Ophthalmologic Techniques for Evaluating Glaucoma

Policy Number: 9.03.06   Last Review: 9/2016

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for ophthalmologic techniques for evaluating glaucoma when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
Analysis of the optic nerve (retinal nerve fiber layer) in the diagnosis and evaluation of patients with glaucoma or glaucoma suspects may be considered medically necessary when using scanning laser ophthalmoscopy, scanning laser polarimetry, and optical coherence tomography.

When Policy Topic is not covered
The measurement of ocular blood flow, pulsatile ocular blood flow or blood flow velocity with Doppler ultrasonography is considered investigational in the diagnosis and follow-up of patients with glaucoma.

Considerations
Optic nerve/retinal nerve fiber analysis may be performed by both ophthalmologists and optometrists.

Description of Procedure or Service

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<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
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<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
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<td>• With open-angle</td>
<td>Evaluation of the optic nerve and</td>
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<td>• Test accuracy</td>
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<td>• Other test performance measures</td>
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Several techniques have been developed to measure the thickness of the optic nerve/retinal nerve fiber layer (RNFL) as a method to diagnose and monitor glaucoma. Measurement of ocular blood flow is also being evaluated as a diagnostic and management tool for glaucoma.

For individuals who have open-angle glaucoma or glaucoma suspect who receive digital imaging of the optic nerve and retinal nerve fiber layer, the evidence includes studies on diagnostic accuracy. Relevant outcomes include test accuracy, other test performance measures, symptoms, morbid events, and medication use. Confocal scanning laser ophthalmoscopy (CSLO), scanning laser polarimetry (SLP), and optical coherence tomography (OCT) can be used to evaluate the optic nerve and retinal nerve fiber layer in patients with glaucoma and glaucoma suspect. Numerous articles describe findings from patients with known and suspected glaucoma using CSLO, SLP, and OCT. These studies report that abnormalities may be detected on these examinations before functional changes are noted. The literature and specialty society guidelines indicate that optic nerve analysis using CSLO, SLP, and OCT has become an additional test that may be used in the diagnosis and management of patients with glaucoma and those who are glaucoma suspects. These results are often considered along with other findings to make diagnostic and therapeutic decisions about glaucoma care. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have open-angle glaucoma or glaucoma suspect who receive evaluation of ocular blood flow, the evidence includes association studies. Relevant outcomes include test accuracy, other test performance measures, symptoms, morbid events, and medication use. Techniques to measure ocular blood flow or ocular blood velocity are used in evaluating various glaucoma treatments. The data for these techniques remain limited. Literature reviews have not identified studies that demonstrate the clinical utility for use of pulsatile ocular blood flow or blood flow velocity in patients with glaucoma. Some publications have described their use in studies comparing medication regimens in glaucoma. Others have suggested that these parameters may be helpful in understanding the variability in visual field changes in patients with glaucoma, ie, this may help explain why patients with similar levels of intraocular pressure may develop markedly different visual impairments. However, data on use of ocular blood flow, pulsatile ocular blood flow, and/or blood flow velocity are currently lacking, and their relationship to clinical outcomes is unclear. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Background**
Glaucoma is a disease characterized by degeneration of the optic nerve (optic disc). Elevated intraocular pressure has long been thought to be the primary etiology, but the relationship between intraocular pressure and optic nerve...
damage varies among patients, suggesting a multifactorial origin. For example, some patients with clearly elevated intraocular pressure will show no optic nerve damage, while other patients with marginal or no pressure elevation will, nonetheless, show optic nerve damage. The association between glaucoma and other vascular disorders such as diabetes or hypertension suggests vascular factors may play a role in glaucoma. Specifically, it has been hypothesized that reductions in blood flow to the optic nerve may contribute to the visual field defects associated with glaucoma.

A comprehensive ophthalmologic exam is required for the diagnosis of glaucoma, but no single test is adequate for establishing the diagnosis. A comprehensive ophthalmologic examination includes an examination of the optic nerve by fundoscopy, evaluation of visual fields, and measurement of ocular pressure. The presence of characteristic changes in the optic nerve or abnormalities in visual field, together with increased intraocular pressure, is sufficient for a definitive diagnosis. However, some patients will show ophthalmologic evidence of glaucoma with normal intraocular pressures, therefore an elevated intraocular pressure is not essential for diagnosis.

Conventional management of the patient with glaucoma principally involves drug therapy, to control elevated intraocular pressures, and serial evaluation of the optic nerve to follow disease progression. Standard methods of evaluation include careful direct examination of the optic nerve using ophthalmoscopy or stereophotography, or evaluation of visual fields. There has been interest in developing more objective, reproducible techniques both to document optic nerve damage and to detect early changes in the optic nerve and retinal nerve fiber layer (RNFL) before the development of permanent visual field deficits. Specifically, evaluating changes in the thickness of the RNFL has been investigated as a technique to diagnose and monitor glaucoma. In addition, there has been interest in measuring ocular blood flow as a diagnostic and management tool for glaucoma. A variety of new techniques have been developed, as described here. (Note: This policy only addresses uses of these techniques related to glaucoma.)

**Techniques to Evaluate the Optic Nerve/Retinal Nerve Fiber Layer**

**Confocal Scanning Laser Ophthalmoscopy**
Confocal scanning laser ophthalmoscopy (CSLO) is a laser-based image acquisition technique, which is intended to improve the quality of the examination compared to standard ophthalmologic examination. A laser is scanned across the retina along with a detector system. Only a single spot on the retina is illuminated at any time, resulting in a high-contrast image of great reproducibility that can be used to estimate the thickness of the RNFL. In addition, this technique does not require maximal mydriasis, which may be a problem in patients with glaucoma. The Heidelberg Retinal Tomography is probably the most common example of this technology.
Canning Laser Polarimetry
The RNFL is birefringent, causing a change in the state of polarization of a laser beam as it passes. A 780-nm diode laser is used to illuminate the optic nerve. The polarization state of the light emerging from the eye is then evaluated and correlated with RNFL thickness. Unlike CSLO, scanning laser polarimetry (SLP) can directly measure the thickness of the RNFL. GDx® is a common example of a scanning laser polarimeter. GDx® contains a normative database and statistical software package to allow comparison to age-matched normal subjects of the same ethnic origin. The advantages of this system are that images can be obtained without pupil dilation, and evaluation can be done in approximately 10 minutes. Current instruments have added enhanced and variable corneal compensation technology to account for corneal polarization.

Optical Coherence Tomography
Optical coherence tomography (OCT) uses near-infrared light to provide direct cross-sectional measurement of the RNFL. The principles employed are similar to those used in B-mode ultrasound except light, not sound, is used to produce the 2-dimensional images. The light source can be directed into the eye through a conventional slit-lamp biomicroscope and focused onto the retina through a typical 78-diopter lens. This system requires dilation of the patient’s pupil. OCT® is an example of this technology. OCT analysis software is being developed to include optic nerve head parameters with spectral domain OCT (SDOCT), analysis of macular parameters, and hemodynamic parameters with Doppler OCT and OCT angiography.

Techniques to Measure Ocular Blood Flow

Pulsatile Ocular Blood Flow
The pulsatile variation in ocular pressure results from the flow of blood into the eye during cardiac systole. Pulsatile ocular blood flow can thus be detected by the continuous monitoring of intraocular pressure. The detected pressure pulse can then be converted into a volume measurement using the known relationship between ocular pressure and ocular volume. Pulsatile blood flow is primarily determined by the choroidal vessels, particularly relevant to patients with glaucoma, since the optic nerve is supplied in large part by choroidal circulation.

Doppler Ultrasonography
Color Doppler imaging has also been investigated as a technique to measure the blood velocity in the retinal and choroidal arteries.

Rationale
The use of various techniques of retinal nerve fiber layer (RNFL) analysis (confocal scanning laser ophthalmoscopy [CSLO], scanning laser polarimetry [SLP], optical coherence tomography [OCT]) for the diagnosis and management of glaucoma was addressed by TEC Assessments in 2001(1) and 2003.(2) The 2003 Assessment offered the following observations(2):
A variety of techniques to evaluate the RNFL were considered, including CSLO, SLP, and OCT. All 3 devices use different principles to directly evaluate the RNFL. All 3 devices give multiple specific measurement of the RNFL that can be followed up over time to evaluate a rate of change in the RNFL. In theory, they are highly sensitive and can detect subtle changes to the RNFL earlier than standard qualitative evaluations. The major potential benefit of these technologies is that they can provide a quantitative objective evaluation in contrast with the subjective evaluation provided by other methods of diagnosing and monitoring primary open angle glaucoma (POAG).

The Assessment evaluated whether adding RNFL analysis to other tests improves health outcomes. It is assumed that RNFL analysis would not influence decisions to begin treatment for suspected POAG when intraocular pressure (IOP) is elevated or results of 2 of 3 conventional tests are positive. Conventional tests include ophthalmoscopic detection of atrophy of the optic nerve, visual field defect on perimetric testing, and increased IOP on tonometry. In patients without clear indications for topical medication, signs of optic nerve atrophy on RNFL analysis seen in advance of meeting other current diagnostic criteria for POAG may be used to begin early treatment. Using RNFL analysis to initiate early topical medication requires knowing how well RNFL results predict the development of visual loss. If the RNFL analysis is a poor predictor of future visual loss, its use could lead to errors in management, leading, eg, to overtreatment.

The best evidence would be direct evidence comparing outcomes of management guided by conventional tests with and without RNFL analysis. No randomized trials were identified that compare the health outcomes of management guided by conventional tests alone with outcomes of management guided by conventional tests plus RNFL analysis in the detection or monitoring of POAG.

Regarding pulsatile ocular blood flow or blood flow velocity (techniques not addressed by the TEC Assessment), there are similar deficiencies reported in the published literature. Specifically, no data from published clinical trials document how these devices should be incorporated into clinical practice and whether treatment decisions based on the use of these devices result in improved patient outcomes compared with the conventional methods of evaluation. Additional information is also needed to (1) document the association between blood flow and glaucoma; (2) determine the relevant vessels for study considering the complex blood supply to the optic nerve; and (3) establish the range of normal values, particularly in relation to other factors such as blood pressure, heart rate, and compliance of the blood vessels. (3-7)

Evidence Subsequent to the 2003 TEC Assessment
Periodic literature updates using the MEDLINE database, and focusing on longitudinal results, have been performed since the 2003 TEC Assessment. The most recent literature update was performed through July 11, 2016. Following is a summary of the key literature to date.
In 2012, the Agency for Healthcare Research and Quality published a comparative effectiveness review of screening for glaucoma.(8) Included in the review were randomized controlled trials, quasirandomized controlled trials, observational study designs including cohort and case control studies, and case series with more than 100 participants. The interventions evaluated included ophthalmoscopy, fundus photography/computerized imaging (OCT, retinal tomography, SLP), pachymetry (corneal thickness measurement), perimetry, and tonometry. No evidence was identified that addressed whether an open angle glaucoma screening program led to a reduction in IOP, less visual impairment, reduction in visual field loss or optic nerve damage, or improvement in patient-reported outcomes. No evidence was identified regarding harms of a screening program. Over 100 studies were identified on the diagnostic accuracy of screening tests. However, due to the lack of a definitive diagnostic reference standard and heterogeneity, synthesis of results could not be completed.

Techniques to Evaluate the Optic Nerve/RNFL
A 2015 Cochrane review assessed diagnostic accuracy of optic nerve head and fiber layer imaging for glaucoma.(9) Included were 103 case-control studies and 3 cohort studies (total of 16,260 eyes) that evaluated the accuracy of recent commercial versions of OCT (spectral domain), HRT III, or SLP (GDx VCC or ECC) for diagnosing glaucoma. The population was patients who had been referred for suspected glaucoma, typically due to an elevated IOP, abnormal optic disc appearance, and/or an abnormal visual field identified in primary eye care. Population-based screening studies were excluded. Most comparisons were for different parameters within the 3 tests, and the parameters with the highest diagnostic odds ratio were compared. The 3 tests (OCT, HRT, SLP) had similar diagnostic accuracy. With specificity close to 0.95, sensitivity was 0.70. Thus, if 200 out of 1000 people referred by primary eye care, the tests would miss about 60 cases out of the 200, and incorrectly refer 50 of 800 patients without glaucoma. Because a case-control design was used in nearly all of the studies, concerns were raised about the potential for bias, overestimating accuracy, and applicability of the findings to clinical practice.

The Confocal Scanning Laser Ophthalmoscopy (CSLO) Ancillary Study, a subset of the Ocular Hypertension Treatment Study (OHTS), was designed to determine whether annual optic disc topographic measurements can accurately predict visual field loss.(10) The OHTS randomly assigned patients with elevated IOP to either topical hypotensive medication or observation. Baseline data reported from the CSLO Ancillary Study did not allow reaching conclusions about how well RNFL analysis measurements predict visual field loss over time.

Follow-up of the CSLO Ancillary Study was reported in 2005.(11) Of 438 participants, 34% had abnormal CSLO values according to HRT criteria. The average interval (SD) between CSLO exams to POAG was 48.4 (25.2) months. Eyes not developing POAG were followed up a mean (SD) of 79.5 (20.8) months. Sensitivity of CSLO for development of POAG using HRT criteria was 55.6% (95% confidence interval [CI], 39.6% to 70.5%), specificity 68.2% (95% CI, 63.5% to 72.5%), and PPV 13.5% (95% CI, 8.9% to 20.0%). The investigators concluded
that "[t]he current analysis did not directly determine whether the prediction model that includes baseline CSLO measurements is improved over the OHTS prediction model that includes baseline stereophotographic cup-disc ratio measurements.... Longer follow-up is required to evaluate the true predictive accuracy of CSLO measures."

At Manchester Royal Eye Hospital (U.K.), HRT and GDx systems were evaluated in cross-sectional (98 normal controls, 152 patients with POAG) and longitudinal studies (240 at risk of developing glaucoma due to high IOP or fellow eye with POAG and 75 with POAG).(12) With specificity set at 95%, sensitivities of the HRT and GDx in detecting POAG were 59% and 45%, respectively, in the cross-sectional study. In the longitudinal study, patients were evaluated biannually over an average 3.5-year follow-up. Evidence of visual field defects developed in 72 of the at-risk group. Poor agreement was found between the HRT and GDx for development of visual field abnormalities. Although sensitivities might vary according to definitions for conversion to a visual field defect, among patients with baseline HRT and GDx abnormalities, sensitivities could be as low as 13% to 39%. The authors concluded that “on account of the fact that the HRT and GDx fail to detect a significant number of cases of conversion, they cannot provide a replacement for visual field examination.”

Longitudinal results have also been reported from the University of California, San Diego Diagnostic Innovations in Glaucoma Study (DIGS).(13,14) In the first publication, eyes from 160 glaucoma suspects evaluated with SLP were followed up for 1.7 to 4.1 years. Visual field damage developed in 16 (10%) participants. Only relative risks for visual field damage were reported as opposed to sensitivities, specificities, and predictive values.(13) From 12 SLP parameters and a 13th calculated from those parameters, 3 were significantly associated with the visual field outcome in multivariate analyses (models were incorrectly specified owing to the small number of outcomes). In a subsequent report, 114 glaucoma suspects were examined with OCT (1 eye per patient).(14) Over a 4.2-year average follow-up, 23 (20%) developed changes consistent with glaucoma. While the relative risk of developing glaucomatous changes was increased with thinner RNFL results (1.5-fold per 10 μm), sensitivities and specificities demonstrating clinical utility were not reported.

A technology assessment issued by AAO in 2007 reviewed 159 studies published between January 2003 and February 2006, evaluating optic nerve head and RNFL devices used to diagnose or detect glaucoma progression.(15) The assessment concluded, “The information obtained from imaging devices is useful in clinical practice when analyzed in conjunction with other relevant parameters that define glaucoma diagnosis and progression.”

Studies continue to report on use of these techniques in patients with glaucoma/glaucoma suspects. In addition, studies report correlation of changes in RNFL analysis and changes in visual fields.(16)
Section Summary: Techniques to Evaluate the Optic Nerve/RNFL

Numerous articles describe findings from patients with glaucoma and glaucoma suspect using CSLO, SLP, and OCT. The literature and specialty society guidelines indicate that optic nerve analysis using CSLO, SLP, and OCT has become an additional test that may be used in the diagnosis and management of patients with glaucoma and those who are glaucoma suspect.

Techniques to Evaluate Ocular Blood Flow

Measurement of ocular blood flow has been studied as a technique for evaluating patients with glaucoma. One potential application is the early detection of normal tension glaucoma.(17) While reports of use have been longstanding, the report by Bafa et al from 2001(18) is an example, the clinical impact of this technique is not known. Reports have commented on the complexity of these parameters(19) and have also noted that these technologies are not commonly used in clinical settings.(20)

In 2012, Calvo et al reported the predictive value of retrobulbar blood flow velocities in a prospective series of 262 glaucoma suspects.(21) At baseline, all participants had normal visual field, increased IOP (mean, 23.56 mm Hg), and glaucomatous optic disc appearance. Blood flow velocities were measured by color Doppler imaging (CDI) during the baseline examination, and conversion to glaucoma was assessed at least yearly according to changes observed with confocal laser scanning. During the 48-month follow-up period, there were 36 (13.7%) converters and 226 nonconverters. Twenty (55.5%) of the converters also showed visual field worsening (moderate agreement, κ=0.38). Mean end-diastolic and mean velocity in the ophthalmic artery were significantly reduced at baseline in subjects who converted to glaucoma compared with subjects who did not convert. Post hoc subgroup analysis comparing patients with resistivity lower than 0.75 to those with resistivity greater than 0.75 revealed statistically significant differences in those not converting to glaucoma (survival of 93.9% vs 81.7%, respectively). The clinical significance of this difference is unclear.

A 2011 publication reported on CDI in normal and glaucomatous eyes.(22) Using data from reported studies, a weighted mean was derived for the peak systolic velocity, end diastolic velocity and Pourcelot's resistive index in the ophthalmic, central retinal and posterior ciliary arteries. Data from 3061 glaucoma patients and 1072 controls were included. The mean values for glaucomatous eyes were within 1 SD of the values for controls for most CDI parameters. Methodologic differences created interstudy variance in CDI values, complicating the construction of a normative database and limiting its utility. The authors noted that because the mean values for glaucomatous and normal eyes have overlapping ranges, caution should be used when classifying glaucoma status based on a single CDI measurement.

Resch et al reported a cross-sectional study of optic disc morphology and ocular perfusion parameters in 103 patients with POAG in 2011.(23) Choroidal and optic nerve head blood flow was assessed using laser Doppler flowmetry, retinal blood velocity was measured with laser Doppler velocimetry, and retinal vessel
diameters were measured with a Retinal Vessel Analyzer. Choroidal blood flow was not significantly associated with measures of glaucomatous damage or with morphologic parameters of the optic nerve head. Reduced retinal vessel diameters were slightly correlated with the degree of glaucomatous damage. Multiregression analysis showed optic nerve head blood flow to be most strongly associated with most measures of structural nerve head damage (eg, $r=0.28$ for RNFL) and visual field loss. As indicated in the TEC Assessment, cross-sectional studies cannot determine whether changes in blood flow precede or are secondary to changes in the optic nerve head. Longitudinal studies are needed to evaluate if changes in blood flow are predictive of future visual loss.

**Section Summary: Techniques to Evaluate Ocular Blood Flow**
Techniques to measure ocular blood flow or ocular blood velocity are used in evaluating various glaucoma treatments. The data for these techniques remain limited. Literature reviews have not identified studies that demonstrate the clinical utility for use of pulsatile ocular blood flow or blood flow velocity in patients with glaucoma.

**Ongoing and Unpublished Clinical Trials**
Some currently unpublished trials that might influence this review are listed in Table 1.

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<tr>
<td>NCT01957267</td>
<td>Longitudinal Observational Study Using Functional and Structural Optical Coherence Tomography to Diagnose and Guide Treatment of Glaucoma</td>
<td>150</td>
<td>Oct 2018</td>
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</table>

NCT: national clinical trial.

**Summary of Evidence**
For individuals who have open-angle glaucoma or glaucoma suspect who receive digital imaging of the optic nerve and retinal nerve fiber layer, the evidence includes studies on diagnostic accuracy. Relevant outcomes include test accuracy, other test performance measures, symptoms, morbid events, and medication use. Confocal scanning laser ophthalmoscopy (CSLO), scanning laser polarimetry (SLP), and optical coherence tomography (OCT) can be used to evaluate the optic nerve and retinal nerve fiber layer in patients with glaucoma and glaucoma suspect. Numerous articles describe findings from patients with known and suspected glaucoma using CSLO, SLP, and OCT. These studies report that abnormalities may be detected on these examinations before functional changes are noted. The literature and specialty society guidelines indicate that optic nerve analysis using CSLO, SLP, and OCT has become an additional test that may be used in the
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SUPPLEMENTAL INFORMATION

Clinical Input Received From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 1 physician specialty society and 3 academic medical centers while this policy was under review in 2009. Most reviewers providing input supported use of these techniques (CSLO, SLP, OCT) in the care of patients with glaucoma and those who are glaucoma suspects. Reviewers provided data to demonstrate that this testing is equivalent to expert assessment of optic disc photography for both detecting glaucoma and showing disease progression. Reviewers also commented on favorable aspects of this testing. For example, in contrast to other glaucoma testing, these tests can be done more easily, eg, this testing does not always need to be done with dilated pupils, and ambient light level may be (is) less critical. In addition, while serial stereophotographs of the optic nerves are considered by many as the criterion standard, these are not always practical, especially for general ophthalmologists. This testing also requires less cooperation from the patient, which can be helpful in some older patients.
Practice Guidelines and Position Statements

American Academy of Ophthalmology
The American Academy of Ophthalmology 2015 primary open angle glaucoma (POAG) suspect and POAG preferred practice patterns recommend evaluating the optic nerve and retinal nerve fiber layer.(24,25)

The documents state that “Although they are distinctly different methodologies, stereoscopic disc photographs and computerized images of the nerve are complementary with regard to the information they provide the clinician who must manage the patient”. The guidelines describe 3 types of computer-based imaging devices that are currently available for glaucoma and are similar in their ability to distinguish glaucoma from controls: CSLO, OCT, and SLP and state that “computer-based digital imaging of the ONH and RNFL is routinely used to provide quantitative information to supplement the clinical examination of the optic nerve...One rationale for using computerized imaging is to distinguish glaucomatous damage from eyes without glaucoma when thinning of the RNFL is measured, thereby facilitating earlier diagnosis and detection of optic nerve damage”. In addition, AAOS concludes that as device technology evolves the performance of diagnostic imaging devices is expected to improve.

American Optometric Association
The American Optometric Association issued a 2010 clinical guideline on the care of the patient with open angle glaucoma.(26) The guideline list states that follow-up examinations for the evaluation of POAG may include but is not limited to biomicroscopy, tonometry, gonioscopy, and optic nerve assessment.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

References:
1. Blue Cross and Blue Shield Technology Evaluation Center (TEC). Retinal nerve fiber analysis for the diagnosis and management of glaucoma. TEC Assessments. 2001;Volume 16, Tab 13. PMID
2. Blue Cross and Blue Shield Technology Evaluation Center (TEC). Retinal nerve fiber layer analysis for the diagnosis and management of glaucoma. TEC Assessments. 2003;Volume 18, Tab 7. PMID


**Billing Coding/Physician Documentation Information**

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<td>Monitoring of intraocular pressure for 24 hours or longer, unilateral or bilateral, with interpretation and report</td>
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<td>92133</td>
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**ICD-10 Codes**

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**Policy Implementation/Update Information**

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<td>New policy; considered investigational</td>
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<td>Policy statement updated to include testing using scanning laser ophthalmoscopy, scanning laser polarimetry, and optical coherence tomography as considered medically necessary in patients with glaucoma and glaucoma suspects. Title changed from Measurement of Pulsatile Ocular Blood Flow to Ophthalmologic Techniques for Evaluating Glaucoma.</td>
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