Optic Nerve and Retinal Imaging Methods

Number: 0344

Aetna considers optic nerve and retinal imaging methods medically necessary for documenting the appearance of the optic nerve head and retina in the following diagnoses/individuals:

- Age-related macular degeneration
- Cystoid macular edema following cataract surgery
- Diabetic retinopathy
- Ethambutol-induced optic neuropathy
- Glaucoma suspects
- Macular edema
- Macular hole
- Persons with glaucoma
- Posterior vitreous detachment
- Pseudotumor cerebri
- Screening and monitoring for chloroquine (Aralen), ethambutol (Myambutol), ezogabine (Potiga), hydroxychloroquine (Plaquenil), ponatinib (Iclusig), and vigabatrin (Sabril) toxicity

Policy History

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Definitions

Additional Information

Clinical Policy Bulletin
Notes
- Vitreomacular traction and vitreomacular adhesion
- Vogt-Koyanagi-Haradas (to quantify subretinal fluid and to follow individuals during treatment)
- Other diseases where the optic nerve head and retina have been affected.

**Note:** Optic nerve imaging for glaucoma more frequently than once per year is considered not medically necessary.

**Note:** Accepted optic nerve and retinal imaging methods include the following:

- Confocal laser scanning ophthalmoscopy
- Nerve fiber layer testing or analysis (confocal laser scanning tomography with polarimetry)
- Optical coherence tomography (OCT)
- Stereophotogrammetry.

Aetna considers optic nerve and retinal imaging methods experimental and investigational as a screening test for the following (not an all-inclusive list):

- Decision on the need for surgery
- Glaucoma and other retinal diseases and for all other indications (e.g., cataracts, dry eye diseases, ocular histoplasmosis, posterior capsule opacification)
- Imaging of the retina as a biomarker for neurodegeneration in frontotemporal degeneration, multiple sclerosis and optic neuritis
- Screening/monitoring persons on fingolimod (Gilenya).

Aetna considers optic nerve and retinal imaging methods experimental and investigational for the following (not an all-inclusive list):

- Evaluation of the neurodegeneration pattern in individuals with intra-cranial tumors
- Evaluation of Parinaud oculoglandular syndrome (cat scratch disease)
- Imaging following intra-ocular lens (IOL) exchange following IOL dislocation.

In addition to annual screening that should begin after 5 years of use (or sooner if there are unusual risk factors), a baseline study of optic nerve and retinal imaging is considered medically necessary before initiation of chloroquine, hydroxychloroquine, or vigabatrin therapy.

See also
CPB 0563 - Retinopathy Telescreening Systems
(../500_599/0563.html)

Background

The appearance of the optic nerve head (the disc) and the nerve fiber layer is evaluated in the diagnosis and follow-up of glaucoma. The standard methods of detecting glaucoma include ophthalmoscopy, tonometry, perimetry, and gonioscopy. These procedures are considered part of the comprehensive ophthalmologic examination. Recently, other methods of measuring the optic disc and the nerve fiber layer have been developed in an attempt to create more accurate and reproducible methods of screening, detecting, and following structural parameters related to glaucoma. These methods include the following:

Confocal Laser Scanning Ophthalmoscopy

Confocal laser scanning ophthalmoscopy, also known as scanning laser ophthalmoscopy (SLO), is a method of examining the eye using confocal laser scanning microscopy (stereoscopic videographic digitized imaging) to make quantitative topographic measurements of the optic nerve.
head and surrounding retina. This may be done with either reflection or fluorescence. Targeted tissues can be viewed in 3-dimensional (3D) high-resolution planes running parallel to the line of sight.

The confocal laser scanning tomographic ophthalmoscope scans layers of the retina to make quantitative measurements of the surface features of the optic nerve head and fundus. It has been used as an alternative to standard ophthalmologic methods of evaluating the optic nerve head and fundus in patients with glaucoma, papilledema, and other disorders affecting the retina. Other terms for confocal laser scanning tomography include: laser scanning topography, confocal scanning laser topography, confocal laser scanning tomography, scanning laser ophthalmoscopy (SLO), and electro-fundus imaging. Types of confocal laser scanning ophthalmoscopes include:

- Heidelberg Laser Tomographic Scanner or Heidelberg Retina Tomograph (HRT) (Heidelberg Engineering, Dossenheim, Germany),
- TopSS Topographic Scanning System (Laser Diagnostic Technologies, San Diego, CA); and the
- Zeiss\textsuperscript{TM} Confocal Laser Scanning Ophthalmoscope. (Zeiss Humphrey Systems, Dublin, CA).

Nerve Fiber Layer Testing or Analysis (Laser Scanning Polarimetry)

Thinning of the nerve fiber layer is associated with glaucomatous damage and has been shown to be correlated with visual field loss. Scanning laser polarimetry, also called confocal scanning laser polarimetry, measures change in the linear polarization (retardation) of light. It uses both a scanning laser ophthalmoscope and a polarimeter (an optical device to measure linear polarization change) to measure the thickness of the nerve fiber layer of the retina. The confocal scanning laser polarimeter is essentially a confocal scanning laser
ophthalmoscope with an additional polarization modulator, a cornea polarization compensator and a polarization detection unit.

The GDx Nerve Fiber Analysis System (Laser Diagnostic Technologies, Inc., San Diego, CA) is a confocal laser scanning ophthalmoscope with an integrated polarimeter. Instead of measuring topography, or height of the retina, like other confocal laser scanners, GDx measures the thickness of the retinal nerve fiber layer and then analyzes the results and compares them to a database of normative values.

The Retinal Thickness Analyzer (RTA) Digital Fundus Imaging (Talia Technology, Inc., Tampa, FL) uses a scanning laser biomicroscope that uses a laser to create a series of slit images of the retina that are digitalized and converted into a topographic map that quantifies retinal thickness.

Optical Coherence Tomography

Optical coherence tomography (OCT) is a noninvasive, transpupillary, retinal imaging technology, which uses near-infrared light to produce high-resolution cross-sectional images. It is suggested for diagnostic use as an alternative to standard excisional biopsy and to guide interventional procedures.

OCT (e.g., Humphrey OCT Scanner (Zeiss Humphrey, Dublin, CA)) has also been used for screening, diagnosis, and management of glaucoma and other retinal diseases. In OCT, low coherence near-infrared light is split into a probe and a reference beam. The probe beam is directed at the retina while the reference beam is sent to a moving reference mirror (AHFMR, 2003). The probe light beam is reflected from tissues according to their distance, thickness, and refractive index, and is then combined with the beam reflected from the moving reference mirror. When the path lengths of the two light beams coincide (known as constructive interference) this
provides a measure of the depth and reflectivity of the tissue that is analogous to an ultrasound A scan at a single point. A computer then corrects for axial eye movement artifacts and constructs a two-dimensional B mode image from successive longitudinal scans in the transverse direction. A map of the tissue is then generated based on the different reflective properties of its components, resulting in a real-time cross-sectional histological view of the tissue.

Barella et al (2013) examined the diagnostic accuracy of machine learning classifiers (MLCs) using retinal nerve fiber layer (RNFL) and optic nerve (ON) parameters obtained with spectral-domain optical coherence tomography (SD-OCT). A total of 57 patients with early-to-moderate POAG and 46 healthy patients were recruited. All 103 patients underwent a complete ophthalmological examination, achromatic standard automated perimetry, and imaging with SD-OCT. Receiver operating characteristic curves were built for RNFL and ON parameters. Ten MLCs were tested. Areas under ROC curves (aROCs) obtained for each SD-OCT parameter and MLC were compared. The mean age was 56.5 ± 8.9 years for healthy individuals and 59.9 ± 9.0 years for glaucoma patients (p = 0.054). Mean deviation values were -1.4 dB for healthy individuals and -4.0 dB for glaucoma patients (p < 0.001).

Spectral domain-OCT parameters with the greatest aROCs were cup/disc area ratio (0.846) and average cup/disc (0.843). Areas under ROC curves obtained with classifiers varied from 0.687 (CTREE) to 0.877 (RAN). The aROC obtained with RAN (0.877) was not significantly different from the aROC obtained with the best single SD-OCT parameter (0.846) (p = 0.542). The authors concluded that MLCs showed good accuracy, but did not improve the sensitivity and specificity of SD-OCT for the diagnosis of glaucoma.

Bidot et al (2013) noted that OCT is used primarily in neuro-ophthalmology to measure thinning of the RNFL in optic neuropathies and to rule out a subtle maculopathy in patients complaining of blurred vision with a "normal" fundoscopic
appearance. Only a few studies address the role of OCT in papilledema secondary to intra-cranial hypertension. Optical coherence tomography has been proposed as a diagnostic tool for mild papilledema, assisting the clinician in differentiating papilledema from optic nerve head drusen (ONHD), and for following the RNFL thickening from papilledema. However, the contribution of OCT in intra-cranial hypertension management is still unclear with the exception of its role in detecting associated maculopathy. Currently, OCT does not replace visual field testing and fundus examination.

In a comparative case-series study, Kulkami et al (2014) evaluated the clinical utility of SD-OCT in differentiating mild papilledema from buried ONHD. A total of 16 eyes of 9 patients with ultrasound-proven buried ONHD, 12 eyes of 6 patients with less than or equal to Frisen grade 2 papilledema owing to idiopathic intra-cranial hypertension were included in this study. Two normal fellow eyes of patients with buried ONHD were included. A raster scan of the ON and analysis of the RNFL thickness was performed on each eye using SD-OCT. Eight eyes underwent enhanced depth imaging SD-OCT. Images were assessed qualitatively and quantitatively to identify differentiating features between buried ONHD and papilledema. Five clinicians trained with a tutorial and masked to the underlying diagnosis independently reviewed the SD-OCT images of each eye to determine the diagnosis. Main outcome measures were differences in RNFL thickness in each quadrant between the 2 groups and diagnostic accuracy of 5 independent clinicians based on the SD-OCT images alone. These investigators found no difference in RNFL thickness between buried ONHD and papilledema in any of the 4 quadrants. Diagnostic accuracy among the readers was low and ranged from 50 % to 64 %. The kappa coefficient of agreement among the readers was 0.35 (95 % confidence interval [CI]: 0.19 to 0.54). The authors concluded that SD-OCT is not clinically reliable in differentiating buried ONHD and mild papilledema.
Stereophotogrammetry

Stereophotogrammetry, (Glaucoma-Scope (OIS, Sacramento, CA)) measures the dimensions of the optic disc in three-dimensional space using stereophotography. Stereophotographs are taken from two camera positions with parallel optical axes. Stereoanalysis of these photographs are used to determine the three-dimensional characteristics of the optic nerve head, and for following glaucomatous change of the optic nerve head over time. Stereoplotters and digital computer processing of scanned images have been used in an attempt to provide more quantitative, objective, and reproducible methods of measuring optic nerve disc changes.

Each of these methods has been used to image the optic nerve head in glaucoma patients. According to available guidelines, these methods may be used for documenting the appearance of the optic nerve head and retina in persons with glaucoma and other retinal diseases. But these devices have not been proven to be of value for screening of asymptomatic persons.

Available methods of optic nerve imaging (e.g., Heidelberg Retinal Tomograph, GDx confocal laser scanning polarimeter, Humphrey OCT Scanner, Glaucoma-Scope) were cleared by the U.S. Food and Drug Administration (FDA) based on a 510 (k) premarket notification due to their “substantial equivalence” to other devices on the market. Thus, the manufacturers were not required to submit to the FDA the evidence that would be required to support a premarket approval application (PMA).

An American Academy of Ophthalmology (AAO)’s Preferred Practice Pattern on Primary Open Angle Glaucoma Suspect (2005) focuses on the management of persons with ocular hypertension or findings suggestive of ocular damage but without established glaucoma. The AAO guidelines define a glaucoma suspect as having one or more of the following characteristics: (i) visual fields suspicious for early
glaucomatous damage; or (ii) intraocular pressure consistently above 21 mm Hg by applanation tonometry; or (iii) appearance of the optic disc or retinal nerve fiber layer that is suggestive of glaucomatous damage. Glaucomatous damage may be suggested by findings such as nerve fiber layer disc hemorrhage, asymmetric appearance of the optic disc or rim between fellow eyes that suggests loss of neural tissue, diffuse or focal narrowing or notching of the disc rim (especially at the inferior or superior poles), or diffuse or localized abnormalities of the retinal nerve fiber layer (especially at the inferior or superior poles). The AAO guidelines conclude that "[c]olor stereophotography or computer-based image analysis of the optic nerve head and retinal nerve fiber layer are the best currently available methods to document optic disc morphology and should be performed."

An AAO Preferred Practice Pattern on Primary Open-Angle Glaucoma (2005), which focuses on management of patients with evidence of glaucomatous damage as manifested by acquired optic nerve or nerve fiber layer abnormalities or typical visual field loss, states that optic nerve head and retinal nerve fiber layer analysis should be performed to document optic nerve head morphology.

Finnish evidence-based guidelines on open-angle glaucoma (Tuulonen et al, 2003) state: “High technology instruments (the Heidelberg retina tomograph, retinal nerve fibre analyser and optical coherence tomography), developed for nerve fibre layer and optic disc imaging and measurements, are not yet ready for routine glaucoma diagnostics. Due to their sensitivity and specificity, some instruments may be used for the follow-up of glaucoma.”

Aetna's position on optic nerve and retinal imaging devices is based on the use of these devices as standard of care for documenting the appearance of the optic nerve head and
retina, in place of retinal drawings or fundus photographs. In addition, optic nerve head imaging methods have been used as a noninvasive alternative to fluorescein angiography and slit-lamp biomicroscopy in assessing the retinal nerve fiber layer, although fluorescein angiography is also a sensitive test to detect leakage of incompetent retinal vessels. Because of the slow rate of progression of glaucoma, repeated optic nerve head imaging is not necessary more frequently than once every year.

Although optic nerve and retinal imaging devices have been used to document the appearance of the optic nerve head and retina, there is a lack of evidence from prospective clinical studies demonstrating that clinical outcomes are improved by incorporating this technology into glaucoma screening. A number of structured evidence reviews have concurred that there is limited evidence of the clinical utility of optic nerve head imaging methods in these situations (AHP, 1996; AHFMR, 1996; Lee, et al., 1996; TEC, 2001; AHFMR, 2003; TEC, 2003; IECS, 2003; AHFMR, 2006). A BlueCross BlueShield Association Technology Evaluation Center (2003) assessment of optic nerve imaging devices (termed RNFL analysis (RNFLA) in the report) in the diagnosis and management of glaucoma and concluded that they do not meet TEC criteria. Using data from the Ocular Hypertension Treatment Study, the assessment found that RNFLA would not be useful in deciding whether to initiate early treatment of glaucoma or change treatment regimens, as the vast majority of patients with abnormal RNFLA test results would not be expected to go on to develop glaucoma. The assessment concluded: "The scientific evidence is insufficient to permit conclusions concerning the effects of RNFLA for the diagnosis or management of POAG [primary open angle glaucoma]; therefore, it is not possible to determine whether the procedure improves net health outcome."
The TEC assessment (BCBSA, 2003) focused on the best available evidence for retinal nerve fiber layer analysis. Although there are many published studies of RNFLA, almost all of them are cross-sectional studies that evaluate the sensitivity and specificity of RNFA by comparing RNFA measurements of normal persons to persons with glaucoma or ocular hypertension. The assessment explains, however, that cross-sectional studies do not follow persons over time and are not designed to assess the relationship between a test result and subsequent development of disease. Studies that follow persons over time (longitudinal studies) are necessary to evaluate the ability of a test to predict which persons will develop disease and need treatment from those that will not develop disease.

Another limitation of published cross-sectional studies of RNFA is that they only compare normal persons to persons with glaucoma or ocular hypertension. Because these studies do not include persons with other ocular conditions, they do not provide information on the ability of RNFLA to distinguish patients with glaucoma or ocular hypertension from other ocular conditions. The subjects of these cross-sectional studies do not accurately reflect the spectrum of conditions that one would expect to see in the usual clinical practice setting (BCBSA, 2001). The external validity of these studies could be strengthened by selecting study subjects from a representative sample of the population of patients suspected of having the disease.

Cross-sectional studies cannot determine whether abnormalities that are detected by RNFA but not by any other standard method are early disease that might benefit from treatment (BCBSA, 2003). The most reliable evidence for assessing the clinical impact of RNFLA would be direct evidence from randomized trials comparing the impact on visual field defects of treatment initiated by different thresholds.
of RNFLA test results. As no such studies are available, technology assessments of RNFLA have had to rely on indirect evidence.

The most reliable indirect evidence to estimate diagnostic performance of RNFLA comes from longitudinal studies with a clinical population of patients suspected of having glaucoma, using follow-up for visual loss as a reference standard (BCBSA, 2003). The key issue in the early detection of glaucoma is how well test results predict the future development of visual loss. Thus, it is critical that the diagnostic performance of an early test be measured against follow-up for visual changes as the reference standard, in a longitudinal study.

The TEC assessment noted that no longitudinal study has yet appeared that selected subjects for whom RNFLA results are most likely to influence management decisions, that is, persons who have normal intraocular pressure and who do not meet conventional diagnostic criteria for glaucoma (BCBSA, 2003). The report identified only two published longitudinal studies that present data showing whether RNFLA changes precede development of visual field defects, on an individual patient basis. The most useful longitudinal evidence for the indication concerning detection of glaucoma comes from a subset of the Ocular Hypertension Treatment Study (Kamal et al, 2000). In this study, 21 patients progressed from ocular hypertension to glaucoma (converters) and 164 patients did not progress (nonconverters). Of the 21 converters, 13 had abnormal RNFLA results and in 11 of these the tests were positive prior to development of visual field defects (average lead time was 5.4 months). Of the 164 nonconverters, 47 had abnormal RNFLA results. Using this study's results to estimate diagnostic performance, the positive predictive value of RNFLA, which is the most relevant index for early detection of glaucoma, is 22% (13/60), so that 78% of persons with signs of progression of glaucoma on RNFLA would not go on to develop visual field changes within the 6-year follow-up.
period of this study. The TEC assessment concluded that "a positive predictive value at this level does not appear to be sufficiently high for use in deciding to initiate early treatment or to change treatment regimens" (BCBSA, 2003). In addition, this study only included persons with ocular hypertension, and may not accurately reflect the performance of RNFLA in a cohort of glaucoma suspects without ocular hypertension. Given that the predictive values are dependent on the prevalence of the target condition in the population, the predictive value RNFLA in a population that includes individuals without ocular hypertension is likely to be even lower than the estimate from this study of ocular hypertensives, given that persons with ocular hypertension, an established glaucoma risk factor, are more likely to develop glaucoma than persons without ocular hypertension.

Chauhan et al (2001) reported on the results of a longitudinal study of RNFLA and visual field testing (perimetry) in patients with glaucoma who were followed for a median of 5.5 years. In 29 percent of cases, progression was detected by both perimetry and RNFLA; when progression was detected by both tests, it was just as common for perimetry to detect it first as it is for RNFLA to detect it first. Although progression was observed by RNFLA alone in 40% of patients, it is unclear from this study how often such patients experience visual progression (true positives versus false positives). The TEC assessment (2003) emphasizes that the key issue in the early detection of glaucoma is how well test results predict the future development of visual loss, as loss of vision is an endpoint that patients experience in terms of quality of life and ability to function.

A report on glaucoma screening prepared for the UK National Screening Committee (Spry and Sparrow, 2003) stated that methods of assessing optic nerve head appearance using images acquired by digital scanning laser instrumentation are quantitative and rapid to perform. The report concluded, however, that “[t]o date, however, scant longitudinal
information is available on individuals who exhibit apparent structural abnormalities with these techniques but no glaucomatous loss of visual function." The ability to utilize optic nerve head appearance in assessing glaucoma risk is limited by the fact that "considerable overlap exists between the distribution of relevant parameters found in patients with glaucoma and normal individuals."

The AAO and the American Glaucoma Society prepared a work group report to provide a "rationale for [insurance] coverage" of optic nerve head imaging (Remey 2002; AAO, 2003; AAO/AGS, 2003). The AAO/AGS Work Group statement (2003) on the clinical utility of optic nerve scanning devices in screening focused exclusively on comparisons with automated perimetry or photography used alone. However, the standard methods of detecting and monitoring glaucoma include ophthalmoscopy (to inspect the optic disk and nerve fiber layer), drawings of the optic nerve head and stereoscopic disc photographs (to document the status of the optic nerve head), tonometry (to measure intraocular pressure), perimetry (to measure visual fields), and gonioscopy (to measure the angle of the anterior chamber).

None of the studies cited in the AAO/AGS Work Group statement (2003) represented prospective clinical outcome studies. The need for prospective clinical outcome studies comparing optic nerve scanning devices to standard methods of evaluation is especially critical given that there is no established gold standard comparison test for predicting the risk of glaucoma development prior to the onset of visual field defects. Although RNFLA devices have been in commercial use for more than a decade, the quality of evidence supporting their use remains limited, and the best available evidence indicates that the ability of RNFLA to predict progression to glaucoma is limited.
The monograph from the AAO/AGS Work Group (2003) commented on the limited quality of evidence supporting the use of optic nerve scanning devices. The monograph stated: "In clinical practice, many patients now are tested with more advanced visual field techniques designed to detect glaucoma earlier. Yet these variations on visual field testing have not required rigorous TEC assessment to determine if they are useful. Clinical experience, cross-sectional studies, and a few longitudinal cohort studies have shown that they are useful improvements in our ability to detect glaucoma and/or progression. The case is similar to RNFLA, where clinicians and researchers have determined that this newer technology surpasses or equals the current clinical assessment of the optic nerve and nerve fiber layer."

Assessment of the evidence supporting the use of optic nerve scanning devices is required because these techniques have been presented as a new technology rather than as an incremental advance over an existing technology such as ophthalmoscopy or other established methods of evaluating the retina and optic nerve head.

The Center for Medicare and Medicaid Services (CMS) has not established a national coverage position on optic nerve imaging devices; CMS has left coverage of optic nerve imaging devices to the discretion of local Medicare carriers.

Optical coherence tomography (OCT) (e.g., Humphrey OCT Scanner (Zeiss Humphrey Systems, Dublin, CA) has also been used for screening, diagnosis, and management of glaucoma and other retinal diseases. Optical coherence tomography (OCT) is a relatively new non-invasive imaging modality that uses reflected light in a manner analogous to the use of sound waves in ultrasonography to create high-resolution (10 micron) cross-sectional images of the vitreoretinal interface, retina and subretinal space, analogous
to histological sections seen through a light microscope. OCT also gives quantitative information about the peripapillary retinal nerve fiber layer thickness.

The Alberta Heritage Foundation for Medical Research (2003) assessed the value of optical coherence tomography (OCT) in the diagnosis of retinal diseases. It stated that “OCT appears promising for diagnosing patients with cystoid macular edema and moderate glaucoma.”

OCT can determine the presence of cystoid macular edema (CME) by visualizing the fluid-filled spaces in the retina. The amount of CME can be monitored over time by quantifying the area of cystoid spaces on a cross-sectional image through the macula. Studies have reported OCT to be comparable to fluorescein angiography in the evaluation of CME. However, fluorescein angiography may be a more sensitive study for leakage of incompetent retinal vessels (Roth, 2001).

OCT, scanning laser ophthalmoscope, and confocal laser tomography may also be useful in macular holes, in establishing the status of the vitreomacular interface and distinguishing full-thickness holes from lamellar holes and macular cystic lesions (Valero and Atebara, 2001). According to the American Academy of Ophthalmology (2003), “[i]n most cases the diagnosis [of macular hole] is made by clinical evaluation. Optical coherence tomography provides information on the anatomy of the macular hole and may aid in the diagnosis and staging.”

OCT has also been used in a variety of other retinal diseases. In diabetic retinopathy, OCT has been used to evaluate retinal swelling and serous retinal detachment. OCT has been able to demonstrate a moderate correlation between retinal thickness and best-corrected visual acuity, and it has been able to demonstrate three basic structural changes of the retina from diabetic retinal edema, i.e., retinal swelling, cystoid edema, and serous retinal detachment (Khan and Lam,
There is, however, a lack of prospective clinical studies demonstrating that clinical outcomes are improved by incorporating OCT into screening of persons with diabetes for retinopathy. Current guidelines from the American Diabetes Association do not incorporate OCT into diabetic retinopathy screening algorithms. Optical coherence tomography can be useful for quantifying retinal thickness, monitoring partial resolution of macular edema, and identifying vitreomacular traction in selected patients with diabetic macular edema caused by a taut posterior hyaloid face (AAO, 2003).

The AAO (2003) states that this test might be considered in diabetic retinopathy patients unresponsive to laser treatment for macular edema for whom the ophthalmologist is considering vitrectomy with removal of the posterior hyaloid face.

OCT has also been used to determine the presence of subretinal fluid and in documenting the degree of retinal thickening in age-related macular degeneration (AMD). This study has shown decreased reflectance at the level of the rod-cone layer indicating that atrophy is present in this layer (Maturi, 2005). According to guidelines from the AAO (2003), “the value of this test in evaluating and treating AMD remains unknown.”

OCT is also being investigated in evaluating choroidal neovascularization (CNV). Well-defined and diffuse CNV have characteristic appearances on OCT, as do subretinal hemorrhages and retinal detachments. Despite the many advantages of OCT, fluorescein angiography remains the imaging modality of choice in the management of CNV. Currently, OCT cannot replace fluorescein angiography in the management of CNV (Wu, 2005).

Alberta Heritage Foundation for Medical Research (2003) stated that “while OCT appears promising for diagnosing patients with cystoid macular edema and moderate glaucoma, it still has a number of practical and theoretical limitations. Its
ability to detect any other of the myriad retinal diseases is unknown. It is clear that OCT in its current state of development is ineffective as a stand alone diagnostic test, but a study has not yet been conducted to assess its value as part of a serial testing strategy. The position of OCT in the scheme of testing needs to be established so that an optimal testing strategy can be identified that is both highly accurate and clinically practical. Randomized controlled trials are also needed to establish the clinical impact of OCT diagnostic imaging on the management, treatment options, and outcomes of patients”. The AHFMR reasoned that “[w]hile OCT appears promising as a tool for diagnosing retinal disease, there are many questions relating to its clinical utility that are not likely to be answered by a cross-sectional study. Longitudinal studies are needed to determine the temporal relationship between OCT RNFL thickness measurements and visual field defects, and to identify any changes in RNFL thickness that could predict future visual deterioration."

A more recent assessment by the Alberta Heritage Foundation for Medical Research (AHFMR, 2006) summarized the current status of ophthalmic scanning devices in glaucoma. The assessment concluded: "B ased on results from three systematic reviews, the value of CSLO [confocal scanning laser ophthalmoscopy] and SLP [scanning laser polarimetry] as diagnostic tools for the detection of early glaucoma remains unclear, although the HRT and GDx methods hold considerable promise for the detection of glaucoma-associated structural change. The available evidence showed that HRT and GDx are able to differentiate between normal individuals and those with glaucoma. However, whether these devices have the sensitivity and specificity to detect the early onset of glaucoma, before the onset of visual field loss, remains to be determined. The available CSLO and SLP devices still await prospective validation against accepted measures of structural and functional change in terms of whether the use of a test results improves patient outcomes and is helpful in patient management and obviates unnecessary treatment."
The United Kingdom National Health Service National Coordinating Centre for Healthcare Technology Assessment (NCCHTA) conducted primary research and a comprehensive systemic review of the ophthalmic scanning devices in glaucoma screening (Kwartz et al, 2005). The assessment concluded "[t]he findings of the glaucoma imaging study suggest that, although optic nerve head tomography and scanning laser polarimetry provide good-quality digital images, their data may contribute little to a patient's clinical diagnosis but would add significantly to the cost of their assessment."

Hickman (2007) reviewed the last 10 years of progress in the imaging of the optic nerve with a particular focus on applications to multiple sclerosis (MS). Development of magnetic resonance imaging (MRI) of the optic nerve has lagged behind imaging of other parts of the CNS. These limitations are due to technical challenges related to the small size and mobility of the optic nerves and artefacts caused by surrounding cerebrospinal fluid, orbital fat, and air-bone interfaces. Nonetheless, the last 10 years has seen significant progress with regard to detecting optic nerve atrophy following optic neuritis, the use of fat- and CSF-suppressed high resolution imaging, the ability to measure magnetization transfer ratio and diffusivity in the optic nerve, and the emergence of SPIR-FLAIR for increasing sensitivity to inflammatory demyelination. Remaining challenges include further reduction of movement artifacts, testing ultra-high field MRI systems and dedicated surface coils, and developing automated segmentation techniques to improve the reproducibility of quantitative measurements. Finally, the role of OCT as a marker of retinal damage needs to be clarified further through correlations with MRI, clinical, and electrophysiologic data.

In a report on optic nerve head and retinal nerve fiber layer analysis by the American Academy of Ophthalmology, Lin and associates (2007) evaluated the current published literature on the use of optic nerve head (ONH) and retinal nerve fiber layer
(RNFL) measurement devices in diagnosing open-angle glaucoma and detecting progression. The authors concluded that ONH and RNFL imaging devices provide quantitative information for the clinician. Based on studies that have compared the various available technologies directly, there is no single imaging device that outperforms the others in distinguishing patients with glaucoma from controls.

In a report on laser scanning imaging for macular disease by the American Academy of Ophthalmology, McDonald and colleagues (2007) examined if laser scanning imaging is a sensitive and specific tool for detecting macular disease when compared with the current standard technique of slit-lamp biomicroscopy or stereoscopic fundus photography. Literature searches conducted in December 2004 and in August 2006 retrieved 370 citations. The Retina Panel members selected 65 articles for the panel methodologist to review and rate according to the strength of the evidence. Of the 65 articles reviewed, 6 provided level I evidence, 9 provided level II evidence, and 50 provided level III evidence. A level I rating was assigned to studies that reported an independent masked comparison of an appropriate spectrum of consecutive patients, all of whom had undergone both the diagnostic test and the reference standard. A level II rating was assigned to an independent masked or objective comparison; a study performed in a set of non-consecutive patients or confined to a narrow spectrum of study individuals (or both), all of whom had undergone both the diagnostic test and the reference standard; or an independent masked comparison of an appropriate spectrum, but the reference standard had not been applied to all study patients. A level III rating was assigned when the reference standard was unobjective, unmasked, or not independent; positive and negative tests were verified using separate reference standards; or the study was performed in an inappropriate spectrum of patients. There are high-level studies of the use of laser scanning imaging to quantify macular thickness and, thereby, macular edema in patients with diabetic retinopathy and to examine
patients with a macular hole. There is lower-quality evidence on the use of laser scanning imaging for other diseases of the macula. There is insufficient evidence to compare the different instruments. The authors concluded that there is level I evidence that laser scanning imaging can accurately and reliably quantify macular thickness in patients with diabetic retinopathy. There is level I evidence that OCT provides additional information to clinical examination when used in patients with a macular hole. Laser scanning imaging provides important information that is helpful in patient management by allowing objective serial quantitative measurements. Although further studies are needed to develop an optimal testing strategy using these imaging modalities, laser scanning imaging is a sensitive, specific, reproducible tool for diagnosing macular edema and, therefore, is likely to be useful for managing diseases that result in macular edema.

In a prospective, controlled, single-center study, Ibrahim and colleagues (2010) examined the applicability of tear meniscus height (TMH) measurement using Visante OCT in the diagnosis of dry eye disease. A total of 24 right eyes of 24 patients (6 males, 18 females; mean age of 63.14 +/- 13.4 years) with definite dry eye according to the Japanese dry eye diagnostic criteria and 27 right eyes of 27 control subjects (12 males, 15 females; mean age of 56.04 +/- 14.22 years) were recruited. All subjects underwent slit-lamp TMH measurement, OCT upper and lower TMH measurements, tear film breakup time (BUT) measurements, vital stainings, and Schirmer test. The results were compared between the 2 groups by Mann-Whitney test. Main outcome measures were the correlation between the clinical findings of slit-lamp TMH, strip meniscometry examination, tear functions, vital staining scores, and the OCT upper and lower TMH parameters were tested by Spearman's correlation test. Receiver operating characteristic (ROC) curve technique was used to evaluate the sensitivity, specificity and cut-off values of OCT TMH examination in the diagnosis of dry eye. The OCT upper and
lower TMH values, slit-lamp TMH, strip meniscometry, tear film BUT, and vital staining scores were significantly lower in the dry eye patients compared with controls (p < 0.001). A significant correlation between the OCT upper and lower TMH measurements as well as slit-lamp TMH, strip meniscometry, tear functions, vital staining scores, and the Schirmer test was found. The ROC curve technique analysis of the OCT lower TMH showed that, when the cut-off value was set at less than 0.30 mm, the sensitivity and specificity of the testing were 67 % and 81 %, respectively. The authors concluded that Visante OCT is a quick, non-invasive method for assessing the TMH, with acceptable sensitivity, specificity, and repeatability, and may have potential applications for the diagnosis and evaluation of dry eye disease. They also stated that further studies on OCT TMH should determine age- and gender-specific cut-off values, sensitivity, specificity of the test in the diagnosis of dry eye disease when performed alone or in conjunction with other dry eye tests.

In a prospective, cross-sectional study, Jeoung et al (2010) evaluated quantitatively the degree of diffuse retinal nerve fiber layer (RNFL) atrophy using Stratus optical OCT. A total of 102 eyes of 102 patients with diffuse RNFL atrophy and 102 healthy eyes of 102 age-matched subjects were enrolled in the Diffuse Atrophy Imaging Study. Two experienced observers graded RNFL photographs of diffuse RNFL atrophy eyes using a previously reported standardized protocol with a 4-level grading system. Readings were taken from the superior and inferior RNFL areas. The OCT-measured RNFL thickness parameters were compared among normal eyes and diffuse atrophy subgroups. Area under the ROCs (AROCs) was calculated for various OCT RNFL parameters. Main outcome measures were average and segmental (4 quadrants and 12 clock-hours) OCT-measured RNFL thicknesses and AROCs for various OCT parameters. For superior and inferior RNFL areas, diffuse atrophy grading by 2 observers agreed in 82.5 % and 83.3 % of cases, respectively, with a substantial agreement (kappa value = 0.760 [p < 0.001] and 0.777 [p <
Significant differences were observed in RNFL thickness among normal and all diffuse atrophy subgroups, especially in the 7 and 11 o’clock sectors (p < 0.0001). The OCT RNFL thickness measurements decreased with increasing severity of RNFL damage. The 7 and 11 o’clock sectors showed the highest AROCs for discrimination of mild RNFL atrophy from normal eyes (0.972 and 0.979, respectively). The authors concluded that the OCT RNFL thickness parameters showed excellent quantitative correlation with the degree of diffuse RNFL atrophy. These findings suggested that Stratus OCT may serve as a useful adjunct in accurately and objectively assessing the degree of diffuse RNFL atrophy. Moreover, the authors noted that further studies are needed to assess the diagnostic ability of the Stratus OCT with its internal normative database to detect diffuse RNFL atrophy.

Cettomai and associates (2010) performed clinical and OCT examinations on 240 patients attending a neurology clinic. Using OCT 5th percentile to define abnormal RNFL thickness, these investigators compared eyes classified by neurologists as having optic atrophy to RNFL thickness, and afferent pupillary defect (APD) to RNFL thickness ratios of eye pairs. Mean RNFL thickness was less in eyes classified by neurologists as having optic atrophy (79.4 +/- 21 μm; n = 63) versus those without (97.0 +/- 15 μm; n = 417; p < 0.001, t-test) and in eyes with an APD (84.1 +/- 16 μm; n = 44) than without an APD (95.8 +/- 17 μm; n = 436; p < 0.001).

Physicians’ diagnostic accuracy for detecting pallor in eyes with an abnormal RNFL thickness was 79% (sensitivity = 0.56; specificity = 0.82). Accuracy for detecting a retinal APD in patients with mean RNFL ratio (affected eye to unaffected eye) less than 0.90 was 73% (sensitivity = 0.30; specificity = 0.86). Ability to detect visual pathway injury via assessment of atrophy and APD differed between neurologists. The authors concluded that OCT reveals RNFL abnormality in many patients in whom eyes are not classified by neurologic examiners as having optic atrophy. They stated that further
study is needed to define the role of OCT measures in the context of examinations for optic atrophy and APD by neuroophthalmologists.

In a retrospective chart review, Ota et al (2010) studied morphologic changes of serous retinal detachment (SRD) and hyper-reflective dots, which have been reported to be precursors of hard exudates, detectable in SRD using OCT to assess whether or not the OCT findings are correlated with the subfoveal deposition of hard exudates in patients with diabetic macular edema (DME) accompanied by SRD. A total of 28 eyes of 19 patients with DME accompanied by SRD were included in this analysis. These researchers imaged SRD and the hyper-reflective dots in SRD using spectral domain OCT (SD-OCT). The number and distribution of the hyper-reflective dots in SRD were evaluated before the initial treatment at the authors' hospital for DME accompanied by SRD. Based on a difference in the SD-OCT findings, the study eyes were divided into 2 groups: (i) eyes with a few dots and (ii) those with many dots. These investigators studied the clinical course of these 2 groups to assess whether or not the findings of SRD and hyper-reflective dots on the SD-OCT images were correlated with deposition of hard exudates in the subfoveal space during follow-up. Main outcome measures were correlation of the SD-OCT findings of SRD and hyper-reflective dots with deposition of hard exudates in the subfoveal space of patients with DME accompanied by SRD. Subfoveal deposition of hard exudates was seen in 11 of the 28 eyes at the final examination. Before initial treatment at the authors' hospital, 14 eyes had a few hyper-reflective dots SRD and 14 eyes had many hyper-reflective dots. Whereas no deposition of hard exudates in the subfoveal space was seen in the former eyes, it was seen in 11 of the latter 14 eyes (p < 0.0001). In addition, using SD-OCT, these researchers found discontinuity of the outer border of detached neurosensory retina in 9 of the 28 eyes. Of these 9 eyes, 1 was in the group with few hyper-reflective dots and 8 were in the group with
many hyperreflective dots ($p = 0.0046$). The authors concluded that in patients with DME accompanied by SRD, SD-OCT revealed that hyper-reflective dots may be associated with the subfoveal deposition of hard exudates during follow-up. Furthermore, they noted that further prospective studies with a larger sample size are needed to elucidate these details of SRD and the reason(s) why foveal deposition of hard exudates occurs in eyes with DME.

Marmor et al (2011) stated that the AAO recommendations for screening of chloroquine (CQ) and hydroxychloroquine (HCQ) retinopathy were published in 2002, but improved screening tools and new knowledge about the prevalence of toxicity have appeared in the ensuing years. No treatment exists as yet for this disorder, so it is imperative that patients and their physicians be aware of the best practices for minimizing toxic damage. New data have shown that the risk of toxicity increases sharply toward 1% after 5 to 7 years of use, or a cumulative dose of 1000 g of HCQ. The risk increases further with continued use of the drug. The prior recommendation emphasized dosing by weight. However, most patients are routinely given 400 mg of HCQ daily (or 250 mg CQ). This dose is now considered acceptable, except for individuals of short stature, for whom the dose should be determined on the basis of ideal body weight to avoid overdosage. A baseline examination is advised for patients starting these drugs to serve as a reference point and to rule out maculopathy, which might be a contraindication to their use. Annual screening should begin after 5 years (or sooner if there are unusual risk factors). Newer objective tests, such as multi-focal electroretinogram (mfERG), spectral domain-OCT (SD-OCT), and fundus auto-fluorescence (FAF), can be more sensitive than visual fields. It is now recommended that along with 10-2 automated fields, at least one of these procedures be used for routine screening where available. When fields are performed independently, even the most subtle 10-2 field changes should be taken seriously and are an indication for evaluation by objective testing. Because mfERG testing is an objective test
that evaluates function, it may be used in place of visual fields. Amsler grid testing is no longer recommended. Fundus examinations are advised for documentation, but visible bull's-eye maculopathy is a late change, and the goal of screening is to recognize toxicity at an earlier stage. Patients should be aware of the risk of toxicity and the rationale for screening (to detect early changes and minimize visual loss, not necessarily to prevent it). The drugs should be stopped if possible when toxicity is recognized or strongly suspected, but this is a decision to be made in conjunction with patients and their medical physicians.

Scanning Computerized Ophthalmic Diagnostic Imaging (OCT) for Patients with Multiple Sclerosis

Saidha et al (2015) examined if atrophy of specific retinal layers and brain substructures are associated over time, in order to further validate the utility of OCT as an indicator of neuronal tissue damage in patients with MS. Cirrus high-definition OCT (including automated macular segmentation) was performed in 107 MS patients biannually (median follow-up of 46 months). Three-Tesla magnetic resonance imaging brain scans (including brain-substructure volumetrics) were performed annually. Individual-specific rates of change in retinal and brain measures (estimated with linear regression) were correlated, adjusting for age, sex, disease duration, and optic neuritis (ON) history. Rates of ganglion cell + inner plexiform layer (GCIP) and whole-brain ($r = 0.45; p < 0.001$), gray matter ($GM; r = 0.37; p < 0.001$), white matter ($WM; r = 0.28; p = 0.007$), and thalamic ($r = 0.38; p < 0.001$) atrophy were associated. GCIP and whole-brain (as well as GM and WM) atrophy rates were more strongly associated in progressive MS ($r = 0.67; p < 0.001$) than relapsing-remitting MS (RRMS; $r = 0.33; p = 0.007$). However, correlation between rates of GCIP and whole-brain (and additionally GM and WM) atrophy in RRMS increased incrementally with step-wise refinement to exclude ON effects; excluding eyes and then patients (to account for a phenotype effect), the
correlation increased to 0.45 and 0.60, respectively, consistent with effect modification. In RRMS, lesion accumulation rate was associated with GCIP ($r = -0.30; p = 0.02$) and inner nuclear layer ($r = -0.25; p = 0.04$) atrophy rates. The authors concluded that over time GCIP atrophy appeared to mirror whole-brain, and particularly GM, atrophy, especially in progressive MS, thereby reflecting underlying disease progression. They stated that these findings supported OCT for clinical monitoring and as an outcome in investigative trials.

This study had several major drawbacks: (i) because the majority of included patients had RRMS, more accurate characterization of the associations between retinal and brain atrophy by MS subtype is needed, requiring the enrollment of greater numbers of progressive MS patients, of both the secondary-progressive (SPMS) and primary-progressive MS (PPMS) subtypes. Larger and longer longitudinal studies would help address these limitations and establish the validity of these findings, (ii) the cohort included in this study is a heterogeneous cohort, both in terms of clinical characteristics and disease-modifying therapies. Thus, it is necessary to exercise caution when extrapolating results from the current study for the purpose of designing future clinical trials, which would more likely be structured toward recruitment of homogenous MS cohorts, (iii) virtually all RRMS patients in the current study cohort were on disease-modifying therapies, and, as a result, it is likely that these results under-estimated true rates of retinal atrophy; retinal rates of atrophy might be hypothetically higher in untreated MS populations. Furthermore, there was variability in terms of the classes of disease-modifying therapies patients were receiving not only at baseline, but also for the duration of study follow-up. This mix in disease-modifying therapies throughout the study duration precluded assessment of the effects of MS treatments on these results. Future investigations including more homogenously treated MS subgroups would allow for
more accurate assessment of the effects of disease modifying therapies on the relationships between rates of retinal and brain atrophy. Such information would be of great utility and assist in guiding future clinical trial designs that incorporate OCT as an outcome measure.

The authors stated that the results of this study indicated that GCIP and brain atrophy in MS closely parallel each other over time, suggesting a role for OCT as a valuable biomarker not only for the purpose of tracking patients clinically, but also in clinical trials for objective investigation of putative neuroprotective and/or neuro-restorative therapies. Although GCIP and brain atrophy are associated in RRMS (especially after refinement for ON history; a factor that should be borne in mind in the interpretation of GCIP measures longitudinally), the associations between GCIP and brain atrophy in progressive MS appeared to be exceptional. These researchers noted that although their findings require independent verification, and should be replicated across larger MS cohorts.

Behbehani and colleagues (2017) stated that OCT with retinal segmentation analysis is used in assessing axonal loss and neuro-degeneration in MS by in-vivo imaging, delineation and quantification of retinal layers. There is evidence of deep retinal involvement in MS beyond the inner retinal layers. The ultra-structural retinal changes in MS in different MS phenotypes can reflect differences in the pathophysiologic mechanisms. There is limited data on the pattern of deeper retinal layer involvement in progressive MS (PMS) versus relapsing remitting MS (RRMS). In a cross-sectional study, these researchers compared the OCT segmentation analysis in patients with RRMS and PMS. A total of 113 MS patients (226 eyes) (29 PMS, 84 RRMS) and 38 healthy controls (72 eyes) were included in this trial; SD-OCT using the macular cube acquisition protocol and segmentation of the retinal layers for quantifying the thicknesses of the retinal layers were carried out. Segmentation of the retinal layers was performed
utilizing Orion software for quantifying the thicknesses of individual retinal layers. The retinal nerve finer layer (RNFL) \( (p = 0.023) \), the ganglion-cell/inner plexiform layer (GCIPL) \( (p = 0.006) \) and the outer plexiform layer (OPL) \( (p = 0.033) \) were significantly thinner in PMS compared to RRMS. There was significant negative correlation between the outer nuclear layer (ONL) and EDSS \( (r = -0.554, p = 0.02) \) in PMS patients. In RRMS patients with prior optic neuritis, the GCIPL correlated negatively \( (r = -0.317; p = 0.046) \), while the photoreceptor layer (PR) correlated positively with EDSS \( (r = 0.478; p = 0.003) \). The authors concluded that patients with PMS exhibited more atrophy of both the inner and outer retinal layers than RRMS. The ONL in PMS and the GCIPL and PR in RRMS can serve as potential surrogate of disease burden and progression (EDSS). The specific retinal layer predilection and its correlation with disability may reflect different pathophysiologic mechanisms and various stages of progression in MS. Moreover, they stated that longitudinal studies using OCT segmentation analysis can better define the significance and the dynamics of the changes in retinal layers in different MS phenotypes and how they relate to disease progression.

The authors noted that this study was limited by its cross-sectional design and its relatively small sample size. Most of the PMS cohort were composed of secondary progressive MS (SPMS) with under-representation of primary progressive MS (PPMS) due to rarity of the latter phenotype. In addition, these investigators combined the primary and secondary progressive cohort as a single group, which may have influenced their findings. However, there is increasing evidence of the phenotypic similarities between PPMS and SPMS and, common genetic susceptibility to MS are similar between and measures of global brain tissue damage and magnetization transfer imaging. Despite that, the OCT findings in this study in the progressive cohort did not strictly apply to PPMS, which
had its unique aspects of indolent course with less frequent visual pathway involvement and thus relative preservation of the inner retinal layers.

Scanning Computerized Ophthalmic Diagnostic Imaging (OCT) for Patients with Vogt-Koyanagi-Haradas

Sakata et al (2014) noted that Vogt-Koyanagi-Harada (VKH) disease is a systemic autoimmune disorder that affects pigmented tissues of the body, with its most dire manifestations affecting the eyes. This review focused on the diagnostic criteria of VKH disease, including some information on history, epidemiology, appropriate clinical and classification criteria, etiopathogenesis, treatment and outcomes. Expert review of most relevant literature from the disease's first description to 2013 and correlation with the experience in the care of VKH disease patients at a tertiary Uveitis Service in Brazil gathered over the past 40 years. The clinical manifestations and ancillary assessment of VKH disease have been summarized in the Revised Diagnostic Criteria proposed in 2001 in a manner that allows systematic diagnosis of both acute and chronic patients. It includes the early acute uveitic manifestations (bilateral diffuse choroiditis with bullous serous retinal detachment and optic disk hyperemia), the late ocular manifestations (diffuse fundus depigmentation, nummular depigmented scars, retinal pigment epithelium clumping and/or migration, recurrent or chronic anterior uveitis), besides the extra-ocular manifestations (neurological/auditory and integumentary). There are 2 exclusion criteria, i.e., absence of previous ocular penetrating trauma or surgery and any other ocular disease that could be confounded with VKH disease. HLA-DRB1*0405 plays an important role in pathogenesis, rendering carriers more susceptible to disease. The primary ocular pathological feature is a diffuse thickening of the uveal tract in the acute phase. Later on, there may be a compromise of choriocapillaris, retinal pigment epithelium and outer retina, mostly due to an "upstream" effect, with clinical correlates as fundus derangements. Functional tests (ERG
and visual field testing) as well as imaging modalities (retinography, fluorescein/indocyanine green angiography (FA/ICGA), OCT and ultrasound) play an important role in diagnosis, severity grading as well as disease monitoring. Though high-dose systemic corticosteroids remain gold-standard therapy, refractory cases may need other agents (cyclosporine A, anti-metabolites and biological agents). In spite of good visual outcomes in the majority of patients, knowledge about disease progression even after the acute phase and its impact on visual function warrant further investigation.

Komuku et al (2015) stated that VKH disease and central serous chorio-retinopathy (CSCR) develop serous retinal detachment; however, the treatment of each disease is totally different. Steroids treat VKH but worsen CSC; therefore, it is important to distinguish these diseases. These investigators reported a case with CSCR, which was diagnosed by en face OCT imaging during the course of VKH disease. A 50-year old man was referred with blurring of vision in his right eye. Fundus examination showed bilateral optic disc swelling and macular fluid in the right eye; OCT showed thick choroid, and en face OCT images depicted blurry choroid without clear delineation of choroidal vessels. Combined with angiography findings, this patient was diagnosed with VKH disease and treated with steroids. Promptly, fundus abnormalities resolved with the reduction of the choroidal thickness and the choroidal vessels became visible on the en face images. During the tapering of the steroid, serous macular detachment in the right eye recurred several times. Steroid treatment was effective at first; however, at the 4th appearance of sub-macular fluid, the patient did not respond. At that time, the choroidal vessels on the en face OCT images were clear, which significantly differed from the images at the time of recurrence of VKH. Angiography also suggested CSCR-like leakage. The tapering of the steroids was effective in resolving the fluid. Secondary CSCR may develop in the eye with VKH after steroid
treatment. The authors concluded that en face OCT observation of the choroid may be helpful to distinguish each condition.

Tsuboi et al (2015) characterized patients with (VKH disease with choroidal folds (CFs) and determine how the foveal choroidal thickness changes after initial treatment using high-penetration OCT (HP-OCT). In this retrospective observational study, these researchers analyzed 42 eyes of 21 patients with new-onset VKH disease to determine the demographic and clinical differences between patients with and without CFs; 24 eyes (57.1 %) of 13 patients with VKH disease had CFs. The mean age (p = 0.0009) of patients with CFs was significantly higher than that of those without CFs (49.1 versus 39.4 years, respectively). The frequency of disc swelling (p = 0.0001) was significantly higher in eyes with CFs than in those without CFs (95.8 % versus 38.9 %). The choroidal thickness at the first visit (p = 0.0011) was significantly greater in eyes with CFs than in those without CFs (794 ± 144 μm versus 649 ± 113 μm). The choroid 6 months after the initial treatment (p = 0.0118) was significantly thinner in eyes with CFs than in those without CFs (270 ± 92 μm versus 340 ± 80 μm). The frequency of sunset glow fundus at 6 months (p = 0.0334) in eyes with CFs was significantly higher than in those without CFs (62.5 % versus 27.8 %). The authors concluded that the development of CFs in patients with VKH disease was significantly correlated with age, disc swelling, and choroidal thickness. The eyes with CFs frequently developed a sunset glow fundus. They stated that these findings suggested that patients with CFs might have severe and longstanding inflammation of the choroidal tissues.

Lee et al (2016) investigated morphologic features of choroid in the choroidal thickening diseases, including CSCR, polypoidal choroidal vasculopathy (PCV), and VKH, by a novel tomographic classification system of the choroid. This cross-sectional study involved 30 patients with active CSC, 30 patients with active PCV, and 27 patients with active VKH, and
30 normal controls. Utilizing enhanced depth imaging OCT (EDI-OCT), these researchers classified the morphology of the choroid into 5 categories: (i) Standard (S), (ii) Dilated outer layer and attenuated inner layer (DA), (iii) Darkened (D), (iv) Marbled (M), and (v) Pauci-vascular (PV) types. Additional tomographic characteristics of the choroid such as choroidal vascular dilation, convolution, scleral invisibility, and choroidal hyper- or hypo-thickening were identified as well. The distribution of 5 choroidal tomographic morphology and additional tomographic characteristics in each group were analyzed. The DA type was observed in the CSCR group more frequently than in the normal control group (53.3 % versus 3.3 %, p < 0.001). Additional tomographic characteristics, such as choroidal vascular dilation (76.7 %), and choroidal hyper-thickening (36.7 %), were more prevalent in the CSCR group than in the control group. The PCV group showed higher prevalence of DA type (33.3 % versus 3.3 %, p = 0.006) than the control group. The VKH group showed a significantly higher frequency of the D type (63.0 %), convolution (40.7 %), and scleral invisibility (70.4 %) than controls (0 % for all 3 findings). The authors concluded that CSCR and PCV shared common morphologic characteristics of choroid, including dilated outer vascular layer and focally attenuated innermost layer. Dense hypo-reflectivity and convolution of choroid were the specific tomographic markers for acute VKH. They stated that a new tomographic classification system of choroid may provide discrimination ability and insight into major pachychoroidopathies.

Hashizume et al (2016) determined the clinical significance of retinal pigment epithelium (RPE) undulations in the acute stage of VKH disease. Retinal pigment epithelium undulations were detected and classified into 3 grades: Grade 1, slight; Grade 2, moderate; and Grade 3, severe undulations, in the EDI-OCT images. The relationship between the clinical characteristics and the presence of RPE undulations was investigated. Among the 61 eyes of 31 patients with VKH
disease, 40 eyes had some degree of RPE undulations (Grade 1 = 12, Grade 2 = 15, and Grade 3 = 13). The patients with RPE undulations in both eyes were significantly older at the onset (p = 0.0002). The eyes with RPE undulations were more likely to develop posterior recurrences (p = 0.032) and have worse vision at 12 months (p = 0.043). Multiple regression analysis revealed that RPE undulations were an independent predictor of posterior recurrences (p = 0.009) and poor visual outcomes (p = 0.035). The authors concluded that retinal pigment epithelium undulations detected by EDI-OCT were relatively frequent occurrences at the acute stage of VKH, and their presence is a predictor of posterior recurrences and poor visual outcomes after high-dose steroid therapy.

Bae et al (2017) examined if the inflammatory composition of sub-retinal fluid in VKH serous retinal detachments is predictive of photoreceptor injury, and quantified photoreceptor recovery, following resolution of these detachments. Optical density (OD) measurements of spectral-domain OCT (SD-OCT) scans were used to derive the fibrinous index, a measure of the inflammatory composition of sub-retinal fluid. In order to assess photoreceptor status, photoreceptor outer segment (PROS) volume was measured from SD-OCT scans. The fibrinous index of sub-retinal fluid in VKH uveitis was strongly correlated with the PROS volume following resolution of sub-retinal fluid (r = -0.70, p = 0.006). Following fluid resolution, both PROS volume (p < 0.0001) and visual acuity (p = 0.0015) improved. The authors concluded that the fibrinous index of sub-retinal fluid during the acute stage of VKH can predict photoreceptor status following resolution of sub-retinal fluid; PROS volume is a useful measure of photoreceptor recovery in VKH.

Aggarwal et al (2018) reported the imaging characteristics of acute VKH disease using OCT angiography (OCTA). In this prospective study, patients with acute VKH (n = 10; mean age of 30.5 ± 13.43 years) underwent multi-modal imaging (baseline and follow-up) using fundus photography, FA, ICGA,
OCT, and OCTA. The OCTA images were analyzed to assess the retino-choroidal vasculature and compared with other imaging techniques. During the active stage, all eyes showed multiple foci of choriocapillaris flow void that correlated with ICGA. These foci decreased in number and size after initiation of therapy. In 1 patient, flow void areas re-appeared after cessation of therapy without any detectable change on ICGA. This patient soon developed clinical recurrence requiring re-initiation of immunosuppression. The authors concluded that OCTA allowed high-resolution imaging of inflammatory foci suggestive of choriocapillaris hypo-perfusion in acute VKH disease non-invasively. They stated that OCTA may be very helpful in the follow-up of such patients.

Liu et al (2016) examined the diagnostic value of OCT for the detection of acute VKH disease. Clinical charts and OCT images were retrospectively reviewed for patients consecutively diagnosed with acute VKH, sub-acute VKH, multifocal CSCR, and posterior scleritis. All patients underwent OCT, fundus photography, and FA before treatment. The characteristics of OCT and FA were analyzed and recorded. The study included 80 eyes with acute VKH, 32 eyes with sub-acute VKH, 33 eyes with CSCR, and 13 eyes with posterior scleritis. The most common OCT features of VKH disease were hyper-reflective dots (70/80; 88 %), sub-retinal membranous structures (64/80; 80 %), retinal detachment higher than 450 μm (63/80; 79 %), and retinal pigment epithelium (RPE) folds (44/80; 55 %). For the detection of VKH disease, sensitivity and specificity were for sub-retinal membranous structures 80 % and 95.6 %, respectively, for high retinal detachment 78.8 % and 76.1 %, respectively, for sub-retinal hyper-reflective dots, 87.5 % and 60.9 %, respectively, and for RPE folds 55 % and 80.4 % respectively. Sub-retinal membranous structures showed the highest positive predictive value (97.3 %) and negative predictive value (65.7 %) of all OCT assessed features. The authors concluded that OCT-related morphological signs had a relatively high predictive value for the diagnosis of acute VKH.
Chee et al (2017) compared EDI-OCT and swept source OCT (SS-OCT) in assessment of VKH disease. All consecutive VKH patients seen at Singapore National Eye Centre during 2012 to 2013 were imaged using both modalities. Sub-foveal choroidal thickness (SFCT) was measured by one masked trained observer. A total of 137 pairs of scans were obtained from 48 patients. SFCT was more likely to be measurable on SS-OCT than EDI-OCT (112, 81.8 %; 84, 61.3 %; p < 0.001 Fisher's Exact test). There was good inter-OCT correlation of SFCT when both scans were measureable (mean of the difference in SFCT ± 2 standard deviations (SD) of -14.5 ± 21.0 μm). The authors concluded that SS-OCT images were superior to EDI-OCT; but the SFCT measurements are comparable when both are readable.

Furthermore, the American Academy of Ophthalmology (2016) states that “The diagnosis of VKH syndrome is essentially clinical; exudative retinal detachment during the acute disease and sunset glow fundus during the chronic phase are highly specific to this entity. In patients presenting without extra-ocular changes, FA, ICG angiography, OCT, FAF imaging, lumbar puncture, and ultrasonography may be useful confirmatory tests. During the acute uveitic stage, FA typically reveals numerous punctate hyper-fluorescent foci at the level of the RPE in the early stage of the study followed by pooling of dye in the sub-retinal space in areas of neurosensory detachment. The vast majority of patients show disc leakage, but CME and retinal vascular leakage are uncommon. In the convalescent and chronic recurrent stages, focal RPE loss and atrophy produce multiple hyper-fluorescent window defects without progressive staining … OCT may be useful in the diagnosis and monitoring of serous macular detachments, CME, and choroidal neovascular membranes. More recently, the combined use of FAF imaging and SD-OCT offers a non-invasive assessment of RPE and outer retina changes in patients with chronic VKH syndrome that may not be apparent on clinical examination".
Frontotemporal Degeneration

Kim and colleagues (2017) noted that whereas Alzheimer disease (AD) is associated with inner retina thinning visualized by SD-OCT, these researchers sought to determine if the retina has a distinguishing biomarker for frontotemporal degeneration (FTD). Using a cross-sectional design, these investigators examined retinal structure in 38 consecutively enrolled patients with FTD and 44 controls using a standard SD-OCT protocol. Retinal layers were segmented with the Iowa Reference Algorithm. Subgroups of highly predictive molecular pathology (tauopathy, TAR DNA-binding protein 43, unknown) were determined by clinical criteria, genetic markers, and a CSF biomarker (total tau: β-amyloid) to exclude presumed AD. These researchers excluded eyes with poor image quality or confounding diseases; SD-OCT measures of patients (n = 46 eyes) and controls (n = 69 eyes) were compared using a generalized linear model accounting for inter-eye correlation, and correlations between retinal layer thicknesses and Mini-Mental State Examination (MMSE) were evaluated. Adjusting for age, sex, and race, patients with FTD had a thinner outer retina than controls (132 versus 142 μm, p = 0.004). Patients with FTD also had a thinner outer nuclear layer (ONL) (88.5 versus 97.9 μm, p = 0.003) and ellipsoid zone (EZ) (14.5 versus 15.1 μm, p = 0.009) than controls, but had similar thicknesses for inner retinal layers. The outer retina thickness of patients correlated with MMSE (Spearman r = 0.44, p = 0.03). The highly predictive tauopathy subgroup (n = 31 eyes) also had a thinner ONL (88.7 versus 97.4 μm, p = 0.01) and EZ (14.4 versus 15.1 μm, p = 0.01) than controls. The authors concluded that FTD was associated with outer retina thinning, and this thinning correlated with disease severity.

The authors stated that one drawback of this study was the different demographics of controls and patients. While all patients were recruited consecutively, differences reflected the different populations of FTD versus controls recruited during a
routine eye examination. Another drawback of these findings was the limited number of patients in the non-tauopathy subgroups; this must be considered before generalizing the results to all patients with FTD. These investigators stated that the findings of this study suggested that measurements of retinal thickness have the potential to serve as biomarkers for FTD and may relate to disease severity; future work should focus on direct comparison of AD patients with FTD patients and comparison of the different subgroups of FTD using similar methods and longitudinal studies with autopsy confirmation.

Diagnosis of Optic Neuritis

In a retrospective, observational study, Xu and colleagues (2019) examined the sensitivity of OCT in detecting prior unilateral optic neuritis. Patients who presented from January 1, 2014, to January 6, 2017, with unilateral optic neuritis and OCT available at least 3 months after the attack were enrolled in this trial. These investigators compared OCT RNFL and GCIPL thicknesses between affected and unaffected contralateral eyes. They excluded patients with concomitant glaucoma or other optic neuropathies. Based on analysis of normal controls, thinning was considered significant if RNFL was at least 9 µm or GCIPL was at least 6 µm less in the affected eye compared to the unaffected eye. A total of 51 patients (18 male and 33 female) were included in the study; RNFL and GCIPL thicknesses were significantly lower in eyes with optic neuritis compared to unaffected eyes (p < 0.001); RNFL was thinner by greater than or equal to 9 µm in 73 % of optic neuritis eyes compared to the unaffected eye; GCIPL was thinner by greater than or equal to 6 µm in 96 % of optic neuritis eyes, which was more sensitive than using RNFL (p < 0.001). When using a threshold less than or equal to 1st percentile of age-matched controls, sensitivities were 37 % for RNFL and 76 % for GCIPL, each of which was lower than those calculated using the inter-eye difference as the threshold (p < 0.01). The authors concluded that these findings
supported the use of OCT in the diagnosis of prior optic neuritis, especially in those with unilateral presentation. There were no patients who had optic neuritis with complaints of vision loss who did not have thinning of the GCIPL on OCT. These researchers stated that although larger prospective studies are needed to confirm the optimal criteria for identifying pathologic thinning of the inner retina by OCT, it is a highly sensitive method of detecting a history of unilateral optic neuritis. This study provided Class III evidence that OCT accurately identified patients with prior unilateral optic neuritis.

The authors stated that this study had several drawbacks. Because this patient cohort consisted of unilateral optic neuritis, these findings were not directly applicable to patients with bilateral optic neuritis or patients with prior episodes of optic neuritis in the concomitant eye. This study excluded any patients with optic nerve pathology in the fellow eye. In patients with bilateral optic neuritis or any other optic neuropathy in the fellow eye, the 1st percentile threshold may be a more sensitive method than the inter-eye difference threshold for detecting optic neuritis, given that inter-eye difference decreases with any bilateral process. Furthermore, depending on the provider's preference or patient's schedule, not all unilateral chronic optic neuritis patients seen during the time period of the study had OCT data (3/54 patients or 5.6 % were excluded due to this). Thus, this could have introduced sampling bias in this retrospective, observational study. The follow-up period for OCT was variable and was as short as 3 months. This could have contributed to the decreased sensitivity in RNFL because continued thinning is expected for at least 6 months after an initial optic neuritis. Nonetheless, these investigators found similar sensitivities when they examined a subset of patients who had follow-up OCT images beyond 6 months and, subsequently, the sensitivities were valid in this cohort. Another drawback of the study was that patients with optic neuritis had a variety of causes, including MS, neuromyelitis optica spectrum disorder (NMOSD), and idiopathic. The cause of optic neuritis can influence the
expected degree of RNFL and GCIPL thinning. However, even after excluding patients with myelin oligodendrocyte glycoprotein (MOG)-IgG and aquaporin-4 (AQP4)-IgG-NMOSD associated optic neuritis, the sensitivity using the proposed 99th percentile cut-offs for inter-eye variability was still 70% and 96% for RNFL and GCIPL, respectively; therefore, OCT remained sensitive for detecting prior optic neuritis for typical demyelinating optic neuritis patients. Lastly, the control group had a higher percentage of male participants than this cohort of optic neuritis. However, male and female participants had the same inter-eye RNFL or GCIPL difference in both the control group and the cohort of patients with optic neuritis (unpublished data). Although traumatic brain injury (TBI) could be a potential confounder in OCT measurements, the control cohort excluded any veterans with TBI. Also, no difference between the 1st-season OCT measurements of the football players and track team players was found in the healthy controls.

In an editorial that accompanied the afore-mentioned study, Saidha and Naismith (2019) states that “The current study is an excellent start, but more work is required before fully recommending OCT as a routine tool for diagnosing ON and subclinical optic neuropathy. Larger studies should be performed within specific disease states such as MS, with subset analyses to evaluate patients at older age or many years from their suspected demyelinating event. Longitudinal studies can help clarify whether inter-eye differences change during the course of disease. The identification of inter-eye asymmetry in an individual patient may be an uncertain basis upon which to conclude that there is definitive evidence of prior ON, especially if asymmetry in both measures are incongruent (e.g., fulfilled by RNFL but not GCIPL). Despite the limitations noted, and the need for further, larger, longitudinal studies, the results of this study are promising. Potentially, OCT could fulfill multiple roles towards diagnosis, prognosis, and treatment monitoring in ON, MS, and related disorders”.

proprietary
Evaluation and Screening for Ethambutol Toxicity

The American Academy of Ophthalmology’s guideline on “Drug-related adverse effects of clinical importance to the ophthalmologist” (Fraunfelder, 2014) stated that “Ethambutol optic neuropathy is usually retrobulbar and bilateral, though sometimes asymmetric. Ethambutol toxicity may affect only the small caliber papillo-macular bundle axons, which are hard to visualize, and optic atrophy will not develop for months after the fibers are lost. This means objective findings on the fundus exam are frequently unrecognized. Optic neuropathy may occur, on average, at 2 to 5 months after starting therapy. The earliest ophthalmologic findings in toxic optic neuropathy from ethambutol may be loss of visual acuity, color vision loss or central scotomas. Ethambutol also has an affinity for the optic chiasm with bi-temporal visual field defects manifesting with toxicity … Consider optical coherence tomography or contrast sensitivity testing as these tests could pick up early ethambutol toxicity not detected with the baseline examination. Optical coherence tomography (OCT) may be the future for following toxic optic neuropathies as subtle retinal nerve fiber layer (NFL) swellings can be visualized with the acute insult and NFL thinning can be visualized from chronic toxicity”.

Furthermore, the Royal College of Ophthalmologists’ RCOphth statement on ethambutol toxicity (2017) stated that “Ethambutol is an effective antibiotic used to treat tuberculosis but optic neuropathy is a potentially serious side effect of the drug, thought to be due to zinc chelation causing mitochondrial dysfunction. Ethambutol toxicity in adults is rare, occurring in less than 2% of patients on the standard dosage of 15 mg/kg/day, but impaired renal function and smoking may increase the risk. Onset of optic neuropathy is typically 2 to 5 months after starting therapy, but may occur within days. Symptoms can be highly variable and may initially be unilateral. Loss of visual acuity, color vision impairment and central/paracentral scotomata may occur; bi-temporal field defects have also been reported due to an affinity of
ethambutol for the chiasm. Although optic atrophy will subsequently develop, signs may be absent in early stages of toxicity, but visual evoked potentials and optical coherence tomography show promise in detecting subclinical optic neuropathy”.

In a review on “Ethambutol optic neuropathy”, Chamberlain and colleagues (2017) provided a summary of the epidemiology, clinical findings, management and outcomes of ethambutol-induced optic neuropathy (EON). Ethambutol-induced optic neuropathy is a well-known, potentially irreversible, blinding but largely preventable disease. Clinicians should be aware of the importance of patient and physician education as well as timely and appropriate screening. Two of the largest epidemiologic studies investigating EON to-date showed the prevalence of EON in all patients taking ethambutol to be between 0.7 and 1.29 %, a value consistent with previous reports of patients taking the doses recommended by the World Health Organization (WHO). Several studies evaluated the utility of OCT in screening for EON. These showed decreased RNFL thickness in patients with clinically significant EON, but mixed results in their ability to detect such changes in patients taking ethambutol without visual symptoms. The authors concluded that ethambutol-induced optic neuropathy is a well-known and devastating complication of ethambutol therapy. It may occur in approximately 1 % of patients taking ethambutol at the WHO recommended doses, although the risk increases substantially with increased dose. All patients on ethambutol should receive regular screening by an ophthalmologist including formal visual field testing. Visual evoked potentials and OCT may be helpful for EON screening, but more research is needed to clarify their clinical usefulness. Patients who develop signs or symptoms of EON should be referred to the ethambutol-prescribing physician immediately for discontinuation or a reduction in ethambutol dosing.

Evaluation of the Neurodegeneration Pattern in
Individuals with Intra-Cranial Tumors

Banc and colleagues (2018) noted that OCT is a non-invasive, high-resolution imaging technique that was suggested to be a powerful biomarker of neurodegeneration. These researchers examined the pattern of retinal OCT changes in patients with visual pathway tumors. A prospective clinical study was conducted and patients with single cerebral tumors with potential of compression on the visual pathway were included. Patients with multiple and/or metastatic tumors were excluded. Each patient underwent a neurosurgical and ophthalmologic evaluation, cranial-cerebral MRI, and ocular OCT in both eyes. The OCT parameters included circumpapillary RNFL thickness (average and sector thickness) and retinal thickness in the macular area (average and sector thickness). A total of 50 patients were examined clinically and by MRI, and 18 patients were excluded; 32 patients were eligible for the study and completed the retinal OCT; 18 patients had tumors with compressive potential on the optic chiasm, 11 patients had tumors close to the optic radiations, and 3 patients had tumors in the occipital lobe. A specific pattern of OCT changes was found for each site. Regional parameters of both optic nerve and macula were altered. The authors concluded that retinal OCT is a promising tool for the in-vivo assessment of the neurodegeneration pattern in patients with intra-cranial tumors. They stated that the evaluation of single intra-cranial tumors with compressive potential on the visual pathway is a good candidate for the study of neurodegeneration.

Evaluation of Parinaud Oculoglandular Syndrome (Cat Scratch Disease)

Perez and colleagues (2010) noted that cat scratch disease (CSD) is the main clinical presentation of Bartonella henselae infection. However, ocular manifestations of bartonellosis occur in about 5 to 10% of the patients, mainly presenting as neuroretinitis, choroiditis or oculoglandular syndrome of
Parinaud. The authors described 2 patients with documented B. henselae infection and typical ocular compromise. Both patients were treated and had a favorable visual outcome.

An UpToDate review on “Microbiology, epidemiology, clinical manifestations, and diagnosis of cat scratch disease” (Spach and Kaplan, 2019) states that “Parinaud oculoglandular syndrome is an atypical form of CSD, which is reported in 2 to 8 % of patients with CSD. Parinaud oculoglandular syndrome is characterized by tender regional lymphadenopathy of the preauricular, submandibular, or cervical lymph nodes associated with infection of the conjunctiva, eyelid, or adjacent skin surface. Usual complaints include unilateral red eye, foreign body sensation, and excessive watering of the eyes. Discharge may be serous or purulent and copious in some patients. The inoculation of the organism occurs via a cat bite or lick near (or in) the eye, as well as by self-inoculation from another site ... Some patients develop a stellate macular exudate (known as a "macular star"). Macular stars are due to vascular leakage from the optic nerve head, and can be seen on fluorescein angiography or optical coherence tomography angiography. Patients with B. henselae-induced neuroretinitis may not develop a macular star until 1 to 4 weeks after initial presentation, and the exudate may persist for months, despite resolution of the neuroretinitis”. However, there is no mentioning of OCT in the “Summary and Recommendations” of this review.

Monitoring of Plaquenil (Hydroxychloroquine) Toxicity

In a retrospective, observational cohort study, Browning (2013) determined the impact of the revised American Academy of Ophthalmology (AAO) guidelines on screening for hydroxychloroquine retinopathy. The setting was a private practice of 29 doctors; study population entailed a total of 183 patients for follow-up and 36 patients for baseline screening. Review of charts, 10-2 visual fields (VFs), multi-focal electroretinograms (mfERG), and spectral-domain optical
coherence tomography (SD-OCT) images before and after the revised guidelines. Main outcome measure was rates of use of ancillary tests and clinical intervention, costs of screening, follow-up schedules, and comparative sensitivity of tests. New hydroxychloroquine toxicity was found in 2 of 183 returning patients (1.1%). Dosing above 6.5 mg/kg/day was found in 28 of 219 patients (12.8%), an under-estimate because patient height, weight, and daily dose were not determined in 77 (35.1%), 84 (38.4%), and 59 (26.9%), respectively. In 10 of the 28 (35.7%), the dose was reduced, in 2 (7.1%) hydroxychloroquine was stopped, but in 16 (57.1%) no action was taken. The cost of screening rose 40%/patient after the revised guidelines. Fundus autofluorescence (FAF) imaging was not used. No toxicity was detected by adding mfERG or SD-OCT. In no case was a 5-year period free of follow-up recommended after baseline screening in a low-risk patient. The author concluded that detection of toxic daily dosing was a cost-effective way to reduce hydroxychloroquine toxicity, but height, weight, and daily dose were commonly not checked.

The revised guidelines, emphasizing mfERG, SD-OCT, or FAF, raised screening cost without improving case detection. The recommended 5-year screening-free interval for low-risk patients after baseline examination was ignored.

In a retrospective, observational, case-series study, Leung et al (2015) reported rapid onset of retinal toxicity in a series of patients followed on high-dose (1,000 mg daily) hydroxychloroquine during an oncologic clinical trial studying hydroxychloroquine with erlotinib for non-small cell lung cancer (NSCLC). Ophthalmic surveillance was performed on patients in a multi-center clinical trial testing high-dose (1,000 mg daily) hydroxychloroquine for advanced NSCLC. The Food & Drug Administration (FDA)-recommended screening protocol included only visual acuity testing, dilated fundus examination, Amsler grid testing, and color vision testing. In patients seen at Stanford, additional sensitive screening procedures were added at the discretion of the retinal physician: high-resolution SD-OCT, FAF imaging, Humphrey visual field (HVF) testing,
and mfERG. Out of the 7 patients having exposure of at least 6 months, 2 developed retinal toxicity (at 11 and 17 months of exposure). Damage was identified by OCT imaging, mfERG testing, and, in 1 case, visual field testing. Fundus autofluorescence imaging remained normal. Neither patient had symptomatic visual acuity loss. The authors concluded that these cases showed that high doses of hydroxychloroquine could initiate the development of retinal toxicity within 1 to 2 years. Although synergy with erlotinib is theoretically possible, there are no prior reports of erlotinib-associated retinal toxicity despite over a decade of use in oncology. These results also suggested that sensitive retinal screening tests should be added to ongoing and future clinical trials involving high-dose hydroxychloroquine to improve safety monitoring and preservation of vision.

In a case-series study, Latasiewicz et al (2017) raised awareness of the emerging issue of serious retinal damage caused by the prolonged use of hydroxychloroquine (HCQ) and the importance of adequate and appropriate monitoring of visual function during treatment. This was a small retrospective case series of 3 patients on long-term HCQ who developed serious symptomatic retinal toxicity confirmed on imaging and functional testing. All 3 patients were treated with HCQ for over 15 years; 2 for rheumatoid arthritis (RA), and the 3rd for systemic lupus erythematosus (SLE). All 3 patients had macular involvement varying in severity confirmed with characteristic features on imaging and functional testing (OCT, autofluorescence (AF) and Humphrey 10-2 visual fields). The authors concluded that HCQ is widely used to treat autoimmune conditions with a proven survival benefit in patients with SLE. However, long-term use can be associated with irreversible retinal toxicity. These cases highlighted that HCQ, like chloroquine, could also cause visual loss in susceptible individuals. These researchers stated that early detection of pre-symptomatic retinal changes by the
introduction of appropriate screening and monitoring is mandatory to limit the extent of irreversible visual loss due to HCQ retinal toxicity.

Kowalski et al (2018) reported the findings of 2 patients with dermatological conditions who developed retinal toxicity after treatment with HCQ that exceeded dosing recommendations. There was no treatment for HCQ retinal toxicity and associated visual loss, so appropriate monitoring is imperative. All members of a patient's multi-disciplinary team should be aware of the ocular risks of HCQ, the importance of dosing within recommended guidelines and appropriate monitoring in reducing the risk of visual loss.

Furthermore, an UpToDate review on “Antimalarial drugs in the treatment of rheumatic disease” (Wallace, 2020) states that “We advise assessment of ocular health within 1 year of starting long-term antimalarial drug therapy. The baseline examination should include a fundus examination of the macula to rule out any underlying disease that may interfere with the interpretation of screening tests. The frequency of subsequent screening during the first 5 years of treatment may be individualized based upon assessment of risk. We prefer annual screening exams for all patients, but the AAO has suggested that for patients with a normal baseline exam who do not have major risk factors for toxic retinopathy, follow-up examinations may be deferred until there have been 5 years of exposure. Major risk factors for toxic retinopathy include a daily dose of HCQ greater than 5 mg/kg real body weight or a daily dose of chloroquine greater than 2.3 mg/kg real body weight, antimalarial use for greater than 5 years, the presence of renal disease, concomitant tamoxifen use, and/or the presence of macular disease. Patients should be alert for any change in visual acuity and should seek medical attention promptly if any visual loss is noted. Antimalarials should be discontinued immediately if there is any suspicion of retinopathy.”
Screening and Monitoring of Ethambutol (Myambutol) Toxicity

Menon et al (2009) evaluated various visual parameters for early detection of ethambutol toxicity. This was a prospective study of 104 eyes of 52 patients being treated with ethambutol in the Directly Observed Treatment Strategy Centre (Dr R P Centre for Ophthalmic Sciences, New Delhi, India). Visual acuity (VA), visual fields, visual evoked responses (VER), stereo-acuity and retinal nerve fiber layer (RNFL) thickness on optical coherence tomography (OCT) were assessed. Examinations were done before the start of therapy, after 1 and 2 months of treatment, and 1 month after stopping ethambutol. No visual functional defect was noted at baseline. On follow-up, VA, color vision, contrast sensitivity, fundus and stereo-acuity were not affected in any patient. Visual field defects developed in 7.69 % (8/104) of the eyes. Pattern-VER showed an increased mean latency of the P(100) wave after 1 and 2 months of therapy (p < 0.001 for both) with 14.42 % (15/104) of eyes showing more than 10 ms increase in latency. On OCT, significant loss of mean temporal RNFL thickness was detected in 2.88 % (3/104) of eyes individually. Overall, 19.23 % (20/104) of the studied eyes showed sub-clinical toxicity. Reversal of this observed toxicity on pattern-VER and visual fields was observed in 80 % of eyes after 1 month of stoppage of ethambutol; however, mean VER latency remained delayed (p = 0.002). The authors concluded that pattern-VER and visual field examinations were sensitive tests to detect early toxicity. Together with OCT, they may help to identify patients who are likely to develop clinical toxicity.

Gumus and Oner (2015) examined the effect of anti-tubercular treatment on RNFL thickness and the efficiency of OCT on early diagnosis of optic neuropathy. A total of 20 patients diagnosed with either pulmonary or extra-pulmonary tuberculosis that were treated with anti-tubercular treatment (isoniazid (INH), rifampicin, ethambutol (ETM), and pyrazinamide) were enrolled in the study. RNFL thicknesses
of the patients were measured via OCT, at baseline (before starting anti-tubercular treatment) and after the 2-month treatment period. Standard ophthalmologic examinations were also performed. Compared to baseline values, after the 2-month treatment period, thinning was detected in the right eye's average and superior quadrant RNFLs ($p = 0.024$ and $p = 0.006$ respectively) and in the left eye's average, superior quadrant, and inferior quadrant RNFLs ($p = 0.001$, $p = 0.008$, $p < 0.001$, respectively). The authors reported that patients receiving INH and ETM, which were the basic medicines of anti-tubercular treatment, experienced thinning in RNFL after the 2-month treatment period. These researchers stated that patients receiving these drugs can be followed via OCT in terms of reduction in RNFL thicknesses for early diagnosis of INH and ETM toxicity.

Kim and Park (2016) noted that tuberculosis in developed countries is on the rise, and the main treatment ethambutol is known to induce ocular toxicity. However, to-date, there are unknown tests or protocols for detecting sub-clinical ethambutol-induced ocular toxicity, which is important as early detection is related to symptom reversibility. These researchers defined ethambutol-induced ocular toxicity as statistically significant change of visual function that was induced by ethambutol. They identified a visual function test for the early detection of sub-clinical ethambutol-induced ocular toxicity. Furthermore, these investigators examined the continuity or reversibility of early sub-clinical changes that were observed during the visual function tests after stopping ethambutol treatment. The age range of 31 patients was from 13 to 72 years. The range of dosage was 15 to 19 mg/kg/day. The average period of dosage was 5 months. These researchers performed a VA test, visual field test, color vision test, contrast sensitivity test, fundus examination, RNFL OCT per month and pattern visual evoked potential test (pattern VEP) every 2 months before and during ethambutol treatment in 62 eyes of 31 patients. Among these patients, selected 21 patients were re-examined by these tests at the 3, 6 and 12
months after stopping ethambutol treatment. These investigators compared the test results from the last follow-up during ethambutol treatment and after ethambutol stoppage with those obtained before ethambutol treatment (baseline). RNFL OCT showed that average RNFL thickness increased 5 months after ethambutol treatment ($p = 0.032$), and pattern VEP showed that P100 latency was delayed in 2 and 4 months after ethambutol treatment ($p = 0.001; p < 0.001$, respectively). These early changes observed on RNFL OCT and pattern VEP progressed 6 months after ethambutol stoppage in 21 patients. Twelve months after ethambutol stoppage, these early changes returned to baseline levels. During the study, no changes in VA, color vision, fundus, contrast sensitivity or visual field were observed. The authors concluded that pattern VEP and RNFL OCT were suitable tests for the early detection of sub-clinical ethambutol-induced ocular toxicity. These tests should be performed until 12 months after ethambutol stoppage.

Pavan Taffner et al (2018) evaluated, through OCT, alterations in retinal thickness, secondary to use of ethambutol in the treatment of patients with tuberculosis, in addition to studying the use of simpler semiological tools, such as Amsler and Ishihara, in the screening of these cases. A total of 30 patients with ethambutol were recruited from the reference service of tuberculosis treatment at the Federal University of Espírito Santo from May 2015 to July 2016. After clinical history, the following parameters were analyzed: best corrected visual acuity (BCVA), biomicroscopy, tonometry, photo-motor reflex testing, Ishihara test, Amsler's grid test, color digital retinography and OCT with CIRRUS HD-OCT (Humphrey-Zeiss) every 2 months during treatment with ethambutol. They were divided into 2 groups according to the treatment: standard group, 2 months of ethambutol; extended group, 9 to 12 months of ethambutol. There was a significant reduction in OCT thickness between the pre- and post-treatment times in 10 eyes of the extended group, mean reduction of 7.8 microns and in 7 eyes of the standard group,
with an average of 5.57 microns. During the study, a significant reduction of retinal thickness was observed in both groups at 2 months of treatment, and the delta percentage was higher in those patients who presented reduction of VA and/or change in the Ishihara test. The authors concluded that there was a significant reduction in the thickness of the nerve fiber layer by OCT in the patients studied, being more pronounced in those submitted to the extended treatment regimen. This reduction was observed 2 months after the start of therapy, and was more significant in the cases that presented changes in the Ishihara test. Moreover, these researchers stated that further studies are needed to elucidate the risk factors and intervals required between OCT screening tests for early signs of ethambutol optic neuropathy.

Jin et al (2019) longitudinally evaluated the visual function and structure of patients taking ethambutol by various modalities and identified useful tests for detection of sub-clinical ethambutol-induced optic toxicity. This retrospective study enrolled 84 patients with newly diagnosed tuberculosis treated with ethambutol; BCVA, color vision, contrast sensitivity, fundus and RNFL photography, automated visual field (VF) test, and OCT were performed: prior to starting; every month during administration, and 1 month after stoppage. These researchers longitudinally compared visual function and structure with the baseline and identified the occurrence of sub-clinical toxicity. BCVA, color vision, and contrast sensitivity showed no change from the baseline. Mean temporal RNFL thickness was significantly increased at 6 months (p = 0.014). Sub-clinical toxicity was found in 22 eyes of 14 patients (i.e., 13% of 168 eyes), in the forms of VFI decrease (VF index, 9 eyes of 6 patients), quadrant RNFL thickness increase (5 eyes of 4 patients), and VF pattern defect (12 eyes of 6 patients); 73% of the patients showed recovery to the baseline at 1 month post-stoppage. The risk factors for occurrence of sub-clinical toxicity were age, cumulative dose, and medication duration. The authors concluded that mean temporal RNFL thickness increased after
administration. The VFI, quadrant RNFL thickness, and VF pattern defect could prove useful in assessment of sub-clinical toxicity; medication duration was shown to be a strong risk factor for occurrence of sub-clinical toxicity.

These investigators noted that in this study, the incidence of clinical toxicity could not be rated, because no patient complained of clinical symptoms. However, they could assume that the incidence would be lower than 1.2 % (1/84), which is compatible with the results of previous studies. The authors stated that this study had several drawbacks. First, none of the participants experienced clinical symptoms, and therefore, incidence of clinical optic neuropathy after sub-clinical change could not be ruled out. They did not stop administration of ethambutol in the sub-clinical cases, and none of these patients developed clinical ethambutol-induced optic neuropathy until 1 month after administration. Thus, the implications of sub-clinical ethambutol-induced toxicity for actual occurrence of clinical toxicity remain to be elucidated in another long-term, prospective studies. Second, these researchers could not evaluate the patients for a sufficient span of time after stoppage of drug administration. Given the retrospective study design, they were unable to control the follow-up visitation, and so 50 % of subjects with sub-clinical changes failed to visit after stoppage of administration (7 of 14 patients), and these investigators were also were unable to collect data beyond 1 month after stoppage. In reversible cases, the resolution of ethambutol-induced optic toxicity typically occurred 3 months after cessation. With a longer follow-up period, sub-clinical changes in VF pattern and RNFL thickness, which remained at 1 month after stoppage in this study, might have been shown to have recovered to the baseline. Furthermore, although GCC analysis was possible with up-graded Cirrus HD-OCT software, the up-graded software was not available at the authors’ institute at the time of the study. Changes in GCC thickness might be more dramatic than changes in RNFL thickness, but they might also be less specific, as they involved 3 different innermost retinal
layers instead of just one. These researchers stated that future study including foveal GCC or GC-IPL should be conducted with more advanced modalities. Finally, the concurrent effect of isoniazid could not be ruled out.

Furthermore, an UpToDate review on “Ethambutol: An overview” (Drew, 2020) states that “Monitoring -- It is generally recommended that patients receiving ethambutol as part of combination therapy for treatment of a mycobacterial infection undergo baseline Snellen visual acuity and red-green color perception testing. All patients should be advised of the side effects associated with ethambutol, most notably those associated with the development of optic neuritis. The need for routine periodic visual acuity testing during therapy is controversial, especially if a dose of 15 mg/kg is chosen, but patients noting changes in their vision should be referred to an ophthalmologist for careful monitoring. In all patients receiving combination therapy for tuberculosis or MAC infections, baseline laboratory studies should be obtained and repeated in the event of suspected drug-related toxicity. Although serum concentration monitoring of ethambutol is not routinely performed, it may be useful in cases of severe renal insufficiency or suspected malabsorption (as demonstrated in some HIV-infected patients receiving anti-tuberculous therapy). If serum drug concentration monitoring is performed, the proposed therapeutic range 2 hours post-dose is 2 to 6 mcg/mL”.

Screening and Monitoring of Ponatinib (Iclusig) Toxicity

An UpToDate review on “Ocular side effects of systemically administered chemotherapy” (Liu et al, 2020) states that “Fibroblast growth factor receptor (FGFR) inhibitors -- Several inhibitors of FGFR (including ponatinib, dovitinib, and erdafitinib) are in clinical trials for a variety of malignancies. Erdaftitinib has now been approved for the treatment of advanced urothelial cancers that harbor certain FGFR mutations. All of these drugs appear to be associated with a
similar type of serous retinopathy (foci of subretinal fluid) to that seen with the MEK inhibitors, possibly because the FGFR pathway intersects with the MEK pathway. In the phase II BLC2001 trial, which included 87 patients with locally advanced or metastatic urothelial cancer that had susceptible FGFR2 or FGFR3 mutations, ocular toxicity resulting in a visual field defect was reported in 25%, with a median time to first onset of 50 days. Grade 3 symptoms, defined as involving the central field of vision causing vision worse than 20/40 or >3 lines of worsening from baseline, were reported in 3% of patients. Dry eye symptoms occurred in 28% of patients during treatment and were grade 3 in 6%. Ocular symptoms resolved in 13% and were ongoing at the study cutoff in 13% … The United States prescribing information for erdafitinib recommends that all patients receive dry eye prophylaxis with ocular lubricants as needed. Monthly ophthalmologic examinations (including an assessment of visual acuity, slit lamp examination, fundus examination, and optical coherence tomography) are recommended during the first 4 months of treatment and every 3 months thereafter, with urgent reevaluation at any time for visual symptoms. It is recommended that the drug be withheld when serous retinal toxicity occurs, regardless of vision, and permanently discontinued if it does not resolve in 4 weeks or if it is grade 4 in severity (i.e., visual acuity 20/200 or worse in the affected eye). However, there were no data provided on the percentage of patients whose symptoms resolved within 4 weeks. There are also recommended dose modification guidelines for patients who develop ocular adverse reactions”.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by “+”:

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<tr>
<td>G40.401 - G40.419</td>
<td>Other generalized epilepsy and epileptic syndromes, not intractable and intractable, with and without status epilepticus [screening for vigabatrin (Sabril) toxicity]</td>
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<tr>
<td>G40.821 - G40.824</td>
<td>Epileptic spasms</td>
</tr>
<tr>
<td>G93.2</td>
<td>Benign intracranial hypertension [pseudotumor cerebri]</td>
</tr>
<tr>
<td>H01.121 - H01.129</td>
<td>Discoid lupus erythematosus of eyelid</td>
</tr>
<tr>
<td>H20.821 - H20.829</td>
<td>Vogt-Koyanagi Syndrome</td>
</tr>
<tr>
<td>H30.001 - H31.9</td>
<td>Chorioretinal inflammations, scars, and other disorders of choroid</td>
</tr>
<tr>
<td>H32 [B39.4 also required]</td>
<td>Chorioretinal disorders in diseases classified elsewhere [retinitis]</td>
</tr>
<tr>
<td>H33.001 - H36</td>
<td>Retinal detachments and defects and other retinal disorders</td>
</tr>
<tr>
<td>H40.001 - H40.9</td>
<td>Glaucoma</td>
</tr>
<tr>
<td>H43.811 - H43.819</td>
<td>Vitreous degeneration [posterior vitreal detachment] [not covered for vitreous degeneration]</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>-----------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>H43.821 - H43.829</td>
<td>Vitreomacular adhesion</td>
</tr>
<tr>
<td>H46.00 - H47.399</td>
<td>Disorders of optic nerve</td>
</tr>
<tr>
<td>H47.9</td>
<td>Unspecified disorder of visual pathways</td>
</tr>
<tr>
<td>H53.40 - H53.489</td>
<td>Visual field defects</td>
</tr>
<tr>
<td>H59.031 - H59.039</td>
<td>Cystoid macular edema following cataract surgery</td>
</tr>
<tr>
<td>L93.0 - L93.2</td>
<td>Lupus erythematosus</td>
</tr>
<tr>
<td>M05.0 - M06.9</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>M32.0 - M32.9</td>
<td>Systemic lupus erythematosus (SLE)</td>
</tr>
<tr>
<td>Q14.0 - Q14.9</td>
<td>Congenital malformations of posterior segment of eye</td>
</tr>
<tr>
<td>Q15.0</td>
<td>Congenital glaucoma (buphthalmos)</td>
</tr>
<tr>
<td>Q85.00 - Q85.01</td>
<td>Neurofibromatosis, unspecified or type 1</td>
</tr>
<tr>
<td>T37.2x1+ - T37.2x4+</td>
<td>Poisoning by antimalarials and drugs acting on other blood protozoa</td>
</tr>
</tbody>
</table>

ICD-10 codes not covered for indications listed in the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
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</thead>
<tbody>
<tr>
<td>A28.1</td>
<td>Cat-scratch disease</td>
</tr>
<tr>
<td>C71.0 - C71.9</td>
<td>Malignant neoplasm of brain [intra-cranial tumors]</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>--------</td>
<td>-------------------------------------------------------------------</td>
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<tr>
<td>G31.01</td>
<td>Frontotemporal dementia</td>
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<tr>
<td>G31.09</td>
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<tr>
<td>G31.9</td>
<td>Degenerative disease of nervous system, unspecified [neurodegeneration pattern]</td>
</tr>
<tr>
<td>H04.121</td>
<td>Dry eye syndrome</td>
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<td>H04.129</td>
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<tr>
<td>H04.561</td>
<td>Stenosis of lacrimal punctum</td>
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<tr>
<td>H04.569</td>
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<tr>
<td>H11.141</td>
<td>Conjunctival xerosis, unspecified</td>
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<tr>
<td>H11.149</td>
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</tr>
<tr>
<td>H16.221</td>
<td>Keratoconjunctivitis sicca, not specified as Sjogren's</td>
</tr>
<tr>
<td>H16.239</td>
<td>Sjogren's</td>
</tr>
<tr>
<td>H25.011</td>
<td>Cataracts</td>
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<tr>
<td>H28</td>
<td></td>
</tr>
<tr>
<td>M35.00</td>
<td>Sicca syndrome [Sjogren]</td>
</tr>
<tr>
<td>M35.09</td>
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<tr>
<td>Q12.0</td>
<td>Congenital lens malformations</td>
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<td>Q12.9</td>
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<tr>
<td>T85.22x+</td>
<td>Displacement of intraocular lens</td>
</tr>
<tr>
<td>Z13.5</td>
<td>Encounter for screening for eye and ear disorders</td>
</tr>
</tbody>
</table>

The above policy is based on the following references:


22. BlueCross and BlueShield Association (BCBSA), Technology Evaluation Center (TEC). Retinal nerve fiber layer analysis for the diagnosis and management of glaucoma. TEC Assessment Program. Chicago, IL: BCBSA; November 2001;16(13).

23. BlueCross and BlueShield Association (BCBSA), Technology Evaluation Center (TEC). Retinal nerve fiber layer analysis for the diagnosis and management of glaucoma. TEC Assessment Program. Chicago, IL: BCBSA; August 2003;18(7).


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tomography, the retinal thickness analyzer, and fundus photography. Retina. 2006;26(1):49-57.


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Amendment to Aetna Clinical Policy Bulletin Number: 0344 Optic Nerve and Retinal Imaging Methods

There are no amendments for Medicaid.

www.aetnabetterhealth.com/pennsylvania revised 06/05/2020

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