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Ophthalmologic Techniques For Evaluating Glaucoma

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Related Policies (if applicable)
None

Disclaimer

Carefully check state regulations and/or the member contract.
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Coverage

Analysis of the optic nerve and retinal nerve fiber layer in the diagnosis and evaluation of individuals with glaucoma or glaucoma suspects **may be considered medically necessary** when using scanning laser ophthalmoscopy, scanning laser polarimetry, and optical coherence tomography.

The measurement of ocular blood flow, pulsatile ocular blood flow, or blood flow velocity **is considered experimental, investigational and/or unproven** in the diagnosis and follow-up of individuals with glaucoma.

Monitoring of intraocular pressure for 24 hours or longer, unilateral or bilateral, **is considered experimental, investigational and/or unproven** using any method of measurement, including but not limited to contact lens sensor technology (e.g., Triggerfish®).

Policy Guidelines

None.

Description

Glaucoma is characterized by degeneration of the optic nerve (optic disc). Elevated intraocular pressure (IOP) has long been thought to be the primary etiology, but the relation between IOP and optic nerve damage varies among patients, suggesting a multifactorial origin. For example, some patients with clearly elevated IOP will show no optic nerve damage, while others with marginal or no pressure elevation will show optic nerve damage. The association between glaucoma and other vascular disorders (e.g., diabetes, 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. Several techniques have been developed to measure the thickness of the optic nerve and retinal nerve fiber layer as a method to diagnose glaucoma. Measurement of ocular blood flow is also being evaluated as a diagnostic tool for glaucoma.

Diagnosis and Management

A comprehensive ophthalmologic exam is required for the diagnosis of glaucoma, but no single test is adequate to establish diagnosis. A comprehensive ophthalmologic examination includes assessment of the optic nerve, 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 IOP, is sufficient for a definitive diagnosis. However, some patients will show ophthalmologic evidence of glaucoma with normal IOPs. These cases of normal-tension glaucoma are considered to be a type of primary open-angle glaucoma. Angle-closure glaucoma is another type of glaucoma associated with an increase in IOP. The increased IOP in angle-closure glaucoma arises from a reduction in aqueous outflow from the eye due to a closed angle in the anterior chamber.

Conventional management of patients with glaucoma principally involves drug therapy to control elevated IOPs, 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 stereo photography, or evaluation of visual fields. There is 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 before the development of permanent visual field deficits. Specifically, evaluating changes in retinal nerve fiber layer thickness has been investigated as a technique to diagnose and monitor glaucoma. However, IOP reduction is not effective in decreasing disease progression in a significant number of patients, and in patients with normal-tension glaucoma, there is never an increase in IOP. It has been proposed that vascular dysregulation is a significant cause of damage to the retinal nerve fiber layer, and there is interest in measuring ocular blood flow as both a diagnostic and a management tool for glaucoma. Changes in blood flow to the retina and choroid may be particularly relevant for diagnosis and treatment of normal-tension glaucoma. A variety of techniques have been developed, as described below. (Note: This medical policy only addresses techniques related to the evaluation of the optic nerve, retinal nerve fiber layer, or blood flow

to the retina and choroid in individuals with glaucoma and monitoring of IOP for 24 hours or longer).

Techniques to Evaluate the Optic Nerve and Retinal Nerve Fiber Layer

Confocal Scanning Laser Ophthalmoscopy

Confocal scanning laser ophthalmoscopy is an image acquisition technique intended to improve the quality of the eye examination compared with 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 retinal nerve fiber layer thickness. In addition, this technique does not require maximal mydriasis, which may be problematic in patients with glaucoma. The Heidelberg Retinal Tomograph is a commonly used technology.

Scanning Laser Polarimetry

The retinal nerve fiber layer is birefringent (i.e., biorefractive), meaning that it causes 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 retinal nerve fiber layer thickness. Unlike confocal scanning laser ophthalmoscopy, scanning laser polarimetry can directly measure the thickness of the retinal nerve fiber layer. GDx is a common scanning laser polarimetry device. GDx contains a normative database and statistical software package that compare scan results with 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 completed in 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 retinal nerve fiber layer. 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 analysis software is being developed to include optic nerve head parameters with spectral domain OCT, analysis of macular parameters, and hemodynamic parameters with Doppler OCT and OCT angiography.

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 IOP. The detected pressure pulse can then be converted into a volume measurement using the known relation between ocular pressure and ocular volume. Pulsatile blood flow is primarily determined by the choroidal vessels, particularly relevant to patients with glaucoma, because the optic nerve is supplied in large part by choroidal circulation.

Techniques to Measure Ocular Blood Flow

A number of techniques have been developed to assess ocular blood flow. They include laser speckle flowgraphy, color Doppler imaging, Doppler Fourier domain OCT, laser Doppler velocimetry, confocal scanning laser Doppler flowmetry, and retinal functional imaging. (1)

Laser Speckle Flowgraphy

Laser speckle is detected when a coherent light source such as laser light is dispersed from a diffusing surface such as retinal and choroidal vessels and the circulation of the optic nerve head. The varying patterns of light can be used to determine red blood cell velocity and retinal blood flow. However, due to differences in the tissue structure in different eyes, flux values cannot be used for comparisons between eyes. This limitation may be overcome by subtracting background choroidal blood flow results from the overall blood flow results in the region of interest.

Color Doppler Imaging

Color Doppler imaging has also been investigated as a technique to measure the blood flow velocity in the retinal and choroidal arteries. This technique delivers ultrasound in pulsed Doppler mode with a transducer set on closed eyelids. The examination takes 30 to 40 minutes and is most effective for the mean velocity of large ophthalmic vessels such as the ophthalmic artery, the central retinal artery, and the short posterior ciliary arteries. However, total blood flow cannot be determined with this technique, and imaging is highly dependent on probe placement.

Doppler Fourier Domain Optical Coherence Tomography (OCT)

Doppler Fourier domain OCT is a noncontact imaging technique that detects the intensity of the light scattered back from erythrocytes as they move in the vessels of the ocular tissue. This induces a frequency shift that represents the velocity of the blood in the ocular tissue.

Laser Doppler Velocimetry

Laser Doppler velocimetry compares the frequency of reflected laser light from a moving particle with stationary tissue.

Confocal Scanning Laser Doppler Flowmetry

Confocal scanning laser Doppler flowmetry combines laser Doppler flowmetry with confocal scanning laser tomography. Infrared laser light is used to scan the retina, and the frequency and amplitude of Doppler shifts are determined from the reflected light. Determinations of blood velocity and blood volume are used to compute the total blood flow and create a physical map of retinal flow values.

24-Hour Intraocular Pressure Monitoring

The need for continuous monitoring of glaucoma patients has been recognized for several years. Diurnal fluctuations in IOP represent an independent risk factor for glaucoma disease progression despite normal IOP readings in the office setting. A significant percentage of glaucoma patients have intraocular peaks or target pressure breakthroughs at night or early

morning. Sensimed (Switzerland) manufactures the Triggerfish®, which is a soft disposable silicone contact lens embedding a micro-sensor that captures spontaneous circumferential changes at the corneoscleral area and is used for 24-hour monitoring of IOP. The output signal is sent wirelessly to the Sensimed Triggerfish® antenna and is directly correlated to fluctuations in IOP. The adhesive antenna, worn around the eye is connected to a portable recorder through a thin flexible data cable. The patient wears the Sensimed Triggerfish® up to 24 hours and assumes normal activities including sleep periods. The patient is encouraged to avoid strenuous activity which leads to excessive sweating. When the patient returns to his doctor, the data is transferred from the recorder to the practitioner's computer via Bluetooth technology for analysis. (2, 3)

Regulatory Status

A number of confocal scanning laser ophthalmoscopy, scanning laser polarimetry, and OCT devices have been cleared by the U.S. Food and Drug Administration (FDA) through the 510(k) process for imaging the posterior eye segment. For example, the RTVue XR optical coherence tomography Avanti™ (Optovue) is an OCT system indicated for the in vivo imaging and measurement of the retina, retinal nerve fiber layer, and optic disc as a tool and aid in the clinical diagnosis and management of retinal diseases. The RTVue XR optical coherence tomography Avanti™ with normative database is a quantitative tool for comparing retina, retinal nerve fiber layer, and optic disk measurements in the human eye with a database of known normal subjects. It is intended as a diagnostic device to aid in the detection and management of ocular diseases. In 2016, the RTVue XR OCT and Avanti™ with AngioVue™ Software was cleared by the FDA through the 510(k) process (K153080) as an aid in the visualization of vascular structures of the retina and choroid. FDA product code: HLI, OBO.

In 2012, the iExaminer™ (Welch Allyn) was cleared for marketing by the FDA through the 510(k) process. The iExaminer™ consists of a hardware adapter and associated software (iPhone® App) to capture, store, send, and retrieve images from the PanOptic™ Ophthalmoscope (Welch Allyn) using an iPhone. FDA product code: HKI.

Table 1 lists select FDA cleared ocular imaging devices. This table may not be an all-inclusive list, therefore refer to <https://fda.gov> for current FDA approved devices.

Table 1. Selected Ocular Imaging Devices Cleared by the U.S. FDA

Device	Manufacturer	Date Cleared	510(k) No.	Indication
3D OCT-1 Maestro2	Topcon Corporation	10/30/2023	K231222	Imaging of optic nerve and retinal nerve fiber Layer.
Phoenix ICON and Phoenix ICON GO	Neo Light, LLC.	09/06/2023	K223575	Imaging of optic nerve and retinal nerve fiber Layer.
Eyer Retinal Camera Nm-Std	Phelcom, Technologies	02/22/2023	K221329	Imaging of optic nerve and retinal nerve fiber

				Layer.
SOLIX	Optovue Inc.	11/9/2022	K222166	Imaging of optic nerve and retinal nerve fiber Layer.
RESCAN 700 CALLISTO eye	Carl Zeiss Meditec AG	1/11/2019	K180229	Imaging of optic nerve and retinal nerve fiber layer.
Retina Workplace	Carl Zeiss Meditec Inc.	10/24/2018	K182318	Imaging of optic nerve and retinal nerve fiber layer.
Spectralis HRA+OCT and variants with High Magnification Module	Heidelberg Engineering GmbH	10/18/2018	K182569	Imaging of optic nerve and retinal nerve fiber layer.
Spectralis HRA+OCT and variants with OCT Angiography Module	Heidelberg Engineering GmbH	9/13/2018	K181594	Imaging of optic nerve and retinal nerve fiber layer.
Spectralis HRA + OCT and variants	Heidelberg Engineering GmbH	8/30/2018	K173648	Imaging of optic nerve and retinal nerve fiber layer.
Image Filing Software NAVIS-EX	Nidek Co. Ltd	7/19/2018	K181345	Imaging of optic nerve and retinal nerve fiber layer.
Avanti	Optovue Inc.	6/8/2018	K180660	Imaging of optic nerve and retinal nerve fiber layer.
P200TE	Optos plc	2/28/2018	K173707	Imaging of optic nerve and retinal nerve fiber layer.
DRI OCT Triton	Topcon Corporation	1/19/2018	K173119	Imaging of optic nerve and retinal nerve fiber layer.
IMAGEnet 6 Ophthalmic Data System	Topcon Corporation	11/1/2017	K171370	Imaging of optic nerve and retinal nerve fiber layer.
Spectralis HRA+OCT and variants Spectralis FA+OCT Spectralis ICGA+OCT Spectralis OCT Blue Peak Spectralis OCT with Multicolor	Heidelberg Engineering GmbH	11/1/2017	K172649	Imaging of optic nerve and retinal nerve fiber layer.

PRIMUS	Carl Zeiss Suzhou Co. Ltd.	6/21/2017	K163195	Imaging of optic nerve and retinal nerve fiber layer.
Retina Workplace	Carl Zeiss Meditec AG	6/21/2017	K170638	Imaging of optic nerve and retinal nerve fiber layer.
iVue	Optovue Inc.	6/9/2017	K163475	Imaging of optic nerve and retinal nerve fiber layer.
3D OCT-1 Maestro	Topcon Corporation	3/3/2017	K170164	Imaging of optic nerve and retinal nerve fiber layer.
EnFocus 2300 EnFocus 4400	Bioptigen Inc.	12/9/2016	K162783	Imaging of optic nerve and retinal nerve fiber layer.
PLEX Elite 9000 SS-OCT	CARL ZEISS MEDITEC INC.	10/26/2016	K161194	Imaging of optic nerve and retinal nerve fiber layer.
3D OCT-1 Maestro	Topcon Corporation	7/28/2016	K161509	Imaging of optic nerve and retinal nerve fiber layer.
LSFG-NAVI	Softcare Co. Ltd	5/12/2016	K153239	Imaging of optic nerve and retinal nerve fiber layer.
Spectralis HRA + OCT and variants (e.g., below) Spectralis FA+OCT Spectralis ICGA+OCT Spectralis OCT Blue Peak Spectralis OCT with Multicolor	Heidelberg Engineering GmbH	5/6/2016	K152205	Imaging of optic nerve and retinal nerve fiber layer.
RTVue XR OCT Avanti with AngioVue Software	OPTOVUE INC.	2/11/2016	K153080	Imaging of optic nerve and retinal nerve fiber layer.
EnFocus 2300 EnFocus 4400	BIOPTIGEN INC.	12/2/2015	K150722	Imaging of optic nerve and retinal nerve fiber layer.
Optical Coherence Tomography	CARL ZEISS MEDITEC INC.	9/1/2015	K150977	Imaging of optic nerve and retinal nerve fiber layer.

OCT-Camera	OptoMedical Technologies GmbH	3/4/2015	K142953	Imaging of optic nerve and retinal nerve fiber layer.
RESCAN 700 CALLISTO EYE	CARL ZEISS MEDITEC AG	11/18/2014	K141844	Imaging of optic nerve and retinal nerve fiber layer.
PROPPER INSIGHT BINOCULAR INDIRECT OPHTHALMOSOPE	PROPPER MANUFACTUR-ING CO. INC.	9/17/2014	K141638	Imaging of optic nerve and retinal nerve fiber layer.
CENTERVUE MACULAR INTEGRITY ASSESSMENT	CENTERVUE SPA	4/23/2014	K133758	Imaging of optic nerve and retinal nerve fiber layer.
AMICO DH-W35 OPHTHALMOSCOPE SERIES	AMICO DIAGNOSTIC INCORPORATED	3/26/2014	K131939	Imaging of optic nerve and retinal nerve fiber layer.
IVUE 500	OPTOVUE INC.	3/19/2014	K133892	Imaging of optic nerve and retinal nerve fiber layer.
RS-3000 ADVANCE	NIDEK CO. LTD.	2/19/2014	K132323	Imaging of optic nerve and retinal nerve fiber layer.

FDA: Food and Drug Administration; No.; number; OCT; optical coherence tomography; U.S.: United States.

In 2016, the Sensimed Triggerfish® (Sensimed AG, Switzerland) received marketing clearance from the FDA. The FDA classifies the Sensimed Triggerfish®, and substantially equivalent devices of this generic type into Class II under the generic name, Diurnal Pattern Recorder System. Sensimed Triggerfish is a prescription device indicated to detect the peak patterns of variation in IOP over a maximum period of 24 hours to identify the window of time to measure IOP by conventional clinical methods in patients 22 years of age and older. Currently, the Triggerfish® contact lens sensor (CLS) is the only commercially available non-implantable device that provides 24-hour IOP data. FDA product code: PLZ. (4)

Unlike the Triggerfish device, which is removable, another device, the Implandata eyemate® system, is a permanently implantable micro sensor. The eyemate system is implanted into the eye to detect IOP and sends measurements to an external hand-held device. The eyemate system has not been cleared or approved by the FDA. (5)

Rationale

This medical policy was created in January 2009 and has been updated regularly with searches of the PubMed database. The most recent literature update was performed through July 5, 2024.

Medical policies assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Medical policies assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Imaging of the Optic Nerve and Retinal Nerve Fiber Layer

Clinical Context and Test Purpose

The purpose of optic nerve and retinal nerve fiber layer imaging in individuals with or suspected to have glaucoma is to inform a decision about appropriate treatment.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population is individuals with glaucoma or who are suspected to have glaucoma and are being evaluated for diagnosis and monitoring of glaucoma progression.

Interventions

The tests being considered for assessment of the optic nerve and retinal nerve fiber layer include confocal scanning laser ophthalmoscopy, scanning laser polarimetry, and optical coherence tomography (OCT). These tests are considered add-ons to the standard clinical evaluation.

Comparators

There is no single criterion standard for the diagnosis of glaucoma. This diagnosis is made from a combination of visual field testing, intraocular pressure (IOP) measurement, and optic nerve and retinal nerve fiber layer assessment by an ophthalmologist.

Outcomes

Relevant outcomes include the clarity of the images and how reliable the test is at evaluating the optic nerve and nerve fiber layer changes. Demonstration that the information can be used to improve patient outcomes is essential for determining the utility of an imaging technology. Although direct evidence on the impact of the imaging technology from controlled trials would be preferred, in most cases, a chain of evidence needs to be constructed to determine whether there is a tight linkage between the technology and improved health outcomes. The outcomes relevant to this medical policy are IOP, loss of vision, and changes in IOP lowering medications used to treat glaucoma.

For individuals with manifest glaucoma, the relevant period of follow-up is the immediate diagnosis of glaucoma. For individuals with suspected glaucoma, longer term follow-up would be needed to detect changes in visual field or retinal nerve fiber layer. Clinical utility might be demonstrated by a change in the management and reduction in glaucoma progression across follow-up.

Study Selection Criteria

For the evaluation of clinical validity of optic nerve and retinal nerve fiber layer imaging, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores).
- Included a suitable reference standard.
- Patient/sample clinical characteristics were described.
- Patient/sample selection criteria were described.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Systematic Reviews

In 2012, the Agency for Healthcare Research and Quality published a comparative effectiveness review of screening for glaucoma. (6) Included were randomized controlled trials (RCTs), quasi-RCTs, observational cohort and case-control studies, and case series with more than 100 participants. The interventions evaluated included ophthalmoscopy, fundus photography or computerized imaging (OCT, retinal tomography, scanning laser polarimetry), pachymetry (i.e., 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 on 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 in study designs, synthesis of results could not be completed.

A Cochrane review (2015) assessed the diagnostic accuracy of optic nerve head and retinal nerve fiber layer imaging for glaucoma. (7) Included were 103 case-control studies and 3 cohort studies (total N=16,260 eyes) that evaluated the accuracy of recent commercial versions of OCT (spectral domain), Heidelberg Retinal Tomograph (HRT) III, or scanning laser polarimetry (with the variable corneal compensator or enhanced corneal compensation) for diagnosing glaucoma. The population was patients 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 examined different parameters within the 3 tests, and the parameters with the highest diagnostic odds ratio were compared. The 3 tests (OCT, HRT III, scanning laser polarimetry) had similar diagnostic accuracy. Specificity was close to 95%, while sensitivity was 70%. Because a

case-control design with healthy participants and glaucoma patients was used in nearly all studies, concerns were raised about the potential for bias, overestimation of accuracy, and applicability of the findings to clinical practice.

A systematic review, conducted by Chou et al. (2022), was commissioned by the U.S. Preventive Services Task Force (USPSTF) to update its recommendations on screening for glaucoma in adults. (8) A total of 83 studies were included, of which 53 evaluated the diagnostic accuracy of screening tests (OCT, optic disc photography, ophthalmoscopy and biomicroscopy, pachymetry, tonometry, and visual fields). Most studies evaluated spectral-domain OCT (29 studies; n=11,434). Retinal nerve fiber layer thickness on spectral-domain OCT was associated with a pooled sensitivity of 0.79 (95% confidence interval [CI], 0.75 to 0.83) and specificity of 0.92 (95% CI, 0.87 to 0.96) for distinguishing between glaucomatous eyes and controls, based on 15 studies; the pooled area under the receiver operating characteristic curve was 0.90 (95% CI, 0.86 to 0.93), based on 16 studies. Evidence on diagnostic accuracy was also robust for tonometry and the Humphrey Visual Field Analyzer but limited for other screening tests.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

A technology assessment, conducted by Lin et al. (2007) for the American Academy of Ophthalmology (AAO), reviewed 159 studies, published between 2003 and 2006, evaluating optic nerve head and retinal nerve fiber layer devices used to diagnose or detect glaucoma progression. (9) 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.” Management changes for patients diagnosed with glaucoma may include the use of IOP lowering medications, monitoring for glaucoma progression, and potentially surgery to slow the progression of glaucoma.

Section Summary: Imaging of the Optic Nerve and Retinal Nerve Fiber Layer

Numerous studies and systematic reviews have described findings from patients with glaucoma using confocal scanning laser ophthalmoscopy, scanning laser polarimetry, and OCT. A recent systematic review found that retinal nerve fiber layer thickness on spectral-domain OCT was associated with a pooled sensitivity of 0.79 and specificity of 0.92 for glaucoma diagnosis. Although the specificity in several studies was high, it is likely that accuracy was overestimated due to the case-control designs used in the studies. The literature and specialty society guidelines have indicated that optic nerve analysis using confocal scanning laser ophthalmoscopy, scanning laser polarimetry, and OCT are established add-on tests that can be

used with other established tests to improve the diagnosis and direct management of patients with glaucoma and those who are glaucoma suspects. Management changes for patients diagnosed with glaucoma may include the use of IOP lowering medications, monitoring for glaucoma progression, and potentially surgery.

Evaluation of Ocular Blood Flow

Clinical Context and Test Purpose

The diagnosis and monitoring of optic nerve damage are essential for evaluating the progression of glaucoma and determining appropriate treatment. Measurement of ocular blood flow has been studied as a technique to evaluate individuals with glaucoma or suspected glaucoma. One potential application is the early detection of normal-tension glaucoma. (10)

The purpose of evaluating ocular blood flow in individuals who have glaucoma or suspected glaucoma is to inform a decision about appropriate treatment.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population is individuals with glaucoma or suspected glaucoma who are being evaluated for diagnosis and monitoring of glaucoma progression. These tests may have particular utility for normal-tension glaucoma.

Interventions

The tests being considered for assessment of the optic nerve and optic nerve layer include color doppler imaging, Doppler Fourier domain OCT, laser Doppler velocimetry, confocal scanning laser Doppler flowmetry, and retinal functional imager.

Many of these procedures are performed with specialized equipment. While reports of use are longstanding (e.g., Bafa et al. [2001][11]), investigators have commented on the complexity of these parameters (12) and have noted that many of these technologies are not commonly used in clinical settings. (13)

Comparators

There is no criterion standard for the diagnosis of glaucoma. The diagnosis of glaucoma is made using a combination of visual field testing, IOP measurements, and optic nerve and retinal nerve fiber layer assessment.

Outcomes

Relevant outcomes include the reliability of the test for evaluating ocular blood flow and the association between ocular blood flow parameters and glaucoma progression. Demonstration that the information can be used to improve patient outcomes is essential to determining the utility of a diagnostic technology. Although direct evidence on the impact of the imaging technology from controlled trials would be preferred, in most cases, a chain of evidence is needed to determine whether there is a tight linkage between the technology and improved

health outcomes. The outcomes relevant to this medical policy are IOP, loss of vision, and changes in IOP lowering medications used to treat glaucoma.

For individuals with manifest glaucoma, the relevant period of follow-up is the immediate diagnosis of glaucoma. For individuals with suspected glaucoma, longer term follow-up would be needed to detect changes in IOP and loss of vision. Clinical utility might be demonstrated by a change in the management and reduction in glaucoma progression across follow-up.

Study Selection Criteria

For the evaluation of clinical validity of optic nerve and retinal nerve fiber layer imaging, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores).
- Included a suitable reference standard.
- Patient/sample clinical characteristics were described.
- Patient/sample selection criteria were described.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

A technology assessment, conducted by WuDunn et al. (2021) for the AAO, reviewed 75 articles published through June 2020, evaluating the utility of OCT angiography of the peripapillary or macular regions to help detect glaucomatous damage associated with the diagnosis of primary open-angle glaucoma. (14) Per the AAO, the majority of data demonstrates that peripapillary microcirculation measured by vessel density on OCT angiography is decreased in glaucomatous versus healthy eyes. Therefore, this technology can be helpful in detecting vessel density loss associated with glaucoma. Furthermore, peripapillary, macular, and choroidal vessel density parameters may complement visual field and structural OCT measurements in the diagnosis of glaucoma.

Systematic Review

Gu et al. (2021) published a systematic review with meta-analysis evaluating the diagnostic value of laser speckle flowgraphy in glaucoma by investigating the mean blur rate in the optic nerve head. (15) A total of 15 studies, including 692 glaucomatous and 386 healthy eyes, were included; only 1 study was based in the U.S. (Tables 2 and 3). Results are summarized in Table 4. Briefly, the mean blur rate was significantly reduced in glaucomatous versus healthy eyes in the entire area, indicating that blood flow velocity in all areas of the optic nerve head was lower in glaucomatous eyes. Furthermore, the mean blur rate was significantly reduced in glaucomatous versus healthy eyes in the tissue area, indicating that there is insufficient blood supply in the deep fundus tissues and optic nerve head ischemia in glaucomatous eyes. Lastly, the mean blur rate was significantly reduced in glaucomatous versus healthy eyes in the vascular area, indicating that patients with glaucoma have an insufficient retinal blood supply. The authors

concluded that while laser speckle flowgraphy is a feasible diagnostic tool for glaucoma, more prospective studies are needed to fully evaluate this technology.

Table 2. Comparison of Trials/Studies Included in SR & M-A

Study	Gu et al. (2021) (15)
Aizawa (2011) (16)	•
Gardiner (2019) (17)	•
Iida (2017) (18)	•
InoueYanagimachi (2018) (19)	•
Kiyota (2017) (20)	•
Kiyota (2017) (21)	•
Kiyota (2018) (22)	•
Kobayashi (2014) (23)	•
Kohmoto (2019) (24)	•
Kuroda (2020) (25)	•
Mursch-Edlmayr (2018) (26)	•
Mursch-Edlmayr (2019) (27)	•
Mursch-Edlmayr (2020) (28)	•
Shiga (2016) (29)	•
Takeyama (2018) (30)	•

M-A: meta-analysis; SR: systematic review.

Table 3. SR & M-A Characteristics

Study	Dates	Trials	Participants	N	Design	Duration
Gu et al. (2021) (15)	Through Dec 2020	15	Patients with glaucomatous or healthy eyes undergoing laser speckle flowgraphy to examine the ocular blood flow. The majority of participants in the included studies were	692 glaucomatous eyes; 386 healthy eyes.	Observational studies or RCTs.	N/A

			Japanese (N=11 studies).			

M-A: meta-analysis; N/A: not applicable; SR: systematic review; RCTs: randomized controlled trials.

Table 4. SR & M-A Results

Study	MBR-Entire Area	MBR-Tissue Area	MBR-Vascular Area
Gu et al. (2021) (15)			
Total N			
Glaucomatous eyes	541	660	573
Healthy eyes	254	372	268
MD (95% CI)	-5.59 (-6.19 to -4.99)	-2.2 (-2.49 to -1.91)	-5.92 (-7.77 to -4.07)
p-value	1	.07	.003

CI: confidence interval; M-A: meta-analysis; MBR: mean blur rate; MD: mean difference; SR: systematic review.

Nonrandomized Studies

Abegao Pinto et al. (2016) reported on the results from the prospective, cross-sectional, case-control, Leuven Eye Study, which included 614 individuals who had primary open-angle glaucoma (n=214), normal-tension glaucoma (n=192), ocular hypertension (n=27), suspected glaucoma (n=41), or healthy controls (n=140). (31) The study objective was to identify the blood flow parameters most highly associated with glaucoma using technology commonly available in an ophthalmologist's office or hospital radiology department. Assessment of ocular blood flow included color doppler imaging, retinal oximetry, dynamic contour tonometry, and OCT enhanced-depth imaging of the choroid. The glaucoma groups had higher perfusion pressure than controls ($p<0.001$), with lower velocities in both central retinal vessels ($p<0.05$), and choroidal thickness asymmetries. The normal-tension glaucoma group, but not the primary open-angle glaucoma group, had higher retinal venous saturation than healthy controls ($p=0.005$). There were no significant differences in macular scans. The diagnostic accuracy and clinical utility were not addressed.

Kurysheva et al. (2017) compared ocular blood flow with choroidal thickness to determine which had a higher diagnostic value for detecting early glaucoma. (32) Thirty-two patients with pre-perimetric glaucoma were matched with 30 control patients. Using OCT, retinal nerve fiber layer thickness between groups was found to be comparable; the ganglion cell complex was thicker in the control patients, and there was no significant difference between groups for choroid foveal loss volume. Mean blood flow velocity in the vortex veins had the highest area under the receiver operating characteristic curve (1.0) and z-value (5.35). Diastolic blood flow velocity in the central retinal artery had a diagnostic value of 2.74 and area under the receiver operating characteristic curve of 0.73. The authors concluded that this study suggested a diagnostic benefit in measuring blood flow velocities.

Witkowska et al. (2017) investigated blood flow regulation using laser speckle flowgraphy in 27 individuals. (33) In this prospective study, the authors specifically looked at mean blur rate blood flow in the optic nerve head and a peripapillary region. First, participants' blood flow was

measured when they were in a sitting position; then, participants were asked to perform an isometric "squatting" exercise for 6 minutes. Compared with baseline (sitting), exercise significantly increased ocular perfusion blood pressure (78.5%), mean blur rate in the tissue of the optic nerve head (18.1%), and mean blur rate in the peripapillary region (21.18.3%) ($p<0.001$). Few studies have used laser speckle flowgraphy to study autoregulation of ocular blood flow during a change in blood pressure, and this study is limited to Japanese populations. Despite the lack of literature and limited population, the authors noted laser speckle flowgraphy could be a valuable tool to study the regulation of blood flow in the optic nerve head, particularly in patients suspected of having glaucoma or patients who have glaucoma.

Rusia et al. (2011) reported on the use of color doppler imaging in normal and glaucomatous eyes. (34) Using data from other studies, a weighted mean was derived for the peak systolic velocity, end-diastolic velocity, and Pourcelot Resistive Index in the ophthalmic, central retinal, and posterior ciliary arteries. Data from 3061 glaucoma patients and 1072 controls were included. Mean values for glaucomatous eyes were within 1 standard deviation (SD) of the values for controls for most color doppler imaging parameters. Methodologic differences created interstudy variance in color doppler imaging 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 had overlapping ranges, caution should be used when classifying glaucoma status based on a single color doppler imaging measurement.

Tables 5 and 6 summarize characteristics and results of key nonrandomized studies, respectively. Tables 7 and 8 summarize study limitations.

Table 5. Summary of Key Nonrandomized Study Characteristics

Study	Study Type	Country	Dates	Participants	Treatment 1	Treatment 2	Follow-up
Kurysheva (2017) (32)	Prospective	Russia	NR	Patients with pre-perimetric glaucoma (n=32) and age-matched controls (n=30)	OCT	N/A	NR
Witkowska (2017) (33)	Prospective	Austria	2015-2016	Healthy subjects (n=27)	Laser speckle flowgraphy All participants were White.	N/A	6 minutes

OCT: optical coherence tomography; N/A: not applicable; NR: not reported.

Table 6. Summary of Key Nonrandomized Study Results

Study	AUC and Diagnostic Value AUC; p-value	Increase in OPP from Baseline	Increase in MTONH from Baseline	Increase in MTPPR from Baseline
Kurysheva (2017) (32)		NR	NR	NR
MBFV in VV	1.0; <0.0001			
MBFV in CRV	0.85; 0.0001			
DBFV in CRA	0.73; 0.006			
DBFV in LSPCAs	0.71; 0.011			
Witkowska (2017) (33)	NR	78.5+/-19.8%	18.1+/-7.7%	21.1+/-8.3%

AUC: area under the receiver operating characteristic curve; CRA: central retinal artery; CRV: central retinal vein; DBFV: diastolic blood flow velocity; LSPCA: lateral short posterior ciliary artery; MBFV: mean blood flow velocity; MTPPR: mean blur rate in the peripapillary region; MTONH: mean blur rate in the tissue of the optic nerve head; NR: not reported; OPP: ocular perfusion pressure; VV: vortex veins.

Table 7. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Kurysheva et al. (2017) (32)	3. Study population included healthy controls; 4. Enrolled populations do not reflect relevant diversity		3. Intervention applied to all patients; No test utilized as comparator	5. Adverse events of test not described	1. Follow-up not reported
Witkowska et al. (2017) (33)	3. Study population was healthy individuals; 4. Enrolled populations do not reflect relevant diversity		3. No test utilized as comparator	5. Adverse events of test not described	1. Follow-up evaluated short-term changes only

The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4. Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 8. Study Design and Conduct Limitations

Study	Selection[a]	Binding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Complete-ness[e]	Statistical[f]
Kurysheva et al. (2017) (32)	1. Selection of patients not described; 2. Selection of control subjects was not randomized, but based on person accompanying patients	1. Examiner not blinded to patient group	4. Evaluator description not provided			
Witkowska et al. (2017) (33)	1. Selection of patients not described	1. All patients were healthy and underwent same treatment, therefore no blinding was utilized				2.Comparison to other tests not included in study, since no comparator utilized

The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.

[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

The clinical utility of techniques to evaluate ocular blood flow is similar to that for other imaging techniques. The objective is to improve the diagnosis and direct management of patients with glaucoma or suspected glaucoma. Measures of ocular blood flow may have particular utility for the diagnosis and monitoring of normal-tension glaucoma.

The only longitudinal study identified is a study by Calvo et al. (2012) on the predictive value of retrobulbar blood flow velocities in a prospective series of 262 who were glaucoma suspect. (35) 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 during the baseline examination, and conversion to glaucoma was assessed at least yearly according to changes observed with confocal scanning laser ophthalmoscopy. During the 48-month follow-up, 36 (13.7%) patients developed glaucoma and 226 did not. Twenty (55.5%) of those who developed glaucoma 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 developed glaucoma compared with subjects who did not.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

The evidence does not permit any inferences about the utility of ocular blood flow evaluation in the evaluation of glaucoma.

Section Summary: Evaluation of Ocular Blood Flow

Techniques to measure ocular blood flow or ocular blood velocity are being evaluated for the diagnosis of glaucoma. Data for these techniques remain limited. Current literature focuses on which technologies are most reliably associated with glaucoma. Literature reviews have not identified studies that suggest whether these technologies improve the diagnosis of glaucoma or whether measuring ocular blood flow in patients with glaucoma or suspected glaucoma improves health outcomes.

24-Hour Intraocular Pressure Monitoring

In 2012, Mansouri and colleagues (39) aimed to examine the safety, tolerability, and reproducibility of IOP patterns during continuous 24-hour IOP monitoring with a contact lens sensor (CLS). Forty patients suspected of having glaucoma (n=21) or with established glaucoma (n=19) were evaluated. Patients participated in two 24-hour IOP monitoring sessions (S1 and S2) at 1-week intervals using Triggerfish CLS. Patients pursued daily activities, and sleep behavior was not controlled. Incidence of adverse events and tolerability (visual analog scale [VAS] score) were assessed. Reproducibility of signal patterns was assessed using Pearson correlations. The mean (SD) age of the patients was 55.5 (15.7) years, and 60% were male. Main adverse events were blurred vision (82%), conjunctival hyperemia (80%), and superficial punctate keratitis (15%). The mean SD VAS score was 27.2 (18.5) mm in S1 and 23.8 (18.7) mm in S2 (P=.22). The overall correlation between the 2 sessions was 0.59 (0.51 for no glaucoma medication and 0.63 for glaucoma medication) (P=.12). Mean SD positive linear slopes of the sensor signal from wake to 2 hours into sleep were detected in both sessions for the no glaucoma medication group but not for the glaucoma medication group. Repeated use of the CLS demonstrated good safety and tolerability. The recorded IOP patterns showed fair to good reproducibility, suggesting that data from continuous 24-hour IOP monitoring may be useful in the management of patients with glaucoma.

In 2014, Hollo et al. (40) reported the results of a trial which evaluated 24-hour continuous IOP monitoring with a telemetric CLS to detect prostaglandin-induced IOP reduction. A total of 9 individuals with ocular hypertensive and primary open-angle glaucoma were washed out from IOP-lowering medication for 6 weeks. One study eye per participant underwent 3 baseline 24-hour measurement curves 4 days apart: 2 curves employing continuous monitoring with a CLS and 1 curve using Goldmann applanation tonometry (GAT). Subsequently, the participants underwent travoprost monotherapy for a total of 3 months. Continuous IOP pressure monitoring using the CLS and GAT curves were repeated on the study eyes under treatment at the end of the third month. The 24-hour GAT IOP (mean ±SD) diminished from 22.91 ± 5.11 to 18.24 ± 2.49 mmHg ($p<0.001$). In contrast, the means of the 3 CLS curves demonstrated no significant difference (152.94, 142.35, and 132.98 au, p=0.273). The authors concluded that the continuous monitoring of IOP utilizing the CLS cannot be clinically used to monitor changes in IOP induced by topical medication in glaucoma and has limited value in identification of transient IOP elevation periods.

In 2015, Mansouri et al. (41) evaluated the efficacy of CLS for monitoring 24-hour IOP related short-term patterns and compare with IOP obtained by pneumatonometry. This prospective clinical trial involved 31 healthy volunteers and 2 glaucoma patients that were monitored for 24

hours in a sleep laboratory. One randomly selected eye was fitted with a CLS (Triggerfish, Switzerland). In the contralateral eye, IOP measurements were taken using a pneumatonometer every 2 hours with subjects in the habitual body positions. Heart rate (HR) was measured 3 times during the night for periods of 6 minutes separated by 2 hours. Performance of CLS was defined in two ways: 1) recording the known pattern of IOP increase going from awake (sitting position) to sleep (recumbent), defined as the wake/sleep (W/S) slope and 2) accuracy of the ocular pulse frequency (OPF) concurrent to that of the HR interval. Strength of association between overall CLS and pneumatonometer curves was assessed using coefficients of determination (R2). The W/S slope was statistically significantly positive in both eyes of each subject (CLS, 57.0 ± 40.5 mVeq/h, $p<0.001$ and 1.6 ± 0.9 mmHg/h, $p<0.05$ in the contralateral eye). In all, 87 CLS plots concurrent to the HR interval were evaluated. Graders agreed on evaluability for OPF in 83.9% of CLS plots. Accuracy of the CLS to detect the OPF was 86.5%. Coefficient of correlation between CLS and pneumatonometer for the mean 24-h curve was R2 = 0.914. CLS measurements compare well to the pneumatonometer and may be of practical use for detection of sleep-induced IOP changes. The CLS also can detect ocular pulsations with good accuracy in a majority of eyes. A limitation of this study is the absence of a control group within the cohort that was without glaucoma, which resulted in the study not addressing the reproducibility and accuracy of IOP measurements in populations with normal or near-normal IOP.

In 2017, Beltran-Agulló et al. performed a small, randomized, cross-over, open label comparative study to determine the difference in IOP measured by the Sensimed Triggerfish contact lens when lying in a supine versus head-up sleeping position (30°) in patients with progressive primary open-angle glaucoma or normotensive glaucoma. (42) Continuous 24-hour IOP monitoring was performed using Triggerfish on 2 separate sessions. Patients were randomly assigned to sleep supine one night and 30° head-up the other. Outputs in arbitrary units were obtained. Sleep and wake periods were defined as 22:00-6:00 and 8:00-22:00. Mean Triggerfish values during sleep and wake periods and wake-sleep and sleep-wake slopes were calculated for each session. Triggerfish output signals were compared between sleep positions. Twelve patients completed the study. Significant mean positive slopes were noted during the sleep period for both positions ($p<0.01$). No significant differences in the Triggerfish mean values were observed between positions ($p=0.51$). Six (54%) patients had mean Triggerfish values significantly higher during the supine session, while 4 (36%) patients had higher values during the head-up session. A significant increase in Goldmann IOP ($p=0.001$) and Triggerfish ($p=0.02$) measurements were observed after 24 hours of Triggerfish wear ('drift phenomenon'). The authors concluded that sleep position affects IOP as measured by Triggerfish in some patients with progressive glaucoma. The upward drift in Triggerfish output was detected in >50% of the patients and requires further investigation to establish whether the increased output values are an artefact induced by the Triggerfish or a real change in IOP.

In 2020, Shioya et al. (43) reported on a study involving 65 subjects characterized by glaucomatous visual field defects and optic disc damage, open iridocorneal angle and the absence of secondary causes of glaucoma. All subjects underwent 24-hour Triggerfish monitoring, and serial GAT measurements every 3 hours over 15 hours. The authors combined

the data for each GAT timepoint with the corresponding Triggerfish data to assess subjects' potential for exceeding the threshold for diagnosis of normal tension glaucoma. The authors reported that sensitivity was at least 60% for 4 out of the 6 timepoints measured. Two specific timepoints (15:00 and 18:00) were highly sensitive, at 100% each. Negative predictive value was above 90% for all timepoints. The authors concluded that "Contact lens sensor information can be used in conjunction with a single tonometric reading to determine patients' potential of having IOP levels exceeding the diagnostic threshold within a 24-hr period, without the need to perform a 24-hr tonometric curve." These results indicate there is some potential role for use of the Triggerfish device in identifying individuals with glaucoma who may be missed with routine screening. However, the results of this trial should be validated in a larger trial with a more robust methodology.

In 2023, Gaboriau et al. (44) reported a prospective cross-sectional study evaluating the Triggerfish device's ability to compare 24-hour IOP-related fluctuation monitoring in 54 participants with OAG. The participants were stratified into two groups based upon different rates of visual field progression measured with standard automated perimetry, < -0.5 dB/year (Group 1) or ≥ -0.5 dB/year (Group 2). Monitoring was begun in the morning for all participants following Goldman applanation tonometry IOP measurement. The Triggerfish device was monitored 24 hours and then removed. At the end of the study period, the magnitude of monitoring curve (24hMagn) was significantly higher in group 1 (343.1 ± 62.3 mV) than in group 2 (274.0 ± 75.0 mV; p=0.0027), as was the absolute value of the area under the monitoring curve (24hArea; p=0.0251). The authors reported an overall accuracy of 77.7%, sensitivity of 81.3%, and specificity of 72.7%. They concluded that use of the Triggerfish device, in addition to other predictive factors, may allow earlier identification of disease progression and appropriate treatment adjustments.

Additional published studies consist of small sample sizes and/or lack long-term follow-up. (45-52) Additional long-term studies with larger sample sizes are needed to determine the accuracy and reproducibility of 24-Hour IOP monitoring and the impact on health outcomes.

Practice Guidelines and Position Statements

American Academy of Ophthalmology

In 2020, the American Academy of Ophthalmology issued 2 preferred practice patterns on primary open-angle glaucoma suspect and primary open-angle glaucoma, both recommending evaluation of the optic nerve and retinal nerve fiber layer (36, 37) The documents stated that stereoscopic visualization and computer-based imaging of the optic nerve head and retinal nerve fiber layer provide different information about the optic nerve and are complementary. Both imaging methods are useful adjuncts as part of a comprehensive clinical examination. The guidelines described 3 types of computer-based imaging devices (confocal scanning laser ophthalmoscopy, scanning laser polarimetry, OCT) currently available for glaucoma, which are similar in their ability to distinguish glaucoma from controls and noted that "computer-based digital imaging of the optic nerve head and retinal nerve fiber layer is routinely used to provide quantitative information to supplement the clinical examination of the optic nerve…. computerized imaging may be useful to distinguish between glaucomatous and

nonglaucomatous retinal nerve fiber layer thinning." In addition, the Academy concluded that, as device technology evolves, the performance of diagnostic imaging devices is expected to improve.

U.S. Preventive Services Task Force Recommendations

The U.S. Preventative Task Force (USPSTF) published recommendations on screening for primary open-angle glaucoma in adults (40 years or older) in 2022. (38) Based on findings from the systematic review by Chou et al. (discussed in Rationale section), the USPSTF concluded that the evidence is insufficient to assess the balance of benefits and harms of screening in these patients. This recommendation is consistent with the previous 2013 statement. With regard to screening tests, the USPSTF states: "Diagnosis of open-angle glaucoma is based on a combination of tests showing degenerative changes in the optic disc, increased IOP [intraocular pressure], and defects in visual fields... Imaging tests such as optical coherence tomography (OCT) or spectral-domain OCT (which analyzes the spectrum of reflected light on the retina) and optic disc photography (to view the optic nerve head, retina, or both) can supplement the clinical examination."

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this policy are listed in Table 9.

Table 9. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05344274	Direct Measures of Retinal Blood Flow and Autoregulation as Robust Biomarkers for Early Glaucoma	90	Sep 2026
NCT01957267	Longitudinal Observational Study Using Functional and Structural Optical Coherence Tomography to Diagnose and Guide Treatment of Glaucoma	160	May 2026
NCT05726058	Ocular Blood Flow Imaging for Glaucoma Assessment	150	Apr 2024
Unpublished			
NCT04646122	Predicting Glaucoma Progression with Optical Coherence Tomography Structural and Angiographic Parameters	100	Mar 2022
NCT02178085	Ocular Blood Flow Assessment in Glaucoma (OBAMAg)	62	Sep 2019

No: number; NCT: national clinical trial.

Summary of Evidence

For individuals who have glaucoma or suspected glaucoma who receive imaging of the optic nerve and retinal nerve fiber layer, the evidence includes studies on diagnostic accuracy. Relevant outcomes are test accuracy, symptoms, morbid events, functional outcomes, and medication use. Confocal scanning laser ophthalmoscopy, scanning laser polarimetry, and optical coherence tomography (OCT) can be used to evaluate the optic nerve and retinal nerve fiber layer in patients with glaucoma and suspected glaucoma. Numerous articles have described findings from patients with known and suspected glaucoma using confocal scanning laser ophthalmoscopy, scanning laser polarimetry, and OCT. These studies have reported that abnormalities may be detected on these examinations before functional changes are noted. The literature and specialty society guidelines have indicated that optic nerve analysis using confocal scanning laser ophthalmoscopy, scanning laser polarimetry, and OCT are established add-on tests that may be used to diagnose and manage patients with glaucoma and suspected glaucoma. These results are often considered along with other findings to make diagnostic and therapeutic decisions about glaucoma care, including use of topical medication, monitoring, and surgery to lower intraocular pressure (IOP). Thus, accurate diagnosis of glaucoma would be expected to reduce the progression of glaucoma. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have glaucoma or suspected glaucoma who receive evaluation of ocular blood flow, the evidence includes association studies. Relevant outcomes are test accuracy, symptoms, morbid events, functional outcomes, and medication use. Techniques to measure ocular blood flow or ocular blood velocity are used to determine appropriate glaucoma treatment options. The data for these techniques remain limited. Literature reviews have not identified studies addressing whether these technologies improve diagnostic accuracy or whether they improve health outcomes in patients with glaucoma. Some have suggested that these parameters may inform understanding of the variability in visual field changes in patients with glaucoma, (i.e., they may help explain why patients with similar levels of IOP 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. The evidence is insufficient to determine the effects of the technology on health outcome.

For individuals with glaucoma, there are no published clinical studies that compare the rates of glaucoma progression in individuals who underwent continuous (>24 hours) monitoring of IOP (i.e., triggerfish device) with individuals who are monitored using the current standard practice. In addition, peer-reviewed studies consist of small study populations and lack long-term follow-up. Additional long term adequately powered randomized controlled trials (RCTs) with sufficiently large sample sizes are needed to determine the effects of this technology on health outcomes.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	92133, 92134, 0198T, 0329T
HCPCS Codes	None

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

References

1. Mohindroo C, Ichhpujani P. Kumar S. Current imaging modalities for accessing ocular blood flow in glaucoma. J Curr Glaucoma Pract. Sep-Dec 2016; 10(3):104-112. PMID 27857490
2. SENSIMED Triggerfish®-Continuous IOP Monitoring. SENSIMED AG. Switzerland. Available at <https://www.sensimed.ch> (accessed July 5, 2024).
3. SENSIMED Triggerfish® provides a 24-hour continuous recording of ocular dimensional changes related to IOP in habitual body position. Mar 2020. Available at <https://www.sensimed.ch> (accessed July 5, 2024).
4. SENSIMED Triggerfish®. U. S. Food and Drug Administration (FDA). Center for Devices and Radiologic Health (Apr 2016). Available at <https://www.accessdata.fda.gov> (accessed July 5, 2024).
5. Mansouri K, Kersten-Gomez I, Hoffmann EM, et. al. Intraocular pressure telemetry for managing glaucoma during the COVID-19 pandemic. Ophthalmol Glaucoma. Sep-Oct 2021; 4(5):447-453. PMID 33358988
6. Ervin AM, Boland MV, Myrowitz EH, et al. Screening for glaucoma: Comparative effectiveness (comparative effectiveness review no. 59). Rockville, MD: Agency for Healthcare Research and Quality; 2012. PMID 22649799
7. Michelessi M, Lucenteforte E, Oddone F, et al. Optic nerve head and fibre layer imaging for diagnosing glaucoma. Cochrane Database Syst Rev. Nov 30 2015; (11):CD008803. PMID 26618332
8. Chou R, Selph S, Blazina I, et al. Screening for glaucoma in adults: Updated evidence report and systematic review for the US Preventive Services Task Force. JAMA. May 24 2022; 327(20):1998-2012. PMID 35608575
9. Lin SC, Singh K, Jampel HD, et al. Optic nerve head and retinal nerve fiber layer analysis: a report by the American Academy of Ophthalmology. Ophthalmology. Oct 2007; 114(10):1937-1949. PMID 17908595
10. Shiga Y, Omodaka K, Kunikata H, et al. Waveform analysis of ocular blood flow and the early detection of normal tension glaucoma. Invest Ophthalmol Vis Sci. Nov 21 2013; 54(12):7699-7706. PMID 24130177
11. Bafa M, Lambrinakis I, Dayan M, et al. Clinical comparison of the measurement of the IOP with the ocular blood flow tonometer, the Tonopen XL and the Goldmann applanation tonometer. Acta Ophthalmol Scand. Feb 2001; 79(1):15-18. PMID 11167279

12. Schmidl D, Garhofer G, Schmetterer L. The complex interaction between ocular perfusion pressure and ocular blood flow-relevance for glaucoma. Exp Eye Res. Aug 2011; 93(2):141-155. PMID 20868686
13. Harris A, Kagemann L, Ehrlich R, et al. Measuring and interpreting ocular blood flow and metabolism in glaucoma. Can J Ophthalmol. Jun 2008; 43(3):328-336. PMID 18443609
14. WuDunn D, Takusagawa HL, Sit AJ, et al. OCT Angiography for the diagnosis of glaucoma: A report by the American Academy of Ophthalmology. Ophthalmology. Aug 2021; 128(8):1222-1235. PMID 33632585
15. Gu C, Li A, Yu L. Diagnostic performance of laser speckle flowgraphy in glaucoma: a systematic review and meta-analysis. Int Ophthalmol. Nov 2021; 41(11):3877-3888. PMID 34327617
16. Aizawa N, Yokoyama Y, Chiba N, et al. Reproducibility of retinal circulation measurements obtained using laser speckle flowgraphy-NAVI in patients with glaucoma. Clin Ophthalmol. 2011; 5:1171-1176. PMID 21887100
17. Gardiner SK, Cull G, Fortune B, et al. Increased Optic Nerve Head Capillary Blood Flow in Early Primary Open-Angle Glaucoma. Invest Ophthalmol Vis Sci. Jul 01 2019; 60(8):3110-3118. PMID 31323681
18. Iida Y, Akagi T, Nakanishi H, et al. Retinal Blood Flow Velocity Change in Parafoveal Capillary after Topical Tafluprost Treatment in Eyes with Primary Open-angle Glaucoma. Sci Rep. Jul 10 2017; 7(1):5019. PMID 28694501
19. Association between mitochondrial DNA damage and ocular blood flow in patients with glaucoma. Br J Ophthalmol. Aug 2019; 103(8):1060-1065. PMID 30190366
20. Kiyota N, Kunikata H, Shiga Y, et al. Relationship between laser speckle flowgraphy and optical coherence tomography angiography measurements of ocular microcirculation. Graefes Arch Clin Exp Ophthalmol. Aug 2017; 255(8):1633-1642. PMID 28462456
21. Kiyota N, Shiga Y, Suzuki S, et al. The Effect of Systemic Hyperoxia on Optic Nerve Head Blood Flow in Primary Open-Angle Glaucoma Patients. Invest Ophthalmol Vis Sci. Jun 01 2017; 58(7):3181-3188. PMID 28654983
22. Kiyota N, Kunikata H, Shiga Y, et al. Ocular microcirculation measurement with laser speckle flowgraphy and optical coherence tomography angiography in glaucoma. Acta Ophthalmol. Jun 2018; 96(4):e485-e492. PMID 29575676
23. Kobayashi W, Kunikata H, Omodaka K, et al. Correlation of optic nerve microcirculation with papillomacular bundle structure in treatment naive normal tension glaucoma. J Ophthalmol. 2014; 2014:468908. PMID 25574382
24. Kohmoto R, Sugiyama T, Ueki M, et al. Correlation between laser speckle flowgraphy and optical coherence tomography angiography measurements in normal and glaucomatous eyes. Clin Ophthalmol. 2019; 13:1799-1805. PMID 31571818
25. Kuroda F, Iwase T, Yamamoto K, et al. Correlation between blood flow on optic nerve head and structural and functional changes in eyes with glaucoma. Sci Rep. Jan 20 2020; 10(1): 729. PMID 31959837
26. Mursch-Edlmayr AS, Luft N, Podkowinski D, et al. Laser speckle flowgraphy derived characteristics of optic nerve head perfusion in normal tension glaucoma and healthy individuals: a Pilot study. Sci Rep. Mar 28 2018; 8(1):5343. PMID 29593269

27. Mursch-Edlmayr AS, Luft N, Podkowinski D, et al. Differences in Optic Nerve Head Blood Flow Regulation in Normal Tension Glaucoma Patients and Healthy Controls as Assessed With Laser Speckle Flowgraphy During the Water Drinking Test. J Glaucoma. Jul 2019; 28(7):649-654. PMID 30950964
28. Mursch-Edlmayr AS, Pickl L, Calzetti G, et al. Comparison of Neurovascular Coupling between Normal Tension Glaucoma Patients and Healthy Individuals with Laser Speckle Flowgraphy. Curr Eye Res. Nov 2020; 45(11):1438-1442. PMID 32255706
29. Shiga Y, Kunikata H, Aizawa N, et al. Optic Nerve Head Blood Flow, as Measured by Laser Speckle Flowgraphy, Is Significantly Reduced in Preperimetric Glaucoma. Curr Eye Res. Nov 2016; 41(11):1447-1453. PMID 27159148
30. Takeyama A, Ishida K, Anraku A, et al. Comparison of Optical Coherence Tomography Angiography and Laser Speckle Flowgraphy for the Diagnosis of Normal-Tension Glaucoma. J Ophthalmol. 2018; 2018:1751857. PMID 29651339
31. Abegao Pinto L, Willekens K, Van Keer K, et al. Ocular blood flow in glaucoma-the Leuven eye study. Acta Ophthalmol. Sep 2016; 94(6):592-598. PMID 26895610
32. Kurysheva NI, Parshunina OA, Shatalova EO, et al. Value of structural and hemodynamic parameters for the early detection of primary open-angle glaucoma. Curr Eye Res. Mar 2017; 42(3):411-417. PMID 27341295
33. Witkowska KJ, Bata AM, Calzetti G, et al. Optic nerve head and retinal blood flow regulation during isometric exercise as assessed with laser speckle flowgraphy. PLoS One. 2017; 12(9):e0184772. PMID 28898284
34. Rusia D, Harris A, Pernic A, et al. Feasibility of creating a normative database of colour Doppler imaging parameters in glaucomatous eyes and controls. Br J Ophthalmol. Sep 2011; 95(9):1193-1198. PMID 21106991
35. Calvo P, Ferreras A, Polo V, et al. Predictive value of retrobulbar blood flow velocities in glaucoma suspects. Invest Ophthalmol Vis Sci. Jun 22 2012; 53(7):3875-3884. PMID 22589447
36. American Academy of Ophthalmology. Preferred Practice Pattern®: Primary Open-Angle Glaucoma. 2020. Available at <https://www.aao.org> (accessed July 5, 2024).
37. American Academy of Ophthalmology. Preferred Practice Pattern®: Primary Open-Angle Glaucoma Suspect. 2020. Available at <https://www.aao.org> (accessed July 5, 2024).
38. Mangione CM, Barry MJ, Nicholson WK, et al. Screening for Primary Open-Angle Glaucoma: US Preventive Services Task Force Recommendation Statement. JAMA. May 24 2022; 327(20):1992-1997. PMID 35608574
39. Mansouri K, Medeiros F, Tafreshi A, et al. Continuous 24-hour monitoring of intraocular pressure patterns with a contact lens sensor: safety, tolerability, and reproducibility in patients with glaucoma. Arch Ophthalmol. Dec 2012; 130(12):1534-1539. PMID 23229696
40. Holló G, Kóthy P, Vargha P, et al. Evaluation of continuous 24-hour intraocular pressure monitoring for assessment of prostaglandin-induced pressure reduction in glaucoma. J Glaucoma. Jan 2014; 23(1):e6-12. PMID 24370812
41. Mansouri K, Weinreb R, Liu J, et al. Efficacy of a contact lens sensor for monitoring 24-h intraocular pressure related patterns. PLoS One. May 5 2015; 10(5):e0125530. PMID 25942434

42. Beltran-Agulló L, Buys Y, Jahan F, et al. Twenty-four hour intraocular pressure monitoring with the SENSIMED Triggerfish contact lens: Effect of body posture during sleep. Br J Ophthalmol. Oct 2017; 101(10):1323-1328. PMID 28270491
43. Shioya S, Higashide T, Tsuchiya S, et al. Using 24-hr ocular dimensional profile recorded with a sensing contact lens to identify primary open-angle glaucoma patients with intraocular pressure constantly below the diagnostic threshold. Acta Ophthalmol. Dec 2020; 98(8):e1017-e1023. PMID 32339402
44. Gaboriau T, Dubois R, Foucque B, et al. 24-Hour monitoring of intraocular pressure fluctuations using a contact lens sensor: diagnostic performance for glaucoma progression. Invest Ophthalmol Vis Sci. 2023; 64(3):3. PMID 36862120
45. Mottet B, Aptel F, Romanet JP, et al. 24-hour intraocular pressure rhythm in young healthy subjects evaluated with continuous monitoring using a contact lens sensor. JAMA Ophthalmol. Dec 2013; 131(12):1507-1516. PMID 24158696
46. Agnifili L, Mastropasqua R, Frezzotti P, et al. Circadian intraocular pressure patterns in healthy subjects, primary open angle and normal tension glaucoma patients with a contact lens sensor. Acta Ophthalmol. 2015; 93(1):e14-e21. PMID 31687621
47. Pajic B, Pajic-Eggspuchler B, Haefliger I, et al. Continuous IOP fluctuation recording in normal tension glaucoma patients. Current Eye Research 2011; 36(12):1129-1138. PMID 21978205
48. Lorenz K, Korb C, Herzog N, et al. Tolerability of 24-hour intraocular pressure monitoring of a pressure-sensitive contact lens. J Glaucoma. 2013; 22(4):311-316. PMID 23524857
49. Marando CM, Mansouri K, Kahook MY, et al. Tolerability and functionality of a wireless 24-hour ocular telemetry sensor in African American glaucoma patients. J Glaucoma. 2019; 28(2):119-124. PMID 30688840
50. Gillmann K, Wasilewicz R, Hoskens K, et al. Continuous 24-hour measurement of intraocular pressure in millimeters of mercury (mmHg) using a novel contact lens sensor: comparison with pneumatonometry. PLoS One. 2021; 23:16(3):e0248211. PMID 33755676
51. Miki A, Kumoi M, Maeda N, et al. Transient changes in refractive error and corneal tomography after 24-h continuous monitoring of intraocular pressure patterns with a contact lens sensor. Jpn J Ophthalmol. 2020; 64(2):127-133. PMID 32056036
52. Yang Z, Mansouri K, Moghimi S, Weinreb RN. Nocturnal variability of intraocular pressure monitored with contact lens sensor is associated with visual field loss in glaucoma. J Glaucoma. Mar 1 2021; 30(3):e56-e60. PMID 33137021

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision	
Date	**Description of Change**
09/15/2024	Document updated with literature review. The following change was made in Coverage: Updated term patients to individuals throughout coverage. Added references 8, 16-30, 36-38 and 44; others updated, some removed.
08/15/2023	Reviewed. No changes.
12/15/2022	Document updated with literature review. The following editorial change was made in Coverage: Added the term "and" to the existing medically necessary coverage statement to state "Analysis of the optic nerve and retinal nerve fiber layer in the diagnosis and evaluation of patients with glaucoma or glaucoma suspects…." Added references 3-5, 13, 14, 24, 29-32; others updated, some removed.
09/01/2021	Reviewed. No changes.
05/15/2020	Document updated with literature review. The following change was made in Coverage: Added "or glaucoma suspects" to the existing medically necessary coverage statement for analysis of the optic nerve (retinal nerve fiber layer) in the diagnosis and evaluation of patients with glaucoma. Added references 14, 15, 21-26.
06/15/2018	Reviewed. No changes.
09/15/2017	Document updated with literature review. The following change was made in Coverage: 1) Removed "known or suspected" from the medically necessary coverage statement for the analysis of the optic nerve (retinal nerve fiber layer) in the diagnosis and evaluation of patients with glaucoma 2) Removed "with Doppler ultrasonography" from the experimental, investigational and/or unproven coverage statement for the measurement of ocular blood flow, pulsatile ocular blood flow or blood flow velocity.
08/15/2016	Document updated with literature review. Coverage unchanged.
01/15/2015	Reviewed. No changes.
07/01/2013	Document updated with literature review. The following was added to Coverage: Monitoring of intraocular pressure for 24 hours or longer, unilateral or bilateral, is considered experimental, investigational and unproven using any method of measurement, including but not limited to contact lens sensor technology (e.g., Triggerfish®).
08/01/2011	Document updated with literature review. The following change was made: 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. CPT/HCPCS code(s) updated.
01/01/2009	New medical document