTERPRETATION:
A positive result indicates that anti-retinal autoantibodies are present, which may indicate Autoimmune Retinopathy. Antibodies against retinal antigens have been associated with autoimmune retinal disorders, including paraneoplastic retinopathy. The most recognized are antibodies against recoverin (23-kDa, “CAR antigen”). However, less than 10% seropositive patients have anti-recoverin antibodies. CAR retinal dysfunction and AAbs manifests prior to the onset of cancer and the underlying cancer can remain undetectable for months or even years. The presence of anti-recoverin antibodies indicates a high likelihood of associated neoplasm, especially small cell carcinoma of the lung and gynecological cancer in women [Adamus G, Ren G, Weleber RG. BMC Ophthalmol 4(1):5, 2004].
Ocular Immunology Laboratory, Oregon Health & Science University
Casey Eye Institute – BRB, Room 253
3181 SW Sam Jackson Park Road
Portland, OR 97239, USA
503-418-2543 (Phone), 503-418-2541 (FAX)
CLIA#38D1045259

Ocular Immunology Laboratory at Oregon Health & Science University offers the following anti-retinal autoantibody tests for CAR, MAR, Autoimmune Retinopathy and anti-optic nerve autoantibodies for Optic Neuropathy in serum and fluids:

- Western blot for anti-retinal autoantibodies, including anti-enolase and anti-recoverin autoantibodies in the serum
- Western blot for anti-retinal autoantibodies, including anti-enolase and anti-recoverin autoantibodies in ocular fluids (vitreous, subretinal fluid)
- Immunohistochemistry for anti-retinal autoantibodies
- Western blot for anti-optic nerve autoantibodies in the serum
- Western blot for anti-optic nerve autoantibodies in CSF

All requests for autoantibody testing from an authorized person using a Test Requisition Form must include:
- Patient’s name
- Sex, age/birthday
- Blood collection date
- Referring clinic/physician name and contact information, including fax number
- Diagnosis or pertinent clinical history and findings
- Test requested
- Pre-payment – we accept check or Visa and Master Card; we do not bill insurance
Autoimmune retinopathies (AIR)

Autoimmune retinopathy (AIR) describes the group of inflammatory-mediated retinopathies characterized by vision loss, photoreceptor dysfunction, and the presence of circulating autoimmune anti-retinal antibodies.

The spectrum of autoimmune retinopathies includes paraneoplastic AIR such as cancer-associated retinopathy (CAR) and melanoma-associated retinopathy (MAR), and retinopathies in the absence of malignancy (presumed non-paraneoplastic autoimmune retinopathy (npAIR) that have similar clinical and immunological features.
Autoimmune retinopathies (AIR)

ERG is sensitive in detecting the retinal abnormalities, often showing significantly reduced responses early on in the disease course, even while funduscopic appearance is normal.

Assays including Western blot (WB) and immunohistochemistry (IHC) are used for detection of antiretinal antibodies in the diagnosis of AIR.
Cancer associated retinopathy (CAR)

CAR is most commonly associated with small-cell carcinoma of the lung, but it has also been reported in patients with gynecologic cancer, colon cancer and other cancers.

Autoantibodies against recoverin (23-kDa) and α-enolase (46-kDa) are commonly associated with CAR.
Melanoma associated retinopathy (MAR)

Melanoma associated retinopathy (MAR) is a type of paraneoplastic retinopathy in patients with a positive history of malignant melanoma. MAR commonly presents after the melanoma is diagnosed, often at the stage of metastases. It is more common in men than in women.

Patients of classic MAR show ffERG abnormality in the dark-adapted b-wave responses (negative ERG) and demonstrate circulating antibodies reacting with bipolar cells.
Intraocular foreign body (IOFB) Case
57 year-old international male
VA: 20/20 OD and 20/25 OS
Full-field ERG

Right Eye

A

Dark-adapted 0.01

B

Dark-adapted 3.0

C

Dark-adapted 3.0 Oscillatory Potentials

D

Light-adapted 3.0

E

Light-adapted 3.0 Flicker

Left Eye
Ocular siderosis

Ocular siderosis is a complication resulting from a metallic intraocular foreign body (IOFB). Retinal photoreceptors and RPE cells are especially susceptible to siderosis. Particularly, accumulation of intracellular iron in retinal pigment epithelium (RPE) and Müller cells of neurosensory retina leads to retinal degeneration. Electroretinogram (ERG) provides quantitative and objective assessment of retinal dysfunction of the rod and cone systems.
Plaquinil toxicity

Hydroxychloroquine (HCQ) (Plaquinil) is used widely for the treatment of conditions such as systemic lupus erythematosus (SLE) and rheumatoid arthritis. HCQ is toxic to the retina. Clinically, the primary damage is to the outer retina, with secondary disruption to the RPE.

Current screening guideline


Screening Tests:
The primary screening tests are automated visual fields plus spectral-domain optical coherence tomography (SD OCT). These should look beyond the central macula in Asian patients. The multifocal electroretinogram (mfERG) can provide objective corroboration for visual fields, and fundus autofluorescence (FAF) can show damage topographically.
Benefits of mfERG testing in screening Plaquinil toxicity:

- It is an objective test
- Provides functional evaluation
- It is sensitive
  - Detects outer retinal dysfunction
  - Sensitivity can be enhanced by using ring ratio analysis
- Gives a topographic view of deficit across the posterior fundus
- Shows change in both the parafoveal and extramacular regions
- Detects preexisting maculopathy
Initial mfERG screening of a 27 year-old female with Plaquinil therapy for SLE

VA: 20/20 OD, 20/20 OS; Humphrey central 10-2 threshold visual field testing: low reliability; Fundoscopy & OCT: unremarkable OD & OS
3. pERG (pattern ERG)

It is used primarily for functional evaluation of ganglion cells in the central retinal area

Recording setting:

Active electrode: DTL microfiber electrode
Stimuli: checkerboard patterns with spatial and temporal contrast modulation
Patient: no dilation, needs optical correction, requires steady and central fixation
Transient vs. steady-state pERG responses

Transient pERG response

Low reversal rates (e.g. 4 rps) elicit transient responses with discrete positive- and negative-going (P50 and N95) components

The P50 component
is partially driven by ganglion cells, but also has origins distal to the ganglion cells

The N95 component:
reflects ganglion cell activities

Steady-state pERG response
High reversal rates (e.g. 16 rps) elicit steady-state pERG responses
Other objective test of ganglion cell function

PhNR (Photopic Negative Response) is a slow negative component after the b-wave of the cone driven ffERG which has been shown to originate primarily from ganglion cell activities.

PhNR allows simultaneous recording of a- and b-waves of ffERG for evaluation of the outer retinal function.
pERG testing of ganglion cell function in clinical care of glaucoma patients

- Potential role in predicting the progression of ocular hypertension to glaucoma

- Early detection of ganglion cell dysfunction resulting from early glaucoma when visual field defects are minimal
28-year-old female with history of optic nerve hypoplasia  
VA: NLP OD, 20/20 OS
Pattern ERG (pERG)

OD

OS
Pattern VEP (pVEP)

OD

OS

5 μV

0 50 100 150 200 250 300 350 ms
Optic nerve hypoplasia (ONH)

ONH is a congenital anomaly characterized by an underdeveloped optic nerve in one or both eyes.

Most patients with ONH present with vision dysfunctions of various severities ranging from nearly normal to no light perception. Abnormality of visual evoked potential (VEP) is typically observed in ONH. VEP responses are correlated with the severity of visual function. Reduction of N95 component in pERG has been observed in patients with ONH.
4. Visual Evoked Potentials (VEP)

Evaluate the integrity of the primary visual pathway serving the central visual field

Recording setting:
Active electrode: gold disc electrode placed on occipital scalp over the visual cortex
Patient: no dilation, needs optical correction, requires steady and central fixation
Stimuli: checkerboard patterns with spatial and temporal contrast modulation (for pattern VEP) or flash (for flash VEP)
VEP waveforms

Pattern Reversal

Flash

Pattern Onset - Offset
46 year-old female with a suspected MS diagnosis based on cortical lesion found in MRI. Noticed decreased central vision with the right eye affected to a greater degree than the left eye. VA: 20/25 OD and 20/20 OS/Fundus examination was unremarkable for OD & OS.

Interocular pVEP comparison for 1 degree (A) and 0.25 degree (B) checkerboard stimuli. Red and blue curves represent the right and left waveforms respectively.
mfERG

Right Eye

Field view

P1 Response Density

P1 Implicit Time

Left Eye

Field view

P1 Response Density

P1 Implicit Time
Retinal neuronal and axonal abnormalities in MS patients and MS suspects

Multiple sclerosis (MS) is a chronic neurologic disease typically associated with inflammatory activity and development of lesions in localized or diffuse areas of the central nervous system (CNS) including the visual system.

Change of optic nerve axonal integrity is commonly reflected by prolongation of the pVEP implicit time, and also by attenuation of the P100 in a subset of MS patients.

Retinal neuronal abnormalities can involve the outer retina as well as ganglion cells. A subset of MS patients show attenuation of mfERG responses indicating neuronal abnormalities in the outer retina.
A 9 year-old girl presented with complaint of blurry distance vision for 2 years in both eyes. No significant ocular history was reported. Past medical history was significant for platinum blonde hair, and blue irides since birth. Patient’s mother is Indian decent and her father is Caucasian decent.
VA: 20/30 OD, 20/30 OS
Pattern Onset/offset VEP

Right Hemisphere

Left Hemisphere

Right Eye Stimulation

Left Eye Stimulation
Ocular albinism

Albinism is a genetic disorder of melanin deficiency resulting in hypopigmentation. Either the eyes (ocular albinism), or the eyes together with the skin and hair may be affected (oculocutaneous albinism). The lack of melanin has a severe impact on the development of the eye and visual system.

Clinical signs comprise foveal hypoplasia, fundus hypopigmentation, iris transillumination, nystagmus, reduced visual acuity, reduced or absent stereopsis, strabismus, and refractive error. However, many patients show incomplete clinical manifestations and foveal hypoplasia is not a retinal feature restricted to albinism. Pattern onset-offset VEP to detect abnormal decussation pattern at the optic chiasm is of particular diagnostic value for these patients.
5. Electro-OculoGram (EOG)
Evaluate the RPE function under dark and light phases

**Recording setting:**
Standing potential is measured under dark and light adaptation
**Patient:** needs dilation
**Active electrode:** gold disc electrodes placed on lateral and nasal canthi

Responses decrease with dark adaptation (*min. value* → 8-12 minutes)
Responses increase with light adaptation (*max. value* → 6-9 minutes)
**Arden ratio** = light peak/dark trough
54 year-old male
The patient noticed decreased central vision of both eyes for four months. The patient denied any peripheral vision or night vision loss in either eye.
VA: 20/20 OD & 20/20 OS
Best’s disease

Best disease, also known as Best vitelliform macular dystrophy, is a progressive hereditary vitelliform dystrophy characterized by abnormal accumulation of subretinal yellowish deposits in the macular region leading to atrophy of the macula or subretinal neovascularization.

The diagnosis of Best vitelliform macular dystrophy is based on characteristic fundus manifestations and electro-oculogram (EOG) findings.

Functionally, reduction of the light rise in the EOG testing is a distinctive feature in Best’s disease.

- abnormal in affected and carriers
- abnormal even with norm VA or fundus
A 39 year-old male, with a recently identified subfoveal deposits.
The patient is visually asymptomatic for both eyes.
VA: 20/25⁻¹ OD and 20/25⁻¹ OS
Electro-OculoGram (EOG)

Right Eye

Time to Peak = 8.6 min
Arden Ratio = 3.557

Left Eye

Time to Peak = 8.1 min
Arden Ratio = 3.381
Adult-onset foveomacular vitelliform dystrophy (AFVD)

Adult-onset foveomacular vitelliform dystrophy (AFVD) is characterized by subretinal vitelliform macular lesions usually diagnosed at or after the age of 40. The yellow lesions slowly fade over the years, progressing to hyperpigmentation or atrophy.

Compared to typical Best disease, AFVD typically shows normal EOG.
Clinical pearls/approach:

- If can’t determine the cause of decreased VA, order a mfERG, to be followed by a pattern VEP if mfERG is normal.
- Always consider ffERG to evaluate the rod system, especially if there are peripheral VF defects or night vision complaints.
- Changes in mfERG can appear before OCT abnormalities.
- Patient must be able to understand the test (i.e. fixate on the target), and not have significant hyper movement (ocular or body) issues for the mfERG.
Thank You