Corneal Hysteresis and Intraocular Pressure Measurement

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Instructions for Use

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Application

UnitedHealthcare Commercial

This Medical Policy applies to all UnitedHealthcare Commercial benefit plans.

UnitedHealthcare Individual Exchange

This Medical Policy applies to Individual Exchange benefit plans in all states except for Colorado.

Coverage Rationale

The following are unproven and not medically necessary due to insufficient evidence of efficacy:

- Measurement of corneal hysteresis
- Measurement of ocular blood flow using a tonometer
- Monitoring of intraocular pressure during vitrectomy
- Continuous monitoring of intraocular pressure for ≥ 24 hours in persons with glaucoma

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

CPT Code	Description
0198T	Measurement of ocular blood flow by repetitive intraocular pressure sampling, with interpretation and report

CPT Code	Description
0329T	Monitoring of intraocular pressure for 24 hours or longer, unilateral or bilateral, with interpretation and report
66999	Unlisted procedure, anterior segment of eye
67299	Unlisted procedure, posterior segment
92145	Corneal hysteresis determination, by air impulse stimulation, unilateral or bilateral, with interpretation and report

Description of Services

Corneal hysteresis (CH) measurement assesses corneal resistance to deformation. CH has been proposed as a possible indicator of the viscoelastic properties in the cornea. The Ocular Response Analyzer® (ORA) is an instrument that measures CH by using a rapid air impulse to apply force to the cornea. An advanced electro-optical system then monitors the deformation. Two independent pressure values are derived from the inward and outward applanation events. The difference between these two pressure values is CH. Low CH demonstrates that the cornea is less capable of absorbing (damping) the energy of the air pulse. Abnormalities in CH have been detected in a variety of corneal diseases, including keratoconus, Fuchs' dystrophy, and in individuals who have had laser in situ keratomileusis (LASIK). Glaucoma is another potential indication for CH measurement. The preferred method of measuring intraocular pressure (IOP) is using a contact applanation method such as a Goldmann tonometer (GAT). Corneal compensated IOP, derived from the CH measure has been suggested as a superior measurement of IOP compared to the GAT measurement.

The ocular blood flow (OBF) tonometer measures IOP and pulsatile OBF. It has been proposed that the IOP and OBF test results taken together increase the detection rate for glaucoma when compared to traditional tonometry, which measures only average IOP. The ocular Blood Flow Analyzer (BFA) is an electronic pneumotonometer that measures IOP 200 times per second over a period of 5-15 seconds and automatically measures OBF. The BFA is basically an OBF tonometer, using a pneumatic mode of operation.

IOP monitoring during vitrectomy may be accomplished indirectly by placing disposable blood pressure transducers into the line tubing utilized for vitrectomy infusion. It may also be monitored by inserting a catheter pressure transducer directly into the vitreous by an extra pars plana incision. In either approach, pressure measurements are obtained simultaneously during the various stages of the vitrectomy, including air-fluid exchange and gas-forced fusion. Monitoring IOP during vitrectomy surgery has been proposed to measure fluctuations in IOP that may have an adverse effect on retinal and optic nerve function and visual acuity recovery.

Devices, including contact lens sensors, are being developed to monitor eye pressure for 24 hours or longer in individuals with glaucoma. Currently, the Triggerfish® contact lens sensor (CLS) (Sensimed, Lausanne, Switzerland) is the only commercially available device that has been shown to be able to provide 24-hour IOP data. This device has received marketing clearance by the U.S. Food and Drug Administration (FDA). The Triggerfish® CLS is a disposable silicone contact lens with an embedded micro-electromechanical system which measures changes in corneal curvature induced by variations in IOP. An antenna, mounted around the eye, receives the data, which are then transmitted to a recorder for analysis. These devices are being studied to determine if they improve detection and allow earlier treatment for individuals with glaucoma.

Clinical Evidence

Corneal Hysteresis Measurement

Current evidence for corneal hysteresis (CH) measurement focuses on the risk, diagnosis and progression of glaucoma however, these studies do not demonstrate how corneal hysteresis measurement influences clinical management or outcomes. Additional clinical trials are necessary to determine its benefit in clinical practice.

In a prospective longitudinal cohort study, Kamalipour et al. (2022) evaluated the role of CH as a risk factor of central visual field (VF) progression in patients with glaucoma and patients with suspected glaucoma. The study included 143 patients (248 eyes, n = 71 glaucoma suspect and n = 177 glaucoma) who were followed for an average of 4.8 years with a minimum of 5 visits

(average number of visits = 7.8) comprised of clinical examinations and several imaging and functional tests including 10-2 and 24-2 VF tests. The majority of the study participants (76.6%) were already on ocular hypertensive eye drops at the beginning of the study. CH measurements were acquired by a trained technician at each visit using the Ocular Response Analyzer (Reichert Ophthalmic Instruments Inc). The authors reported that CH was significantly associated with 10-2 and 24-2 VF progression in the univariable trend-based analysis where male gender, higher baseline 10-2 pattern standard deviation (PSD), worse baseline 24-2 mean deviation (MD), higher baseline 24-2 PSD, and lower baseline CH were associated with a faster rate of 10-2 VF progression. In the multivariable trend-based analyses, lower mean intraocular pressure (IOP) during follow-up, worse baseline 24-2 MD, and lower baseline CH were significantly associated with a faster rate of 10-2 VF progression. Limitations of the study include the variability and intensity of treatments that participants received from their attending ophthalmologists during the course of the study, the use of the baseline CH measurement as predictors of central VF progression, and that the patients were at various stages of disease progression at the onset of their participation. The authors concluded that lower baseline CH is associated with a statistically significant, but relatively small, increased risk of central VF progression in patients with primary open-angle glaucoma including those with early disease and that CH is a significant predictor of glaucomatous central and peripheral VF progression. The authors recommended that clinicians consider using CH to assess the risk of progression in patients with primary open-angle glaucoma including those with early disease. The study however does not address the clinical utility of using CH, as opposed to other metrics, in the management of glaucoma.

Rojananuangnit et al. (2021) conducted a retrospective cross-sectional study of CH from 465 non-glaucomatous eyes from 465 patients and in 695 glaucomatous eyes from 429 patients at a single outpatient clinic to collect the normal value data of CH and to study the variation of corneal hysteresis in glaucomatous eyes. The participants with affected eyes included patients with primary-open angle glaucoma (POAG; n = 434 eyes), primary close-angle glaucoma (PACG; n = 74 eyes), normal tension glaucoma (NTG; n = 143 eyes) and ocular hypertension (OHT; n = 44 eyes). The demographics of the patients with non-glaucomatous eyes showed a mean age of 57.21 ±14.43 years, 70% female (n = 327) with a CH of 10.18 ±1.48 mmHg, a corneal-compensated intraocular pressure (IOPcc) of 15.01 ±3.04 mmHg and a Goldmann-correlated intraocular pressure (IOPg) of 14.16 ±3.06 mmHg. The authors reported that the OHT group was the youngest group, while the average ages between OAG, ACG, and NTG were similar and that women were observed more frequently than men in the PACG and NTG groups. They also noted that glaucoma treatment options were also different between groups in that all patients in the POAG and NTG groups received prescribed anti-glaucoma medication while 39.2% of the PAGC group underwent phacoemulsification. Their analysis showed the lowest CH was in the POAG group, 8.74±1.52 mmHg, followed by the PACG group, 9.09 ±1.72 mmHg, then the NTG group, 9.55 ±1.67 mmHg, while the highest was OHT, 10.10 ±1.40 mmHg and that the difference of CH between glaucoma severity was found to be negatively correlated with the more advanced glaucoma stage in the POAG and PACG groups. Limitations noted by the authors included the variation of CH found among different races and ages while their study including a population from a single center, the larger proportion of women in their study, the retrospective cross-sectional design of the study with lack of data to compare in the long term. They also noted that the average CH in glaucoma might not represent the original CH, because all patients' IOP were already controlled with anti-glaucoma treatment in their study. The authors found moderate negative correlation between age and CH; however, the correlation between age and IOPcc, and age and IOPg was not detected, and that CH was lower in glaucomatous eyes than in non-glaucomatous eyes. They concluded that CH was a reliable and repeatable value of ocular biomechanics that can be measured in a clinical setting.

In a historical cohort study, Jiménez-Santos et al. (2021) evaluated CH, acquired with ocular response analyzer (ORA), as a risk factor for glaucoma progression in early-stage POAG. Patients diagnosed in 2011 with early-stage POAG and followed up until glaucomatous progression development were included in the study. All the participants in this study were Caucasian. Cox regression was used to obtain hazard ratios (HR) to evaluate baseline variables (CH, central corneal thickness, gender, age, IOP and glaucoma family history) as risk factors for perimetric glaucoma progression. A likelihood ratio test for interaction was performed in order to assess the effect of the combination of CH and central corneal thickness (CCT) on the risk of progression. Of the cohort of 1573 patients, 11.38% developed early-stage POAG progression during the follow-up. The mean follow-up time was 3.28±1.92 years. Patients without progression had a higher CH (11.35 ±1.43 vs 9.07 ±1.69 mmHg; $p < 0.001$) and CCT (570.75 ±17.71 vs 554.51 ±23.20; $p < 0.001$). In the multivariate analysis, each 1 mmHg of lower CH was associated with an increase of 2.13 times in the HR of progression (95% CI: 1.92-2.32; $p < 0.001$). CH hazard ratio was modified by CCT, with higher values of CCT and CH resulting in a higher HR of early glaucoma progression ($p < 0.001$). The authors concluded that CH can be considered as a risk factor of progression in early-stage POAG. The risk associated with CH changed depending on CCT values, acting synergistically slowing the risk of glaucoma progression with higher values. The authors indicated that the results of this study cannot be used to predict the benefits of CH for all ethnic groups or glaucoma stages. According to the authors, further studies should be performed to assess the reproducibility of their findings amongst other

ethnic groups and glaucoma types and stages. The study however did not test whether the use of CH improves care or patients' outcomes.

Katiyar et al. (2021) evaluated the effect of acute IOP elevation on CH and corneal resistance factor (CRF) and the associations of these biomechanical parameters with glaucomatous disease. Subjects participating in this prospective, longitudinal glaucoma research study had CH and CRF measured before and during ophthalmodynamometry during visits in the years 2011 to 2012. All participants were diagnosed with primary open-angle glaucoma, ocular hypertension, glaucoma suspect, or normal eyes and had a minimum of 3 years of study participation with at least five reliable visual field (VF) tests. Changes in CH, CRF, and IOP induced by ophthalmodynamometry were compared between diagnostic groups and evaluated for relationships with existing and future glaucomatous VF loss. In 248 eyes of 248 subjects followed up for 7.7 ±2.3 years, ophthalmodynamometry induced a mean IOP increase from 15.1 to 29.9 mmHg, causing a mean 34 ±28% increase in CRF and 21 ±25% decrease in CH. Magnitude of CH change did not differ between diagnostic groups or between eyes that did (n = 20) and did not (n = 95) develop new VF loss during the study period, nor was it related to rate of future VF progression. The authors concluded that ophthalmodynamometry-induced IOP elevation resulted in significant acute changes in CH and CRF in this study; this suggests accounting for IOP may be important in clinical interpretation of these parameters. The authors indicated that because the degree of CH change was not related to glaucoma or its progression, acute changes in CH and CRF do not seem to have a prognostic value for glaucoma.

In a prospective observational cohort study, Chan et al. (2021) investigated the longitudinal change in CRF and CH as risk factors for visual field progression. A total of 72 eyes of 48 glaucoma or glaucoma suspect patients were followed for an average of 4.5 years. Baseline and follow-up CH and CRF measurements were performed with the Ocular Response Analyzer. Evaluation of rates of visual field change during follow-up was performed using visual field mean deviation. Univariable and multivariable linear mixed models assessed the relationship of visual field progression with baseline CRF and CH as well as with changes in CRF and CH. The mean baseline CH was 9.0 (95% confidence interval: 8.6-9.4) mm Hg and the mean baseline CRF was 9.3 (95% confidence interval: 8.8-9.9) mm Hg. There was no statistically significant difference in average CH and CRF measurements over time. In multivariable modeling adjusting for age, race, and mean intraocular pressure during follow-up, each 1 mm Hg lower in baseline CH and 1 mm Hg decrease in CRF over time were associated with a 0.12 (p = 0.042) and 0.14 dB/year (p = 0.007) faster rate of visual field mean deviation loss, respectively. Similar findings were found in glaucoma eyes but not found in glaucoma suspect eyes. The authors concluded that visual field progression was associated with a lower baseline CH and a decrease in CRF over time. According to the authors, assessment of corneal resistance and elasticity at baseline and during follow-up examinations should be considered to identify those eyes at highest risk of visual field progression. The authors indicated that study limitations include the small study population which may not be large enough to detect subtle changes in CH and CRF. In addition, the sample size was not large enough for stratified analysis between all stages of glaucoma. Another study limitation is that although surgically treated glaucomatous eyes were excluded, the vast majority of eyes had some form of medical treatment, which can impact the interpretation of the stability of CRF and CH over time. According to the authors, future studies directed at measuring CH and CRF before and after glaucoma surgery with longitudinal follow-up of visual field progression would provide further insight on the role of biomechanics in monitoring for glaucoma progression.

Susanna et al. (2018) conducted a prospective observational cohort study to investigate the role of CH as a risk factor for development of glaucoma. Two hundred and eighty-seven eyes of 199 individuals suspected of having glaucoma were observed for approximately 4 years. Participants underwent a comprehensive ophthalmologic examination including IOP measured using GAT, gonioscopy, stereoscopic optic disc examination, visual field testing, and CCT measurements via ultrasound pachymetry and were assessed at baseline and every 6 months thereafter. A minimum follow-up period of 18 months and 4 separate visits were required. Development of glaucoma was defined as occurrence of 3 consecutive abnormal standard automated perimetry tests during the follow-up period. Fifty-four (19%) eyes developed repeatable visual field defects during follow-up. Each 1 mmHg lower CH measurement was associated with an increase of 21% in the risk of developing glaucoma during follow-up (95% confidence interval [CI]: 1.04–1.41; p = 0.013]. After adjusting for age, intraocular pressure, central corneal thickness, PSD, and treatment, CH was still predictive of development of glaucoma (hazard ratio = 1.20; 95% CI: 1.01–1.42; p = 0.040). The authors concluded that the decrease in CH measurements represents a risk factor for developing glaucoma. Study limitations included but were not limited to study design, lack of information on participants lost to follow up, as well as uncontrolled confounding by unmeasured factors, such as family history of glaucoma. Additionally, the study doesn't test whether the use of CH improves care. Future studies should be performed to further clarify the clinical utility of using CH as part of glaucoma management on patient outcomes.

A 2018 Hayes report identified 16 studies that evaluated CH testing for diagnosis of glaucoma, or for predicting the progression or response to treatment of glaucoma. Eleven prospective or retrospective cohort studies and 5 prospective case-control studies were examined, involving from 52 to 443 patients with follow-up times ranging from zero to 6.6 years. The report concluded that the test has some capacity to diagnose glaucoma, to predict risk for glaucoma progression, and to predict response of glaucoma to certain types of treatment; however, the evidence is of very poor quality and lacked the rigor to determine diagnostic or prognostic accuracy. The role of CH testing in the management of patients with glaucoma and its impact on long-term health outcomes could not be determined due to the lack of evidence on the clinical utility of this test. Additional studies are needed. The 2020 Hayes update indicated that evidence regarding clinical utility is unchanged since the 2018 Hayes report (Hayes, 2018; updated January 2022).

Murphy et al. (2017) conducted a cross sectional study with 123 patients (one eye each) to determine if CH differs between patients with glaucoma, OHT and glaucoma-like optic discs (GLD). The secondary aim was to investigate whether corneal resistance factor (CRF) and CCT differ between these patient groups. A One-way Analysis of Covariance (ANCOVA) was conducted to evaluate the mean difference in CH between the 3 diagnostic groups (glaucoma, OHT and GLD), correcting for potential confounding factors, IOP and age. Analysis was repeated for CRF and CCT. There was a significant difference in mean CH across the 3 groups. Mean CH was significantly higher for GLD compared to glaucoma, and significantly higher for OHT compared to glaucoma. Mean CH was slightly lower in patients with GLD than those with OHT, but this difference was not statistically significant. A similar pattern was seen when the analysis was repeated for CRF and CCT. The authors concluded that higher CH in GLD and OHT compared to glaucoma suggests increased viscoelasticity of ocular tissues may have a protective role against glaucoma. Additional studies are still needed to clarify the utility of CH in the risk, diagnosis and clinical management of glaucoma. This study was also included in the Hayes report (2018).

Zhang et al. (2016) conducted a cohort study to evaluate the relationship between CH and progressive retinal nerve fiber layer (RNFL) loss among patients with glaucoma. At baseline and at 6-month intervals thereafter, participants received a comprehensive ophthalmologic examination and several other imaging and functional tests. A total of 186 eyes (133 patients) with glaucoma were followed for an average of 3.8 ±0.8 years (range: 2.0 to 5.2 years). The average baseline RNFL thickness was 76.4 ±18.1 μm and average baseline CH 9.2 ±1.8 mmHg. CH had a significant effect on rates of RNFL progression. In the univariable model, including only CH as a predictive factor along with time and their interaction, each 1 mmHg lower CH was associated with a 0.13 μm/year faster rate of RNFL decline ($p = 0.011$). A similar relationship between low CH and faster rates of RNFL loss was found using a multivariable model accounting for age, race, average IOP and CCT ($p = 0.015$). The authors concluded that lower CH was significantly associated with faster rates of RNFL loss over time. While this study provides evidence that CH is an important factor to be considered in the assessment of the risk of progression, there is no evidence that CH measurement will affect patient management; further research is still needed to prove the utility of CH measurement in the clinical setting. This study was also included in the Hayes report (2018).

Carbonaro et al. (2014) conducted a cross-sectional study to determine whether corneal hysteresis and central corneal thickness are independent risk factors for glaucoma. Subjects were recruited from the Twins UK Adult Twin Registry at St Thomas' Hospital in London and invited to have an eye examination. The Ocular Response Analyzer (ORA) was used to measure CH, IOP, and CCT. Two measurements were performed on each eye; first and second tests were taken on 1 eye and then, on the other eye. If needed, a third reading was taken to ensure accuracy. Multivariable linear regression was performed to analyze corneal hysteresis with respect to other glaucoma-related endophenotypes including vertical cup-to-disc ratio, optic disc size, and optic cup areas. The final analytic sample included 1,645 individuals. CH was negatively associated with age (beta coefficient, -0.03; 95% CI, -0.03 to -0.02, $p < 0.0005$) and IOP (beta coefficient, -0.06; 95% CI, -0.09 to -0.03; $p = 0.001$). CH was also found to be associated with CCT (beta coefficient, 0.02; 95% CI, 0.021 to 0.025; $p < 0.0005$). There was no significant association between corneal hysteresis and optic disc area ($p = 0.62$), cup area ($p = 0.77$), vertical cup-to-disc ratio ($p = 0.51$), or spherical equivalent ($p = 0.07$). The authors concluded that in this population of healthy British twins, CH is not independent risk factors for glaucoma.

Mansouri et al. (2012a) conducted a cross-sectional study to investigate the association between corneal biomechanical parameters using the Ocular Response Analyzer (ORA) and glaucoma severity. Each participant underwent a complete ophthalmologic examination, including visual acuity assessment, slit-lamp biomicroscopy, gonioscopy, dilated fundoscopic examination using 78-diopter (D) lens, stereoscopic disc photography, and standard automated perimetry using the 24-2 Swedish Interactive Threshold Algorithm. CCT was measured using an ultrasound pachymeter over an undilated pupil and the mean of 3 readings was recorded. To study the influence of corneal biomechanical parameters as measured by the ORA on the visual field and RNFL thickness, eyes suspected of having the disease as well as those with confirmed glaucoma were

included. A total 299 eyes of 191 participants (151 suspect and 148 glaucoma eyes) with a mean age of 68.1 years (SD: 11.0 years; range 30–91 years) participated in the study. CH and CRF were both positively associated with mean defect (MD) (R2 = 0.03; p < 0.01 and R2 = 0.10; p < 0.01, respectively). In multivariable analysis, the association between CRF and MD remained significant while CH to MD did not (p < 0.01 and p = 0.77). In the GDx ECC subgroup (204 eyes), there was a weak association between CH and CRF and average RNFL thickness (R2 = 0.07; p < 0.01 and R2 = 0.05; p < 0.01, respectively), which was not observed in the SD-OCT subgroup (146 eyes) (R2 = 0.01; p = 0.30 and R2 = 0.01; p = 0.21). After adjusting for central corneal thickness, age, and axial length, the relationship of CH and CRF to RNFL thickness no longer reached statistical significance. The authors concluded that they found only a weak relationship between corneal biomechanical parameters and measures of structural and functional damage in glaucoma. Additional studies are needed to investigate the relationship between corneal biomechanics and long-term risk of glaucoma progression. This study was also included in the Hayes report (2018).

Clinical Practice Guidelines

American Academy of Ophthalmology (AAO)

In an Ophthalmic Technology Assessment on the use of corneal hysteresis (CH) for the diagnosis of glaucoma and assessment of risk progression, the AAO reviewed 19 articles and assigned each study a level of evidence rating based on the rating scale developed by the Oxford Centre for Evidence-Based Medicine. Based on this review, the AAO concluded that corneal hysteresis is lower in patients with glaucoma compared with normal subjects and that measurement of CH appears to provide additional information that could be useful for the clinical assessment of glaucoma suspects and patients; however, interpretation of CH measurements in an individual patient is complicated by the effects of intraocular pressure, as well as medical, laser and surgical therapy and other influencing parameters and that a causal relationship remains to be demonstrated (Sit, 2022).

The AAO Preferred Practice Pattern (PPP) for POAG states that risk factors for glaucoma progression include decreased corneal hysteresis. The AAO also states that the association between risk factors such as low corneal hysteresis and the development of glaucomatous optic nerve damage has not been demonstrated consistently (Gedde, 2021).

Measurement of Ocular Blood Flow by Intraocular Pressure Sampling

There is insufficient clinical evidence that measuring ocular blood flow by interocular pressure sampling will impact treatment decisions and demonstrate improved health outcomes. Further studies are needed to determine the clinical utility of this test.

In a single center cross-sectional observational study by Bayraktar et al. (2022), ocular blood flow (OBF) and choroidal thickness (CT) were evaluated as potential markers and/or risk factors that may measure the progression of OHT to glaucoma. The authors performed a detailed ophthalmological examination including visual acuity, slit-lamp biomicroscopy, gonioscopy, applanation tonometry and axial length (AL) measurement on 63 patients, of which 32 patients (60 eyes) had OHT and the remaining 31 were control patients (61 eyes). The authors used color Doppler imaging (CDI) of the ophthalmic artery (OA), central retinal artery (CRA), medial and lateral branches of short posterior ciliary arteries (MPCA, LPCA) to collect OBF data for peak systolic velocity (PSV), end-diastolic velocity (EDV), resistivity index (RI) and pulsatility index (PI). Retrobulbar blood flow velocities and calculated vascular resistive indices (RI) were measured by the same radiologist who was blinded as to whether each patient had OHT or was a control. Optical coherence tomography (OCT) was used to measure the retinal nerve fiber layer, ganglion cell complex, and central corneal thickness. The authors reported that when the blood flow values of the OA, CRA, MPCA, and LPCA arteries were compared in both groups, EDV of all arteries were significantly lower in the OHT group while the PI and RI values of all arteries were statistically significantly increased in the OHT group. Limitations of this study include the single center cross-sectional design, and the small sample size. The authors concluded that OBF decline, and choroidal thinning occurred in the OHT group compared with controls and that the use of CDI and OCT to monitor OBF and CT measurements may help to prevent and reduce potential optic nerve damage. They recommend larger long-term studies to evaluate OBF and CT with newer technological imaging methods. The study doesn't however address the clinical utility of OBF.

Wang et al (2022) completed a longitudinal, observational cohort study to determine the relationship between optical coherence tomography angiography (OCTA) measurements and visual field (VF) progression in patients with NTG. There were 335 eligible eyes from 179 patients with NTG at the baseline examination; however, 65 eyes were excluded due to image quality control, which left 270 eyes from 164 patients with NTG in the final analysis. The study participants were followed for at least two years (mean of 48.58 ±7.98 months). Each participant underwent comprehensive ophthalmic examinations at baseline and semiannually during follow-up, including measurements of best-corrected visual acuity, refractive error by an autorefractor, axial length, IOP by Goldmann applanation tonometry, CCT by a noncontact tonopachymeter, slit-lamp biomicroscopy examination

of the optic disc and retina and dilated fundus examination. OCTA images were taken at the peripapillary region and the macular region to gather ocular blood flow metrics including circumpapillary vessel density (cpVD), vessel diameter index (VDI) and fractal dimension (FD) in the radial superficial capillary network and macular vessel density, foveal avascular zone (FAZ) area, FAZ circularity and macular FD in superficial capillary plexus (SCP) and deep capillary plexus (DCP) areas, respectively. The authors reported that 15.56% of the NTG eyes (n = 42) developed VF deterioration and that baseline OCTA metrics revealed lower cpVD at superotemporal sectors in the peripapillary region in progressed NTG eyes compared with non-progressed eyes. They concluded that eyes with lower superotemporal cpVD at baseline were associated with a higher risk of glaucoma progression over time, independent of previously reported risk factors including age, gender, and blood pressure. Limitations of the study included the small sample size, the limited OCTA metrics that were included, the inclusion of only eyes that had mild-to-moderate glaucoma at baseline, the relatively short follow-up period and the potential for bias due to the inclusion of both eyes in the same patient. The authors stated that the results of the study showed that the edition of cpVD measurement at baseline enhanced predictive discrimination on glaucoma progression and that their findings provided further evidence supporting the prognostic role of OCTA in the risk assessment of NTG progression. They recommended further studies to confirm their findings. The clinical utility of these measures is not addressed in this study.

Kueten et al. (2021) investigated the relationship of ocular blood flow (via arteriovenous passage time, AVP) and contrast sensitivity (CS) in healthy individuals as well as individuals with NTG in a single-center comparative prospective trial. Twenty-five patients with NTG but no medication and 25 healthy test participants were recruited. AVP as a measure of retinal blood flow was recorded via fluorescein angiography after CS measurement using digital image analysis. Association of AVP and CS at 4 spatial frequencies (3, 6, 12, and 18 cycles per degree, cpd) was explored with correlation analysis. Significant differences regarding AVP, visual field defect, intraocular pressure, and CS measurement were recorded in-between the control group and NTG patients. In NTG patients, AVP was significantly correlated to CS at all investigated cpd (3 cpd: $r = 0.432$, $p < 0.03$; 6 cpd: $r = 0.629$, $p < 0.0005$; 12 cpd: $r = 0.535$, $p < 0.005$; and 18 cpd: $r = 0.58$, $p < 0.001$), whereas no significant correlations were found in the control group. Visual acuity was significantly correlated to CS at 6, 12, and 18 cpd in NTG patients ($r = 0.68$, $p < 0.002$; $r = 0.54$, $p < .02$, and $r = 0.88$, $p < 0.0001$ respectively), however not in healthy control patients. Age, visual field defect MD, and PSD were not significantly correlated to CS in in the NTG group. MD and PSD were significantly correlated to CS at 3 cpd in healthy eyes ($r = 0.55$, $p < 0.02$; $r = 0.47$, $p < 0.03$). The authors concluded that retinal blood flow alterations show a relationship with contrast sensitivity loss in NTG patients which may reflect a disease-related link between retinal blood flow and visual function. This association was not recorded in healthy volunteers. According to the authors, further studies are necessary to verify that including CS testing as well as blood flow measurement is beneficial in the assessment and care of patients with glaucoma.

Barbosa-Breda et al. (2019) conducted a cohort analysis to determine vascular factors that better describe patients with NTG compared to those with POAG. A total of 384 patients with glaucoma (202 POAG and 182 NTG) from the Leuven Eye Study (LES) database were included. Four different devices were used to assess ocular pulse amplitude, ocular blood flow, retinal oximetry and choroidal thickness. Three multivariate logistic regression models were developed: a conventional model (conventional parameters only, including vascular-related self-reported phenomena, such as migraine or peripheral vasospasm); an advanced vascular model (advanced vascular parameters only: ocular blood flow, retinal oximetry, ocular pulse amplitude and choroidal thickness); and a global model, in which both types of parameters were allowed. Receiver operating characteristic (ROC) curves and corresponding areas under the curve (AUC) were calculated and compared between models. Patients with NTG had a higher resistive index and lower early systolic acceleration (ESA) in their retrobulbar vessels and a smaller arteriovenous retinal oxygen saturation difference. The global model (AUC 0.743) showed a significantly better discriminative ability when compared to either the conventional (AUC 0.687, $p = 0.049$) or the advanced vascular (AUC 0.677, $p = 0.005$) models. Also, the conventional and the advanced vascular models showed a similar discriminative ability ($p = 0.823$). The authors concluded that patients who have NTG have more signs of vascular dysfunction. And, that the conventional parameters, such as asking simple vascular-related questions, combined with advanced vascular examinations provide information to better understand the value that non-IOP-related factors contribute to NTG. However, future studies are needed to validate these results and to clarify whether advanced vascular examinations are relevant to predict disease progression or provide benefit for the management of patients with NTG or POAG.

Janulevičiene et al. (2011) conducted a single-center, randomized, double-masked intervention study with an observational component to evaluate hemodynamic parameters as possible predictors for glaucoma progression. Patients with OAG and characteristic glaucomatous visual field loss, optic nerve head damage, and IOP not adequately controlled with timolol maleate (BID) were eligible for participation. After a timolol baseline examination, patients were randomly assigned to double-masked fixed combination treatment: dorzolamide/timolol (DTFC) or and latanoprost/timolol (LTFC). Examinations were carried out in

both eyes and the study eye was chosen randomly. The examinations were conducted at baseline and at months 1, 6, 12, and 18 of treatment. The examinations included a full ophthalmic examination, visual acuity, Goldmann IOP, CCT Humphrey visual field examination (24-2 SITA Standard) and scanning laser polarimetry. A total of 30 OAG patients (15 patients in each study group) with a mean age of 58.13 (SD 8.6) participated in the study. There were no statistically significant differences between baseline parameters of either treatment group. The DTFC and LTFC groups had similar IOP lowering effect over 18 months of observation ($p = 0.653$). Six patients in DTFC and 7 in LTFC group met glaucoma progression criteria. Patients with progressing glaucoma had higher nerve fiber index, lower systolic BP, OPP, DPP, higher ophthalmic and central retinal artery vascular resistance, and lower pulse volume ($p < 0.05$). The authors concluded that structural changes consistent with glaucoma progression correlate with non-IOP-dependent risk factors. And, stated that larger group studies with longer follow-up, standardization of measurement techniques for glaucoma progression, and OBF parameters are required to elicit a clear understanding of vascular risk factors in glaucoma progression. The study however does not address the clinical utility of adding measurement of ocular blood flow by intraocular pressure sampling to improve patient care.

Clinical Practice Guidelines

American Academy of Ophthalmology (AAO)

The AAO Preferred Practice Pattern for primary open-angle glaucoma does not address measurement of ocular blood flow for the evaluation and management of glaucoma (Gedde, 2021).

Monitoring of Intraocular Pressure during Vitrectomy

There is limited evidence to support that intraoperative IOP monitoring will improve health outcomes in patients undergoing vitrectomy. Additional clinical trials are necessary to determine its benefit.

In a retrospective, single-blind, single-center study to evaluate the precision of digital IOP measurement in silicone oil (SO) filled eyes during vitrectomy, Xue et al. (2020) found that the use of digital IOP may be an acceptable technique for experienced surgeons. Their study included 131 patients with a mean age of 51.0 ±16.1 years who underwent vitrectomy with SO injection for treatment of retinal detachment (RD). During the surgery performed by one of seven surgeons, the patient's IOP was digitally measured and then measured by a rebound tonometer. When the authors compared the digitally measured IOP with the rebound tonometer and calculated the absolute deviation in IOP (△IOP) between the two methods, they found that there was no significant difference in IOPs between digital measurement and the rebound tonometer (15.6 ±4.3 mm Hg vs 15.7 ±5.1 mm Hg). Their results showed a mean △IOP of 2.0 ±1.9 mm Hg with 58 eyes (44.3%) having △IOP within 1 mm Hg, 98 eyes (74.8%) within 3 mm Hg, and 122 eyes (93.1%) within 5 mm Hg. A subgroup analysis of levels of surgeons' experience showed that the correlations were not as strong in cases performed by surgeons with less than 10 years of experience as it was in cases performed by more experienced surgeons. These weaker correlations were also shown to be the case for pseudophakic eyes in general, while refractive status and lens status were found to have no significant correlations with △IOP. The authors noted that the relatively smaller sample size of the most and least experienced surgeon groups may have brought bias to the study and that the small, retrospective, single-center design were limitations of their study. Furthermore, the study did not measure the impact of the technology on clinical outcomes of the surgery. They recommended future prospective, multi-center studies with larger sample sizes to confirm their findings.

Yang et al. (2017) conducted a prospective case series analysis to evaluate IOP during in vivo routine vitrectomy. In this study, the primary aim was to compare IOP measurements between two vitrectomy machines with integrated IOP monitoring devices. A total of 61 eyes of 61 consecutive patients were assigned to one of two types of micro-incisional vitrectomy systems: Accurus system (n = 32, group 1) and Constellation system (n = 29, group 2). Prior to vitrectomy, the mean IOP in group 1 was 20.3 ±2.4 mmHg using conventional vented gas forced infusion system and 20.0 ±0.0 mmHg in group 2 using active IOP control at 20 mmHg ($p = 0.532$). During core vitrectomy, the mean IOP change was -8.6 ±4.3 mmHg in group 1 and -0.8 ±1.1 mmHg in group 2 ($p < 0.001$). Maximum IOP was significantly decreased in group 1 compared with group 2 (-17.0 ±2.6 mmHg and -4.1 ±2.2 mmHg, respectively; $p < 0.001$). During vitrectomy, partial ocular collapse was only observed in group 1 (78.1%). Peak IOP significantly increased during scleral compression and gas and fluid injection but was not significantly different between the groups (all $p \geq 0.147$). The IOP fluctuation range was 50-70 mmHg in both groups. The authors concluded that IOP fluctuated significantly during routine vitrectomy using both systems. Hypotony and partial ocular collapse were more frequently observed with the Accurus system than with the Constellation system, and both systems were vulnerable to IOP surge during indentation and intravitreal injection. While this study suggests usefulness of intraocular pressure monitoring during vitrectomy in the research setting, its benefit in routine clinical practice remains to be established.

In a prospective, interventional, consecutive case series, Sugiura et al. (2011) measured ophthalmodynamometric pressure (ODP) during vitrectomy in 75 patients with proliferative diabetic retinopathy (PDR). Multiple regression analysis revealed that ODP had a significant correlation with diastolic blood pressure, presence of rubeosis iridis, and severity of PDR. There is no evidence from this study that this information will affect patient management.

Moorhead et al. (2005) conducted a case series of 10 patients to directly measure dynamic IOP during vitrectomy and to determine whether disposable pressure transducers placed in the infusion line can indirectly measure with accuracy the dynamic IOP during vitrectomy. The directly measured IOP varied between 0- and 120-mm Hg during vitrectomy. During fluid flow, the indirectly measured IOP, calculated from the infusion line pressures, accurately corresponded with the directly measured IOP. The investigators concluded that closed vitrectomy causes wide fluctuations in IOP. The IOP can be accurately measured during fluid flow with inline sensors. The authors report that no "patients had adverse effects such as cataract, vitreous hemorrhage, or retinal tear as a result of this study." According to the authors, the physiologic significance of these findings requires further study.

Monitoring of Intraocular Pressure for 24 Hours or Longer

There is insufficient clinical evidence demonstrating the safety and/or efficacy of monitoring of intraocular pressure for 24 hours or longer.

In a single-center test validation study assessing the safety and tolerability of a contact lens sensor (CLS) tonometer system for continuous three- and 24-hour IOP monitoring, Zhang et al (2022) recruited 25 subjects with a mean age of 24.1 ±3.4 years for a 3-hour IOP measurement by CLS test. One eye in each participant was fitted with the CLS who then wore it for three hours. Once it was removed, they underwent corneal fluorescein staining (CFS) which revealed an increase from 0.6 ±0.7 to 2.4 ±1.5. Following the 3-hour IOP measurement arm of the study, the authors recruited 30 more participants with a mean age of 30.9 ±9.8 years (10 control subjects and 20 patients with open-angle glaucoma) for the 24-hour IOP monitoring phase of the study. In this group, again, each participant was fitted with a CLS in only one eye. Each participant was evaluated using ocular surface disease index (OSDI) before and one day after measurement, the contact lens dry eye questionnaire-8 was assessed immediately after measurement, visual analog scale (VAS) of discomfort was measured before, immediately after, and one day after measurement, best-corrected visual acuity (BCVA), tear break-up time (TBUT), and CFS were assessed before, immediately after, and 1 day after measurement. The authors reported that the OSDI increased from 9.1 ±9.7 to 18.0 ±12.4, the CLDEQ-8 score was 11.6±5.8 while the VAS increased from 11.1 ±14.2 to 35.2 ±21.8 after measurement then decreased to 26.7 ±18.4 one day later and the BCVA decreased from 1.0 ±0.01 to 0.8±0.1 and returned to 0.9 ±0.1 after one day. Other results included a decrease in TBUT from 5.1 ±3.9 to 2.6 ±1.5 s which then returned to 4.8 ±2.5 s and the CFS increased from 0.7 ±0.9 to 4.3 ±0.8 then dropped to 0.8 ±0.7 at 1 day after measurement. No significant difference was found for all variations of indicators between normal subjects and glaucoma patients. Limitations include the relatively young age of the participants, the short (1 day) follow up period, the small sample size and the single-center design. The authors concluded that the CLS showed great potential for safe and tolerable 24-hour IOP monitoring in patients with and without glaucoma; however, they also noted that worsening clinical signs and symptoms after CLS wear require attention. Further study was recommended to further assess the worsening signs and symptoms after measurement.

Shioya et al. (2020) evaluated the use of a contact lens sensor (CLS) to record a 24-hour ocular dimensional profile on 65 patients in a prospective open-label, single-center evaluation of Japanese patients previously diagnosed with NTG to determine the potential for misclassifying patients with POAG with NTG. All patients had been characterized by glaucomatous visual field defects and optic disc damage, open iridocorneal angle and the absence of secondary causes of glaucoma and all had undergone a complete ophthalmic examination that CCT measurements and standard automated visual field testing. To be considered for enrollment in the study, the patients had discontinued any glaucoma medication at least 4 weeks prior to the first procedures and had not undergone any ocular surgery. Each patient underwent IOP measurement with tonometry on one eye every 3 hours from 9 am to midnight on day 1 of the study then had a 24-hour CLS profile recorded on the same eye the next day. Following the two days of IOP measurements, patients were reclassified as NTG when their IOP was consistently below 20 mmHg or with POAG when their IOP was ≥ 20mmHg in at least 1 of the time-points in the study The authors reported that five patients (7.7%) were reclassified as POAG following the diurnal measurement and that two of the classifiers (15:00 CLS and 18:00 CLS) showed high sensitivity and negative predictive value (100%) that identified all of the POAG patients. Limitations noted by the authors included the fact that the tests could not be done simultaneously as no tonometry measurement can be performed when the CLS is placed on the patient's eye, and the inclusion of only Japanese subjects from a single center. They recommend additional studies to include other ethnicities. The authors concluded that CLS information

can be used in conjunction with a single tonometric reading to determine a patient's potential of having IOP levels exceeding the diagnostic threshold within a 24-hour period, without the need to conduct a 24-hour tonometric curve.

In a cross-sectional controlled study, Kim et al. (2020) investigated 24-hour nyctohemeral IOP-related patterns with contact lens sensors (CLSs) in eyes with POAG with normal baseline IOP (i.e., normal-tension glaucoma [NTG]) and healthy controls. Thirty eyes of 30 patients with NTG, who had had a wash-out period for their IOP-lowering treatment, and 20 eyes of 20 healthy volunteer subjects were included in the study. Patients and subjects were hospitalized for the purposes of 24-hour CLS (SENSIMED Triggerfish; Sensimed AG, Lausanne, Switzerland) measurement. The IOP-related patterns during wake and sleep times over the course of the 24 hours were compared between the 2 groups. The 24-hour ambulatory blood pressure and posture were monitored simultaneously. A generalized linear model was used to find the factors associated with NTG. The main outcome measures included the IOP-related patterns, including mean and standard deviation (SD) of measurements, amplitude of cosine-fit curve, acrophase (signal peak), and bathyphase (signal trough) values (millivolt equivalents [mVEq]). The SDs of the 24-hour CLS measurements were significantly greater in NTG eyes than in healthy controls (112.51 ±26.90 vs. 85.18 ±29.61 mVEq, p = 0.002). The amplitudes of cosine-fit curve (141.88 ±39.96 vs. 106.08 ±41.49 mVEq, p = 0.004) and acrophase values (277.74 ±129.80 vs. 190.58 ±127.88 mVEq, p = 0.024), mostly measured during nocturnal period, were significantly greater in NTG eyes than in healthy controls. The NTG subjects slept longer in the lateral decubitus posture than the healthy controls (199.1 ±137.8 vs. 113.2 ±86.2 minutes, p = 0.009). In the multivariable generalized linear model, the greater amplitude of cosine-fit curve (β = 0.218, p = 0.012) and greater time of decubitus posture during sleep (β = 0.180, p = 0.004) were found to be significantly associated with NTG. The authors concluded that continuous monitoring of 24-hour IOP-related values with CLS can be useful for assessment of glaucoma risk, especially for patients with NTG whose IOP appears to be in the normal range. Fluctuation of 24-hour IOP-related values and posture during sleep time might be associated with NTG. According to the authors a study limitation was that although the false discovery rate was controlled for using the Benjaminie-Hochberg method, multiple hypotheses were tested against a relatively small number of subjects to support the main outcome of the study. Therefore, further validation for those variables with borderline significance or broad range of confidence interval is needed. The study did not address the utility of the data for clinical management of glaucoma.

Mansouri et al. (2015) conducted a clinical trial to evaluate the performance of a contact lens sensor (CLS, (Triggerfish, Sensimed, Switzerland) for 24-hour monitoring of IOP-related short-term patterns compared with IOP obtained by pneumatonometry. Thirty-one healthy volunteers and 2 patients with glaucoma stayed in a sleep laboratory for 24 hours. One randomly selected eye was fitted with the CLS, which measures changes in ocular circumference. In the contralateral eye, IOP measurements were taken using a pneumatonometer every two 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 the 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). A total of 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. The authors concluded that CLS measurements were comparable to the pneumatonometer and may be of practical use for detection of sleep-induced IOP changes. Additional studies with larger sample sizes are needed to accurately confirm these findings. Furthermore, the clinical utility of this approach to manage patients with glaucoma remains to be demonstrated.

Mansouri et al. (2012b) examined the safety, tolerability, and reproducibility of IOP patterns during repeated continuous 24-hour IOP monitoring with the Triggerfish CLS. Patients suspected of having glaucoma (n = 21) or with established glaucoma (n = 19) were included in the study. Correlation between the 2 sessions was moderate, suggesting good reproducibility of the IOP recordings. There was also no difference in adverse events or survey scores for tolerability between those with established glaucoma compared with those with suspected glaucoma. Main adverse events were blurred vision (82%), conjunctival hyperemia (80%), and superficial punctate keratitis (15%). The authors concluded that repeated use of the contact lens sensor demonstrated good safety and tolerability. According to the authors, 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. However, this study did not address how this approach can be used to improve physician decision-making and patient care.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

On January 20, 2004, the Ocular Response Analyzer® (ORA) by Reichert Inc. received FDA clearance for the intended use to measure intra-ocular pressure of the eye and the biomechanical response of the cornea for the purpose of aiding in the diagnosis and monitoring of glaucoma. More information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K081756. (Accessed February 13, 2023)

Information on other similar ocular tonograph devices can be found using Product Code HKX at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed February 13, 2023)

On October 21, 2002, the Blood Flow Analyzer (BFA) received FDA marketing clearance. More information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K023245. (Accessed February 13, 2023)

Information on other similar ocular blood flow tonometer devices can be found using Product Code NJJ at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (February 13, 2023)

On March 4, 2016, the Triggerfish® contact lens sensor (CLS) received FDA marketing clearance. More information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/denovo.cfm?id=DEN140017. (February 13, 2023)

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Policy History/Revision Information

Date	Summary of Changes
10/01/2023	**Application** ***Individual Exchange Plans*** • Removed language indicating this Medical Policy does not apply to Individual Exchange benefit plans in the states of Massachusetts, Nevada, and New York **Supporting Information** • Archived previous policy version 2023T0133Z

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. UnitedHealthcare Medical Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.