



# Quantitative Pupillometry/Pupillography

**Number: 0879**

## **Policy**

*\*Please see amendment for Pennsylvania Medicaid at the end of this CPB.*

Aetna considers the use of quantitative pupillometry/pupillography experimental and investigational for all indications including the following (not an all-inclusive list) because its effectiveness has not been established.

- Acute mountain sickness
- Brain death determination
- Brain injury
- Congenital central hypoventilation syndrome
- Excessive sleepiness/narcolepsy
- Glaucoma
- Impaired consciousness
- Pain assessment
- Prediction of outcome after cardiac arrest
- Pre-transplant screening and post-transplant monitoring in persons undergoing liver transplantation
- Rheumatic diseases (e.g., rheumatoid arthritis, Sjogren's syndrome, systemic lupus erythematosus, and systemic sclerosis)

## Policy History

**Last Review** 10/27/2016

Effective: 03/21/2014

Next Review: 10/26/2017

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### **Review History**

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### **Definitions**

## Additional Information

### **Clinical Policy Bulletin Notes**

Aetna considers the use of chromatic pupillography for detection of glaucoma, and evaluation of Gaucher disease experimental and investigational because its effectiveness has not been established.

## **Background**

Pupillary examination has been used as a basic measure in critically ill patients and is important for the prognosis and management of disease. Traditionally, pupillary measurements have been carried out in a subjective manner -- by means of a pen flash-light to evaluate for reactivity and a pupil gauge for pupil size. Pupillometry refers to an objective way of measuring the diameter of the pupil. The NeurOptics NPi-100 Pupillometer is a hand-held infrared device that allows for objective measurement of pupillary light reflex and pupil size. Moreover, the numeric scale of the Neurological Pupil index (NPi), allows for a more rigorous interpretation and classification of the pupillary response. The Pupillometer and its NPi scale reduce subjectivity from the measurement by comparing the pupillary light reflex against normative data in the NPi model and automatically deriving whether the pupillary reflex falls within the normal range or outside of the normal range and provide a reliable way to quantitatively classify the pupillary light response.

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

Bertinotti and colleagues (2002) stated that the central and peripheral nervous systems are variably affected in the rheumatic diseases. Automated standardized infrared pupillometry allows for safe, non-invasive assessment of the pupillary innervation. 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. Besides providing autonomic innervation, sensory nerves fibers are able to control iris diameter. 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 SP-stimulated 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. The role of pupillometry in the management of patients with rheumatic diseases has not been established; its clinical value has to be ascertained via well-designed studies.

Taylor et al (2003) prospectively used a new hand-held pupillometer to assess pupillary function quantitatively. 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. In healthy volunteers the resting pupillary aperture averaged 4.1 mm and the minimal aperture after stimulation was 2.7 mm, resulting in a 34 % change in pupil size. Constriction velocity averaged 1.48 +/- 0.33 mm/second. 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 out-patients, 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.

Chen and colleagues (2005) noted that glaucomatous damage to upper and lower retina is often unequal. 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.

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. A total of 148 patients with glaucoma (mean age of  $67 \pm 11$  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 step-wise regression or forward selection with Akaike information criterion and validated by 5-fold cross-validation. 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 infero-nasal 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. Moreover, they stated that with refinement, pupil testing may provide a simple approach for glaucoma screening.

Kjesbu et al (2005) noted that the iris is a dynamic organ in which the ANS regulates the activity. Iris activity reflects physiological reactions to different sensory stimuli, resulting in a variation in pupil size. There are many different diagnostic tools that assess iris activity. These investigators reviewed the methods of pupillary assessment as a research tool and in clinical use. The basis for this study was obtained by searches on Medline and ISI Web of Knowledge. Reference lists were further checked for other relevant studies. The authors stated that pupillometry is a research tool that is adopted in an increasing number of medical fields. In the past, this method was used mostly within ophthalmology and neurology; today it has spread to a wide range of medical fields (e.g., pharmacology and physiology). There are continuous improvements in the flexibility and recording capacity of pupillometers and they are used in an increasing number of medical fields, though they are still most useful within research.

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. The recent introduction of a portable, user-friendly, infrared pupillometer (ForSite, NeuroOptics 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.

Wilson et al (2008) noted that gross pupil dynamics were used as an indirect measure of brain function. 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 questionnaires 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) performed an observational study of pupil assessment with automated pupillometry in clinical liver transplantation (LT) settings, including pre-transplant evaluations and post-transplant surveillance. 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 needed.

Payen et al (2012) noted that pupillary size reflects the balance between sympathetic and parasympathetic systems. 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.

Patwari et al (2012) 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. 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.

An UpToDate review on “Disorders of ventilatory control” (Johnson, 2013) states that “Congenital central hypoventilation syndrome (CCHS) is associated with a nearly absent respiratory response to hypoxia and hypercapnia, no respiratory discomfort during CO<sub>2</sub> inhalation, mildly elevated arterial carbon dioxide

tension (PaCO<sub>2</sub>) during wakefulness, and markedly elevated PaCO<sub>2</sub> during non-REM sleep. Patients with CCHS increase their ventilation and maintain relatively normal PaCO<sub>2</sub> levels during exercise, and lower their PaCO<sub>2</sub> during passive leg cycling due to nonchemoreceptive inputs. CCHS can occur in association with Hirschsprung's disease, a condition characterized by abnormalities of the cholinergic innervation of the gastrointestinal tract. The estimated incidence of Hirschsprung's disease among patients with CCHS (also called Ondine-Hirschsprung syndrome or Haddad syndrome) ranges from 10 to 50 percent. Patients with CCHS are also at increased risk of neuroblastoma and ganglioneuroma. These associations, and the demonstration of subtle autonomic abnormalities in relatives of patients with CCHS, suggest that autonomic neuropathy, particularly of the parasympathetic system, is pathophysiologically important in CCHS. Abnormalities of the gene encoding the transcription factor PHOX2b, which is active during neuronal development, have been implicated in the pathogenesis of CCHS". This review does not mention the use of pupillometry as a management tool. Thus the role of pupillometry in the management of CCHS has yet to be established.

Martinez-Ricarte et al (2013) stated that pupil assessment is a fundamental part of the neurological examination. 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. These researchers described the fundamentals of infrared

pupillometry and discussed potential applications in the monitoring of neuro-critical patients. They also presented some recommendations in the routine assessment of pupils in 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.

An UpToDate review on “Quantifying sleepiness” (Freedman, 2013) states that “Pupillometry is not widely used because the equipment is not readily available. Further research is necessary to determine its role in the assessment of excessive sleepiness”.

In a single-blinded, observational study, Olson et al (2016) examined inter-rater reliability of pupil exam findings between 2 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.

### 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. 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 7.34 mm. Pediatric pupils were larger than adult pupils (right pupil 5.53 versus 4.73 mm p: 0.018; left pupil 5.87 versus 4.77 mm 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. 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.

Furthermore, UpToDate reviews on "Gaucher disease: Pathogenesis, clinical manifestations, and diagnosis" (Hughes,

2015a) and “Gaucher disease: Initial assessment, monitoring, and clinical course” (Hughes, 2015b) do not mention pupillometry as a diagnostic tool.

### 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. 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 pupillary constriction velocity and diameter with pain scores illustrated the potential for using 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. 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 allowed for discrimination of different parameters. For any of the given 6 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.

#### Prediction of Outcome of After Cardiac Arrest:

Heimburger and colleagues (2016) noted that predicting outcome after cardiac arrest (CA) is particularly difficult when therapeutic hypothermia (TH) is used. In a prospective observational study, these researchers investigated the performance of quantitative pupillometry and trans-cranial Doppler (TCD) in this context. This study included 82 post-CA patients. Quantitative assessment of PLR and TCD measurements of the 2 middle cerebral arteries were performed at admission (day 1) and after 24 hours (day 2) during TH (33 to 35°C) and sedation. Neurological outcome was assessed at 3 months using cerebral performance category (CPC) scores; patients were classified as having good (CPC 1 to 2) or poor (CPC 3 to 5) outcome. Prognostic performance was analyzed using area under the receiver operating characteristic curve (AUC-ROC). Patients with good outcome ( $n = 27$ ) had higher PLR amplitude than patients with poor outcome ( $n = 55$ ) both at day 1, 13 % (10 to 18) (median of 25<sup>th</sup> to 75<sup>th</sup> percentile) versus 8 % (2 to 11) ( $p < 0.001$ ), and at day 2, 17 % (13 to 20) versus 8 % (5 to 13) ( $p < 0.001$ ), respectively. The

AUC-ROC curves at days 1 and 2 were 0.76 (95 % CI: 0.65 to 0.86) and 0.82 (95 % CI: 0.73 to 0.92), respectively. The best cut-off values of PLR amplitude to predict a 3-month poor outcome were less than 9 % and less than 11 %, respectively. A PLR amplitude of less than 7 % at day 2 predicted a 3-month poor outcome with a specificity of 100 % (95 % CI: 86 to 100) and a sensitivity of 42 % (95 % CI: 28 to 58). No differences in TCD measurements were found between the 2 patient groups. The authors concluded that PLR measurements might be informative in the prediction of outcome of post-CA patients even under sedation and hypothermia.

#### Chromatic Pupillography for Detection of Glaucoma:

In a cross-sectional study, Rukmini and associates (2015) examined if a chromatic pupillometry test can be used to detect impaired function of intrinsically photosensitive retinal ganglion cells (ipRGCs) in patients with primary open-angle glaucoma (POAG) and determined if pupillary responses correlate with optic nerve damage and visual loss. A total of 161 healthy controls recruited from a community polyclinic (55 men; 151 ethnic Chinese) and 40 POAG patients recruited from a glaucoma clinic (22 men; 35 ethnic Chinese) 50 years of age or older were included in this study. Subjects underwent monocular exposure to narrowband blue light (469 nm) or red light (631 nm) using a modified Ganzfeld dome. Each light stimulus was increased gradually over 2 minutes to activate sequentially the rods, cones, and ipRGCs that mediate the pupillary light reflex. Pupil diameter was recorded using an infrared pupillography system. Pupillary responses to blue light and red light were compared between control subjects and those with POAG by constructing dose-response curves across a wide range of corneal irradiances (7 to 14 log photons/cm<sup>2</sup>/second). In patients with POAG, pupillary responses were evaluated relative to standard automated perimetry testing (Humphrey Visual Field [HVF]) and scanning laser ophthalmoscopy parameters (Heidelberg Retinal Tomography [HRT]). The pupillary light reflex was reduced in patients with POAG only at higher irradiance levels, corresponding to the

range of activation of ipRGCs. Pupillary responses to high-irradiance blue light associated more strongly with disease severity compared with responses to red light, with a significant linear correlation observed between pupil diameter and HVF mean deviation ( $r = -0.44$ ;  $p = 0.005$ ) as well as HRT linear cup-to-disc ratio ( $r = 0.61$ ;  $p < 0.001$ ) and several other optic nerve head parameters. The authors concluded that in glaucomatous eyes, reduced pupillary responses to high-irradiance blue light were associated with greater visual field loss and optic disc cupping. They stated that in POAG, a short chromatic pupillometry test that evaluated the function of ipRGCs can be used to estimate the degree of damage to retinal ganglion cells that mediate image-forming vision; this approach could prove useful in detecting glaucoma. These findings need to be validated in well-designed studies.

Furthermore, UpToDate reviews on “Overview of glaucoma in infants and children” (Olitsky and Reynolds, 2016) and “Open-angle glaucoma: Epidemiology, clinical presentation, and diagnosis” (Jacobs, 2016) do not mention pupillography as a diagnostic tool.

In summary, there is currently insufficient evidence to support the use of chromatic pupillometry/quantitative pupillometry/pupillography for any clinical application.

CPT Codes / HCPCS Codes / ICD-10 Codes	
<i>Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":</i>	
<b>ICD-10 codes will become effective as of October 1, 2015:</b>	
<b>CPT codes not covered for indications listed in the CPB:</b>	
0341T	Quantitative pupillometry with interpretation and report, unilateral or bilateral
<b>ICD-10 codes not covered for indications listed in the CPB (not all inclusive):</b>	
D75.1	Secondary polycythemia [acute mountain sickness]

G47.00 - G47.9	Sleep disorders
H40.001 - H42	Glaucoma
M05.00 - M14.89	Rheumatoid arthritis and other inflammatory polyarthropathies
M32.0 - M32.9	Systemic lupus erythematosus
M34.0 - M34.9	Systemic sclerosis [scleroderma]
M35.00 - M35.09	Sicca syndrome [Sjögrens]
R40.0	Somnolence [impaired]
S06.0x0+ - S06.9x9+	Intracranial injury
T70.29x+	Other effects of high altitude [acute mountain sickness]
Z48.21 - Z48.298	Aftercare following organ transplant [liver transplantation]
Z76.82	Awaiting organ transplant status [liver transplantation]

**The above policy is based on the following references:**

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**AETNA BETTER HEALTH® OF PENNSYLVANIA**

**Amendment to  
Aetna Clinical Policy Bulletin Number: 0879  
Quantitative Pupillometry/Pupillography**

There are no amendments for Medicaid.