# **Medical Policy**



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> \*Current Policy Effective Date: 7/1/25 (See policy history boxes for previous effective dates)

# **Title: Quantitative Pupillometry/Pupillography**

## **Description/Background**

Part of the clinical evaluation of patients with suspected or known brain injury or impaired consciousness involves the examination of pupil size and reactivity. Scientific literature has proven that alterations of the pupillary light reflex are correlated with the outcome of traumatic brain injury. In addition, neurosurgeons use pupillary response as one of the methods for triaging patients into conservative therapy vs. immediate surgical evacuation of a mass lesion. Literature has also shown that patients who undergo prompt intervention (i.e., surgery or hyperosmolar therapy) after a new pupil abnormality have a better chance of recovery.

Typically, pupil measurements are performed in a subjective manner, using a pen flashlight for evaluating pupil reactivity and using a pupil gauge to determine pupil size. Various terms have been used to describe pupillary light reflex and pupil size, including, "unilateral" or "bilateral nonreactive pupils," and other terms such as "fixed" or "dilated" pupils, and adjectives such as "brisk," "sluggish" and "non-reactive." All of these terms are subjective and can be applied without a standard clinical protocol or definition which can result in a pronounced level of inter-examiner variability and error.

The results of pupillary examination are often used as an indication that surgery is required. Unequal pupil size (anisocoria) can indicate a pathological process or neurological dysfunction, particularly if the difference in size is greater than 1 mm. A unilateral dilated, sluggishly reactive of nonreactive pupil can be an indication of transtentorial herniation and compression of the third cranial nerve. It has also been proposed that this development can be used as indicator of functional recovery following transtentorial herniation.

Pupil changes have been shown to be highly correlated with brainstem oxygenation and perfusion, as evidenced by blood flow imaging. Pupil changes have been used in conjunction

with of other parameters such as age, mechanism of injury and the Glasgow Coma Scale (GCS) and can help determine the presence and location of intracranial mass lesions. Pupillary information is often used for triaging patients into either conservative therapy or surgery. It has been shown that patients who have been promptly operated on after discovery of a new pupil abnormality may have a better chance of successful recovery.

The NeurOptics® NPi<sup>™</sup>-100 Pupillometer is a handheld portable infrared device which has been designed to provide a reliable and objective measurement of pupillary light reflexes and pupil sizes. The numeric scale of the Neurological Pupil index (NPi<sup>™</sup>) is designed to allow an objective interpretation and classification of pupil response. The Pupillometer and its NPi<sup>™</sup> scale reduce subjectivity from the measurement by comparing the pupillary light reflex against normative data in the NPi<sup>™</sup> model and automatically deriving whether the pupil reflex falls within the normal range ("brisk") or outside of the normal range ("sluggish") and provide a reliable and effective way to quantitatively classify the pupil light response.

The potential implications of pupillometry in the clinical assessment of neurosurgical patients, including its complex relationship to intracranial pressure changes, mandate the undertaking of prospective clinical studies validating the clinical significance of this noninvasive, diagnostic modality.

## **Regulatory Status**

The NeurOptics NPi-100 pupillometer, developed by NeurOptics, is an FDA approved handheld pupillometer which analyzes each variable of the pupillary light reflex.

## **Medical Policy Statement**

Quantitative pupillometry/pupillography is experimental/investigational for all indications. The clinical utility of the use of this device has not been established in medical literature.

## **Inclusionary and Exclusionary Guidelines**

Inclusions: N/A

Exclusions: Investigational for all indications

**CPT/HCPCS Level II Codes** (Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)

## **Established codes:**

N/A

## Other codes (investigational, not medically necessary, etc.):

92499 95919

# Rationale

While pupillometry has been used in many clinical applications, its clinical value has yet to be established through well-designed studies.

Bertinotti et al (2002) stated that the central and peripheral nervous systems are variably affected in the rheumatic diseases.<sup>1</sup> Pupillometry has already been used in studying the autonomic nervous system (ANS) in various rheumatic diseases. In systemic lupus erythematosus, the irideal parasympathetic branch of ANS was more affected than the sympathetic branch. In Sjogren's syndrome, signs of pupillary parasympathetic denervation have been reported. In rheumatoid arthritis, pupil parasympathetic dysfunction has been shown to correlate with ocular dryness. In systemic sclerosis (SSc), both sympathetic as well as parasympathetic irideal impairment have been demonstrated. Exogenous ocular instillation of substance P (SP) can determine an omathropine-resistant, non-cholinergic myosis, acting on specific receptors present on the iris sphincter muscle.

These investigators first studied pupillary SPergic responsiveness in SSc, evaluating SPstimulated pupillary diameters by pupillometry. A higher basal and SP-stimulated myosis was found in limited cutaneous SSC (ISSc) versus both diffuse cutaneous SSc (dSSc) and controls, whereas no differences existed between dSSc and controls. From the literature, the pupillary parasympathetic nervous system seems to be more affected than the sympathetic branch of ANS in the rheumatic diseases characterized by an inflammatory status. However, the authors found in SSc both sympathetic and parasympathetic pupil control to be equally impaired. From their experience, the authors concluded that pupillary nervous control is differently affected in the 2 subsets of SSc, and that the SPergic system seems to be impaired only in ISSc. Based on this limited study, the role of pupillometry in the management of patients with rheumatic diseases has not been established. Its clinical value needs to be ascertained via welldesigned clinical trials.

In 2003, Taylor et al prospectively used a new hand-held, point-and-shoot pupillometer to assess pupillary function quantitatively.<sup>2</sup> Repetitive measurements were initially made in more than 300 healthy volunteers aged from 1 to 87 years, providing a total of 2,432 paired (alternative right eye, left eye) measurements under varying light conditions. The authors studied 17 patients undergoing a variety of non-intracranial, non-ophthalmological, endoscopic, or surgical procedures and 20 seniors in a cardiology clinic to learn more about the effects of a variety of drugs. Additionally, the authors carried out detailed studies in 26 adults with acute severe head injury in whom intra-cranial pressure (ICP) was continuously monitored. Finally, 5 patients suffering from sub-arachnoid hemorrhage were also studied. Quantitative pupillary measurements could be reliably replicated in the study participants. Pupillary symmetry was striking in both healthy volunteers and patients without intra-cranial or uncorrected visual acuity disorders. In the 2,432 paired measurements in healthy volunteers, constriction velocity was noted to fall below 0.85 mm/second on only 33 occasions and below 0.6 mm/second on 8 occasions (less than 1 in 310 observations).

In outpatients, the reduction in constriction velocity was observed when either oral or intravenous narcotic agents and diazepam analogs were administered. These effects were transient and always symmetrical. Among the 26 patients with head injuries, 8 were found to have elevations ICP above 20 mm Hg and pupillary dynamics in each of these patients remained normal. In 13 patients with a midline shift greater than 3 mm, elevations of ICP above 20 mm Hg, when present for 15 mins, were frequently associated with a reduction in constriction velocity on the side of the mass effect to below 0.6 mm/second (51 % of 156 paired observations). In 5 patients with diffuse brain swelling but no midline shift, a reduction in constriction velocities did not generally occur until the ICP exceeded 30 mm Hg. Changes in the percentage of reduction from the resting state following stimulation were always greater than 10 %, even in patients receiving large doses of morphine and propofol in whom the ICP was lower than 20 mm Hg. Asymmetry of pupillary size greater than 0.5 mm was observed infrequently (less than 1%) in healthy volunteers and was rarely seen in head-injured patients unless the ICP exceeded 20 mm Hg. The authors concluded that pupillometry is a reliable technology capable of providing repetitive data on quantitative pupillary function in states of health and disease. However, this study did not determine how the use of pupillometry would ultimately affect patient outcomes.

Chen and colleagues (2005) noted that glaucomatous damage to upper and lower retina is often unequal.<sup>3</sup> These researchers have developed a rapid, objective, quantitative measure of asymmetry of retinal sensitivity, using infrared pupillometry and pairs of large stimuli that were symmetric about the horizontal meridian. Results for a group of 11 young subjects free of eye disease indicated that the distribution of asymmetry is close to a normal distribution centered near upper/lower symmetry. Some subjects showed modest amounts of asymmetry, which was relatively uniform within each eye, and between the 2 eyes, of the subject. The authors concluded that this approach to determination of asymmetry within an eye is potentially applicable to testing patients with glaucoma. The narrowness of the distribution should make it possible to detect asymmetries caused by disease.

Fountas et al (2006) stated that pupillometry has been widely employed in the evaluation of a large number of pathological conditions, including intra-cranial pathology.<sup>4</sup> The recent introduction of a portable, user-friendly, infrared pupillometer (ForSite, NeurOptics Inc., Irvine, CA) has enabled the accurate and reproducible measurement of several pupillary parameters, such as maximum and minimum apertures, constriction and dilation velocities, and latency period. It should be noted that various clinical conditions, especially neurological and ocular diseases, as well as numerous medications, may interfere with the measurements. Furthermore, a number of physiological parameters (e.g., the intensity of retinal illumination, the level of patient's alertness, the intensity of ambient light, and the time of day that the examination is performed) may alter the obtained values. The potential implications of pupillometry in the clinical assessment of neurosurgical patients, including its complex relationship to ICP changes, mandate the undertaking of prospective clinical studies validating the clinical significance of this non-invasive, diagnostic modality.

In 2008, Wilson et al noted that gross pupil dynamics are used as an indirect measure of brain function.<sup>5</sup> Changes in hypoxia and ICP are thought to alter pupil responses to light. These investigators assessed a portable hand-held pupillometer in the field investigating the changes in pupil size, speed of reaction, and rate of constriction/dilatation with hypoxia induced by changes in altitude. A correlation between pupil dynamics and acute mountain sickness (AMS)

was sought. A total of 17 volunteers were studied following acute exposure to 3,450 m and then during a trek to 4,770 m in Ladakh, India. The pupillometer was used to record maximum and minimum pupil diameter in response to a standard light source with calculation of latency, constriction and dilatation velocities. Acute mountain sickness was recorded using Lake Louise self-completed guestionnaires both in the morning and afternoon on each day. Acute altitude exposure resulted in a significant reduction of percentage change in pupil size (36.5 % to 24.1 % p = 0.001), significant delay in pupillary contraction (latency; 0.208 to 0.223 seconds p =0.015) and a significant slowing of the rate of contraction (constriction velocity; -2.77 mm/s to -1.75 mm/s p = 0.012). These changes reverted to normal during a period of acclimatization. A significant diurnal variation in pupil size was also observed. There was no significant difference between subjects with and without AMS. The authors concluded that the hand-held pupillometer is a suitable tool for monitoring changes in pupil dynamics in the field. With acute exposure to hypobaric hypoxia associated with an ascent to a moderate altitude, there is a general slowing of pupil function that reverted to normal within a few days of acclimatization. There appears to be a marked diurnal variation in pupil size. While the measurements demonstrated an effect of hypoxia on cerebral function, but these changes did not relate to moderate AMS.

Yan et al (2009) conducted an observational study of pupil assessment with automated pupillometry in clinical liver transplantation (LT) settings, including pre-transplant evaluations and post-transplant surveillance.<sup>6</sup> The results showed that unconscious patients (grade 4 hepatic encephalopathy) had a prolonged latency phase (left side: 283 +/- 80 milliseconds; right side: 295 +/- 96 milliseconds) and a reduced pupillary constrictive ratio (left direct response: 0.23 +/- 0.10; left indirect response: 0.21 +/- 0.07; right direct response: 0.20 +/-0.08; right indirect response: 0.21 + - 0.08) in comparison with normal and conscious patients. After liver transplantation, the recovery of pupillography in these patients was slower than that in conscious patients. However, the surviving recipients without major complications all had a gradual recovery of pupillary responses, which occurred on the 1st or 2nd post-transplant day. These researchers also reported 4 cases of futile LT in the absence of pre-transplant pupillary responses and other pupillary abnormalities revealed by automated pupillometry in this study. The authors concluded that patients with grade 4 hepatic encephalopathy had a sluggish pupil response and a delayed recovery pattern after LT. They stated that an automated pupillometer is potentially a supplementary device for pre-transplant screening and post-transplant monitoring in patients undergoing LT, but further prospective studies are required.

Payen et al (2012) stated that pupillary size reflects the balance between sympathetic and parasympathetic systems.<sup>7</sup> Due to technological advances, accurate and repeated measurements of pupillary size are possible using infrared, video-recorded pupillometers. Two pupil size reflexes were assessed: (i) the pupillary reflex dilation during noxious stimulation; and (ii) the pupil light reflex when the pupil was exposed to the light. The pupillary reflex dilation estimated the level of analgesia in response to a painful procedure or to a calibrated noxious stimulus, i.e., tetanic stimulus, in non-verbal patients. This might be of particular interest in optimizing the management of opioids in anaesthetized patients and in assessing pain levels in the intensive care unit. The pupil light reflex measurement was part of the routine monitoring for severely head-injured patients. The authors stated that the impact of pupillometry in this condition remains to be determined.

In 2012, Patwari et al noted that congenital central hypoventilation syndrome (CCHS) is characterized by alveolar hypoventilation, ANS dysregulation (ANSD), and mutations in the

paired-like homeobox 2B (PHOX2B) gene.<sup>8</sup> Autonomic nervous system dysregulation in CCHS affects multiple systems and includes ophthalmologic abnormalities. These researchers hypothesized that quantitative pupil measures, obtained using pupillometry, would vary between cases with CCHS and controls and within those with CCHS by PHOX2B genotype. A total of 316 monocular measurements were taken under dark-adapted conditions with a fixed light stimulus from 22 PHOX2B mutation-confirmed cases with CCHS and 68 healthy controls. Measures known to be illustrative of sympathetic and parasympathetic response (pre-stimulus, maximum pupil diameter, percentage of pupil constriction after light stimulus, and average constriction and dilation velocities) were significantly reduced in those with CCHS as compared with controls (all p < 0.05). The authors concluded that these reductions were indicative of both sympathetic and parasympathetic deficits in CCHS, which is in keeping with the role of PHOX2B in ANS development. An inverse linear relationship was apparent in pupil diameter and velocity measurements among the cases with CCHS with the most common heterozygous PHOX2B polyalanine expansion repeat mutations, suggesting a graded phenotype/genotype dose response based on polyalanine repeat length. They stated that these results confirmed their central hypotheses while offering the first objective measures of pupillary dysfunction and ophthalmologic-specific ANSD in CCHS. This study did not compare results of testing using the pupillometry device vs conventional testing for pupillary response.

In a prospective case-control study, Chang et al (2013) developed and validated an associative model using pupillography that best discriminated those with and without glaucoma.<sup>9</sup> A total of 148 patients with glaucoma (mean age of 67 ± 11 years) and 71 controls (mean age of  $60 \pm 10$  years) were enrolled in this study. This prototype pupillometer was designed to record and analyze pupillary responses at multiple, controlled stimulus intensities while using varied stimulus patterns and colors. These investigators evaluated 3 approaches: (i) comparing the responses between the 2 eyes; (ii) comparing responses to stimuli between the supero-nasal and infero-nasal fields within each eye; and (iii) calculating the absolute pupil response of each individual eye. Associative models were developed using stepwise regression or forward selection with Akaike information criterion and validated by 5-fold crossvalidation. These researchers assessed the associative model using sensitivity, specificity and the area-under-the-receiver operating characteristic curve (AUC). Persons with glaucoma had more asymmetric pupil responses in the 2 eyes (p < 0.001); between supero-nasal and inferonasal visual field within the same eye (p = 0.014); and smaller amplitudes, slower velocities and longer latencies of pupil responses compared to controls (all p < 0.001). A model including age and these 3 components resulted in an AUC of 0.87 (95 % confidence interval [CI]: 0.83 to 0.92) with 80 % sensitivity and specificity in detecting glaucoma. This result remained robust after cross-validation. The authors concluded that using pupillography, they were able to discriminate among persons with glaucoma and those with normal eye examinations. They stated that with refinement, pupil testing may provide a simple approach for glaucoma screening. This study did not compare pupillary testing using automated pupillography vs pupil testing using conventional methodologies.

Martinez-Ricarte et al (2013) stated that pupil assessment is a fundamental part of the neurological examination.<sup>10</sup> Size and reactivity to light of each pupil should be recorded periodically since changes in these parameters may represent the only detectable sign of neurological deterioration in some patients. However, there is great intra-observer and inter-observer variability in pupil examination due to the influence of many factors, such as the difference in ambient lighting, the visual acuity and experience of the examiner, the intensity of the luminous stimulus, and the method used to direct this stimulus. In recent years, digital cameras have incorporated infrared devices allowing the development of user-friendly portable

devices that permit repeated, non-invasive examinations of pupil size and its reactivity to light with an objective, accessible and inexpensive method. The purpose of the review was to describe the fundamentals of infrared pupillometry and discuss potential applications in the monitoring of neuro-critical patients. The authors concluded that the possibility of evaluating the changes in pupil reactivity in an early, objective and almost continuous way provides a new non-invasive monitoring method. This method could improve the predictive factor of neurological deterioration and the bedside monitoring of the neurological state of the patient, avoiding unnecessary examinations and enabling early therapeutic intervention. The authors stated that infrared pupillometry "has significant advantages compared with direct observation of the pupillary response, given that: (a) it standardizes intensity of the light stimulus, which eliminates measurement errors; (b) it permits measurement of the response to the light stimulus; (c) it enables measurement of parameters that cannot be assessed clinically such as constriction/dilation velocity and percentage, and response latency, the importance of which is currently unknown; (d) it enables establishment of normal values to allow detection of pathological states, and (e) it lets us record, save, and process data in computerized systems for future comparisons. These possible uses will depend on the publication of new studies to corroborate and expand on findings that have been observed up until now.

In 2014, J. W. Chen et al discussed the role of pupillary dysfunction in dictating subsequent treatment strategies in neurological injury.<sup>11</sup> Patients were monitored closely with an infrared pupillometer, using NPi technology, for acute changes in pupillary function. (NPi technology applies a scalar value to pupillary function.) A retrospective chart review was performed of traumatic brain injury patients with acute unilateral pupillary dilation, admitted to Legacy Emanuel Medical Center's NeuroTrauma Unit, Portland, OR, and followed as outpatients, between January 2012 and December 2013. Clinical exam findings of pupillary size, NPi scores, and brain Magnetic Resonance Imaging and Computed Tomography images were analyzed. Five traumatic brain injury patients were identified with unilateral pupillary dysfunction with long-term follow-up after the initial injury. Each patient was monitored closely in the trauma bay for neurological deterioration with a pupillometer and the clinical exam. Two patients underwent subsequent intracranial pressure monitoring based on a deteriorating clinical scenario, including consistent abnormal unilateral NPi scores. One patient with consistent abnormal NPi scores and an improved clinical exam did not undergo invasive interventions. Two patients showed early improvement in NPi scores correlating with the normalization of their pupillary reactivity. Anisocoria improved in all patients despite concurrent abnormal NPi scores. Magnetic Resonance Imaging and Computed Tomography imaging studies, with a focus on the third nerve, revealed focal abnormalities consistent with the clinical findings. A unilateral blown pupil and abnormal NPi score in a traumatic brain injury patient are not necessarily indicative of intracranial pressure issues, and must be correlated with the entire clinical scenario, to determine the etiology of the third nerve injury and direct potential therapeutic interventions. Early NPi score normalization suggests pupillary function may improve. The authors found that NPi scores, as a component of the clinical exam, provide a sensitive, noninvasive and quantitative means of following pupillary function acutely and chronically after a traumatic brain injury. Further studies are needed to determine the ultimate role of pupillometry in the final assessment, treatment and outcomes of neurologically injured patients.

A 2014 article by Zafar and Suarez concluded that pupillometry monitoring can serve as an important tool in the ICU. The authors performed an electronic literature search to identify original studies on the use of the automated pupillometer in the ICU. They identified 7 articles that met the inclusion criteria and reviewed them critically and assessed the quality of evidence

by using the Grading of Recommendations Assessment, Development, and Evaluation approach. They found that the study grade was low, and study quality was low to moderate for all the reviewed manuscripts. Based on this data, they concluded that pupillometric measurements had better precision and reproducibility compared with the manual pupillary examination. However, they also stated that further large-scale studies on patients in the neurocritical care unit and medical ICU are needed to support the routine use of automated pupillometry.<sup>12</sup>

In a single-blinded, observational study, Olson et al (2016) examined inter-rater reliability of pupil exam findings between two practitioners and between practitioners and a pupillometer. From 2,329 paired assessments, the inter-rater reliability between practitioners was only moderate for pupil size (k = 0.54), shape (k = 0.62), and reactivity (k = 0.40). Only 33.3 % of pupils scored as non-reactive by practitioners were scored as non-reactive by pupillometry. The authors concluded that despite the strong emphasis placed on the traditional pupil examination, especially for patients with a neurological illness, there is limited inter-rater reliability for subjective scoring of pupillary assessments. Thus, the use of automated pupillometers should be examined as a potential method to increase the reliability of measuring of pupil reactivity.<sup>13</sup>

#### **Brain Death**

Olgun et al (2015) noted that the determination of brain death in neonates, infants, children and adults relies on a clinical diagnosis based on the absence of neurological function with a known irreversible cause of brain injury.<sup>14</sup> Evaluation of pupil size and non-reactivity is a requisite for determination of brain death. There are no studies in the literature that quantitatively assess pupil size in brain dead children and adults. Infants, children and adults diagnosed with brain death were included in the study. Pupils were measured with a quantitative pupillometer (Forsite; Neuroptics, Irvine, CA). Median, minimum and maximum pupil sizes were documented, and the results were adjudicated for age, vasopressor use and temperature. Median right and left pupil sizes were  $5.01 \pm 0.85$ mm and  $5.12 \pm 0.87$ mm, respectively, with a range between 3.69 and 7.34mm. Pediatric pupils were larger than adult pupils (right pupil 5.53 versus 4.73mm p: 0.018; left pupil 5.87 versus 4.77mm p: 0.03), and there was no correlation of pupil size with temperature or increasing number of vasopressors. The authors concluded that this was the first study in the literature objectively evaluating pupil sizes in infants, children and adults diagnosed with brain death. They observed variation between observed pupil size and that expected based on brain death determination guidelines.

## **Gaucher Disease**

Narita et al (2014) stated that the hallmark of neuronopathic Gaucher disease (GD) is oculomotor abnormalities, but ophthalmological assessment is difficult in uncooperative patients.<sup>15</sup> Chromatic pupillometry is a quantitative method to assess the pupillary light reflex (PLR) with minimal patient cooperation. These researchers examined if chromatic pupillometry could be useful for neurological evaluations in GD. In these neuronopathic GD patients, red light-induced PLR was markedly impaired, whereas blue light-induced PLR was relatively spared. In addition, patients with non-neuronopathic GD showed no abnormalities. The authors concluded that these novel findings showed that chromatic pupillometry is a convenient method to detect neurological signs and monitor the course of disease in neuronopathic GD.

#### **Pain Assessment**

In a single-center, prospective, observational study, Connelly et al (2014) explored proof of concept for the use of pupillometry in pediatric patients.<sup>16</sup> Changes in pupil parameters before and after opioid exposure also were evaluated. Children 9 to 17 years of age undergoing

elective surgical correction of pectus excavatum were enrolled into a protocol approved by the human ethical committee (institutional review board). Pupil size and reactivity were measured using a hand-held pupillometer. Pain was assessed using age-appropriate, validated pain self-report scales. A total of 30 patients were enrolled. Each point change on a 10-cm visual analog pain intensity scale was associated with a statistically significant mean change of 0.11 mm/s in maximum pupil constriction velocity, and of approximately 0.4 % in pupil diameter. As expected, there was an association between total opioid dose (expressed as morphine equivalents) and pupil diameter. Age, sex and baseline anxiety scores did not correlate significantly with pupillary response. The authors concluded that the association of maximum pupillometry as a non-invasive method to objectively quantitate pain response/intensity in children. They stated that the technique holds promise as a pharmacodynamic "tool" to assess opioid response in pediatric patients.

## **Brain Injury**

Truong and Ciuffreda (2016) examined if mild traumatic brain injury (mTBI) adversely affects the PLR.<sup>17</sup> The PLR was evaluated in mTBI and compared to normal individuals under a range of test conditions. A total of 9 pupil parameters (maximum, minimum and final pupil diameter, latency, amplitude and peak and average constriction and dilation velocities) and 6 stimulus conditions (dim pulse, dim step, bright pulse, bright step, bright red step and bright blue step) were assessed in 32 adults with mTBI (21 to 60 years of age) and compared to 40 normal (22 to 56 years of age). The Neuroptics, infrared, DP-2000 binocular pupillometer was used (30-Hz sampling rate; 0.05 mm resolution) with binocular stimulation and recording. Different test conditions, 5-to-8 of the 9 pupillary parameters were statistically different (p < 0.05) between the 2 diagnostic groups. The most promising parameters for diagnostic differentiation were constriction latency, all pupillary diameters, average constriction velocity and peak dilation velocity. The authors concluded that mTBI adversely affects the PLR suggesting an impairment of the ANS. They stated that these findings suggested the potential for quantitative pupillary dynamics to serve as an objective mTBI biomarker.

Anderson et al (2018) examined the use of pupillometers in the setting of acute traumatic brain injury (TBI).<sup>18</sup> The use of pupillometry as a bedside tool in the routine care of patients with severe TBI (Glasgow Coma Scale score  $\leq$  8) has not been described. The authors performed a quality improvement project to implement routine use of quantitative pupillometry in the neurotrauma intensive care unit. Nursing staff were trained on device use and the project's aim in a 30-minute in-service session. Nurses caring for severe TBI patients completed standard pupil assessments using (a) a flashlight and (b) a pupillometer to quantify pupil size and reactivity (Neurological Pupil index) every hour. Abnormal results were reported to on-call providers. Surveys were then administered to evaluate knowledge, practical use of the pupillometer data, and satisfaction with the device every 3 months. Data were available for 22 nurses at 4 separate time points. Staff were positive about their ability to use and understand the device ( $\mu$  = 8.7 and 9.1, respectively, on a 10-point scale) and reported that it added value to patient care and critical decision-making. Use of automated pupillometry appears to be acceptable to nursing staff in a neurotrauma intensive care unit, and staff believed that pupillometry results enhanced clinical decision-making.

In 2020, Godau et al reported on a cross-sectional observational study to assess whether the neurological pupil index (NPi) is altered in nonconvulsive status epilepticus (NCSE).<sup>19</sup> In 128 consecutive adult emergency patients who had experienced a suspected seizure, have not

reached their prior functional level regarding level of consciousness, mental status or focal deficits, had no obvious clinical signs of status epilepticus and had an EEG indication as determined by the treating clinician for exclusion of NCSE were examined by routine EEG and pupillometry. Exclusion criteria were ocular comorbidity (n = 21) and poor EEG quality (n = 4). Pupillometry was performed once directly before the beginning of EEG recording. NCSE diagnosis (no NCSE, possible NCSE and confirmed NCSE) was established according to Salzburg consensus criteria blinded to pupillometry results. Group comparison was performed for right NPi, left NPi, lowest NPi of both sides (minNPi) and the absolute difference of both sides (diffNPi) applying non-parametric testing. In post-hoc analysis, receiver operating characteristics (ROC) of NCSE diagnosis (combined confirmed NCSE and possible NCSE) were performed for minNPi and diffNPi. From 103 patients included in the final analysis, 5 (4.9%) had confirmed NCSE, 7 (6.8%) had possible NCSE. Right NPi (p = 0.002), left NPi (p < (0.001) and minNPi (p < 0.001) were significantly lower in "confirmed NCSE" and "possible" NCSE" compared to "no NCSE"; diffNPi was significantly higher in "confirmed NCSE" and "possible NCSE" compared to "no NCSE" (p < 0.001). There was no significant difference of minNPi and diffNPi between "confirmed NCSE" and "possible NCSE". ROC analysis showed an optimal cut-off of minNPi for NCSE diagnosis of 4.0 (AUC = 0.93, 95% CI 0.86-0.99). Optimal ROC analysis cut-off of diffNPi for NCSE diagnosis was 0.2 (AUC = 0.89, 95% CI 0.80-0.99). The authors concluded that Infrared pupillometry may be a helpful diagnostic tool in the assessment of NCSE and should be studied further in larger populations.

In 2021, Traylor et al described associations between quantitative infrared pupillometry values and loss of consciousness (LOC), intracranial hypertension and functional outcomes in patients with traumatic brain injury (TBI).<sup>20</sup> A prospective study of patients evaluated at a Level 1 trauma center between November 2019 and February 2020. Pupillometry values including the Neurological Pupil Index (NPi), constriction velocity (CV), and dilation velocity (DV) were obtained. Thirty-six consecutive TBI patients were enrolled. The median (range) age was 48 (range 21-86) years. The mean Glasgow Coma Scale score on arrival was 11.8 (SD = 4.0). DV trichotomized as low (<0.5 mm/s), moderate (0.5-1.0 mm/s), or high (>1.0 mm/s) was significantly associated with LOC (P = .02), and the need for emergent intervention (P < .01). No significant association was observed between LOC and Npi (P = .16); nor between LOC and CV (P = .07). The authors concluded that further investigation of the relationship between discrete pupillometric variables and NPI is needed.

Trent et al (2023) examined the effectiveness of quantitative pupillometry (QP) in predicting neurological decline within 24 hours of admission following acute TBI.<sup>21</sup> There were 95 participants included in the analysis; of whom 35 experienced neuro worsening, defined by change in GCS of >2 within the first 24 hours of admission. There was a significant association between an abnormal Neurological Pupil index (Npi), defined as Npi of <3, and neuro worsening (p < .0001). The sensitivity (51.43%) and specificity (91.67%) of abnormal Npi in predicting neuro worsening were varied. Although there was a strong association between abnormal Npi and neuro worsening, further studies are warranted.

## **Cardiac Arrest**

In a systematic review and meta-analysis, Kim et al (2022) examined the usefulness of the quantitative pupillary light reflex as a prognostic tool for neurological outcomes in post-cardiac arrest patients treated with targeted temperature management (TTM).<sup>22</sup> These investigators searched Medline, Embase, and the Cochrane Library for studies on post-cardiac arrest patients treated with TTM that had measured the percent constriction of pupillary light reflex

(%PLR) with quantitative pupillometry as well as evaluated the neurological outcome. For an assessment of the methodological quality of the included studies, 2 authors employed the prognosis study tool independently. A total of 618 patients from 4 studies were included in this systematic review. Standardized mean differences (SMDs) were calculated to compare patients with good or poor neurological outcomes. A higher %PLR measured at 0 to 24 hours following hospital admission was related to good neurological outcomes at 3 months in post-cardiac arrest patients treated with TTM (SMD 0.87; 95 % CI: 0.70 to 1.05; I2 = 0 %). A higher %PLR amplitude measured at 24 to 48 hours following hospital admission was also associated with a good neurological outcome at 3 months in post-cardiac arrest patients treated with TTM, but with high heterogeneity (SMD of 0.86; 95 % CI: 0.40 to 1.32; I2 = 70 %). The evidence supporting these findings was of poor quality. For poor neurological outcome, the prognosis accuracy of %PLR was 9.19 (pooled diagnostic odds ratio [DOR], I2 = 0 %) and 0.75 (AUC). The authors concluded that this meta-analysis could not reveal that change of %PLR was an effective tool in predicting neurological outcomes for post-cardiac arrest patients treated with TTM owing to a paucity of included studies and the poor quality of the evidence.

Nyholm et al (2023) conducted a study to validate pre-specified thresholds of quantitative pupillometry by quantitatively assessing the percentage reduction of pupillary size (qPLR) <4% and Neurological Pupil index (NPi) 2 and in predicting unfavorable neurological outcome.<sup>23</sup> Both as an isolated predictor and combined with guideline-suggested neuron-specific enolase (NSE) threshold >60 lg L1 in the current prognostication strategy algorithm. This pre-planned diagnostic sub-study in the randomized, controlled, multicenter clinical trial "Blood Pressure and Oxygenation Targets after Out-of-Hospital Cardiac Arrest-trial." Blinded to treating physicians and outcome assessors, measurements of qPLR and NPi are obtained from cardiac arrest survivors at time points (±6 hours) of admission, after 24, 48, and 72 hours, or until the time of awakening or death. The authors found that specific thresholds of all quantitative pupillometry parameters, measured at any time following hospital admission until day 3, predicted a 90-day unfavorable outcome with 0 % FPR in comatose patients resuscitated from OHCA; however, at 0 % FPR, thresholds resulted in low sensitivity. Moreover, these researchers stated that these findings should be further validated in larger multi-center clinical trials.

## SUMMARY OF EVIDENCE

There is currently insufficient evidence to support the use of quantitative pupillometry/pupillography for any clinical application. There is insufficient documentation that the use of quantitative pupillometry will ultimately improve patient clinical outcomes.

#### SUPPLEMENTAL INFORMATION

#### **Practice Guidelines and Position Statements**

No practice guidelines or position statements were identified for quantitative pupillometry.

#### **Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in Table 1.

#### Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date

Ongoing			
NCT05248035	Pupillometry for prediction of delirium (PODIUM)	213	Jun 2025
NCT05248035	PupillOmetry for Prediction of DelirIUM (PODIUM)	213	Jun 2026
NCT06642896	Quantitative Pupillometry in Brain Injury Children: Variation After Osmotherapy (OSMOPUPILLO)	90	Apr 2028
NCT06733207	Pupillometry Use & Professional's Inspection: Leveling Subjectivity (PUPILS)	30	Sep 2025
NCT05811208	Use of Pupillometry for Pain Assessment in ICU Patients with Delirium	50	Jan 2026
Unpublished			
NCT02978079	Pupillometry in Horner's Syndrome	135	Dec 2022 (unknown)
NCT02847195	Pupillometry in pediatric intensive care unit (PICU)	66	Aug 2020 (completed)
NCT05019898	Comparison Between Pupillometry and the Numerical Rating 320 Scale		Aug 2022
NCT05567978	Comparison of 2 Pupillometric Indices in Cerebral Brain 30 Patients (LYNX)		Apr 2024
NCT05386303	Quantitative Pupillometry (HYDRO-NiP)	60	Jan 2024

NCT: national clinical trial

#### Government Regulations National:

There is no national or WPS local coverage determination on this topic.

#### Local:

Code 0341T was deleted effective 12/31/19, no replacement code.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

## **Related Policies**

N/A

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through March 2025, the date the research was completed.

# Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
3/1/15	12/9/14	12/29/14	Joint policy established
7/1/16	4/19/16	4/19/16	Routine maintenance, add references and updated rationale. No change in policy status.
7/1/17	4/18/17	4/18/17	Updated rationale and references (added # 17). No change in policy status.
7/1/18	4/17/18	4/17/18	Updated rationale section, added reference #18. Updated clinical trials section. No change in policy status.
7/1/19	4/16/19		Routine policy maintenance, no change in policy status.
7/1/20	4/14/20		Routine policy maintenance, CPT 0341T deleted, no replacement. No change in policy status.
7/1/21	4/20/21		Routine policy maintenance added reference #19. No change in policy status.
7/1/22	4/19/22		Routine policy maintenance, no change in policy status.
7/1/23	4/18/23		Added code 95919 as E/I. Routine policy maintenance, no change in policy status. Vendor managed: N/A. (ds)
7/1/24	4/16/24		Rationale updated, references 20- 23 added. Updated clinical trial section. Routine policy maintenance, no change in status. Vendor managed: N/A (ds)
7/1/25	4/15/25		Routine policy maintenance, no change in status. Vendor managed: N/A (ds)

Next Review Date: 2<sup>nd</sup> Qtr. 2026

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# BLUE CARE NETWORK BENEFIT COVERAGE POLICY: QUANTITATIVE PUPILLOMETRY/PUPILLOGRAPHY

## I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered.
BCNA (Medicare	See government section.
Advantage)	
BCN65 (Medicare	Coinsurance covered if primary Medicare covers the
Complementary)	service.

#### II. Administrative Guidelines:

N/A