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
- Age-related macular degeneration (monitoring the progression of disease and assessing changes in retinal function that result from treatments)
- Alzheimer's disease
- Brain death determination
- Brain injury
- Congenital central hypoventilation syndrome
- Detection of impaired cerebral autoregulation in critically ill persons
- Discriminating compressive lesions from microvascular ischemic third nerve palsy
- Excessive sleepiness/narcolepsy
- Glaucoma

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.*
• Impaired consciousness
• Neuromonitoring of delirium in sedated mechanically
  ventilated critically ill persons
• Pain assessment
• Parkinson disease
• 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).

Aetna considers the use of chromatic pupillography
experimental and investigational for the following (not an all-
inclusive list) because its effectiveness has not been
established:

• For detection of glaucoma
• For detection of Leber congenital amaurosis
• For detection of optic nerve diseases (e.g., optic neuritis
  and non-arteritic anterior ischemic optic neuropathy)
• For detection of retinitis pigmentosa
• For evaluation of Gaucher disease
• For evaluation of hemianopia
• For monitoring of progression of retinal and optic nerve
  diseases or recovery after treatment.

**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 iridal 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 iridal 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 ± 11 years) and 71 controls (mean age of 60 ± 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, 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.

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 first or second 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 CO2 inhalation, mildly elevated arterial carbon dioxide tension (PaCO2) during wakefulness, and markedly elevated PaCO2 during non-REM sleep. Patients with CCHS increase their ventilation and maintain relatively normal PaCO2 levels during exercise, and lower their PaCO2 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±0.85mm and 5.12±0.87mm, 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. 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.

Narayan and colleagues (2018) noted that TBI is a leading cause of pediatric morbidity and mortality worldwide and ICP monitoring plays a crucial role in its management. Based on existing literature, these investigators reviewed the current practicing non-invasive ICP monitoring devices and their accuracy in predicting increased ICP in pediatric TBI. They carried out a thorough literature search on PubMed, Medline, and the Cochrane database, articles were selected systematically and reviewed completely, and relevant data were summarized and discussed. A total of 27 articles pertaining to pediatric TBI were included and reviewed. These researchers found various modalities of non-invasive ICP
monitoring devices used over the last few years. The non-invasive modalities so far attempted in pediatric TBI and so reviewed were transcranial Doppler, optic nerve sheath diameter, oto-acoustic emission, near-infrared spectroscopy, contrast-enhanced ultrasonography, and quantitative pupillometry. The authors conclude that invasive monitoring methods are the current gold standard for monitoring ICP; however, complications caused by their invasive nature are of concern. Of all the non-invasive methods based on the literature, these investigators found transcranial Doppler and optic nerve sheath diameter assessment to be the best tools to monitor ICP in pediatric TBI. They stated that the promising results and developments of non-invasive ICP monitoring modalities with its ideal features of high sensitivity, diagnostic accuracy, and simple acquisition technique may make it the future of neuro-intensive monitoring in pediatric TBI.

Jahns and colleagues (2019) noted that elevated ICP is frequent after TBI and may cause abnormal pupillary reactivity, which in turn is associated with a worse prognosis. Using automated IR pupillometry, these researchers examined the relationship between (NPi and invasive ICP in patients with severe TBI. This was an observational cohort of consecutive subjects with severe TBI (Glasgow Coma Scale [GCS] of less than 9 with abnormal lesions on head CT) who underwent parenchymal ICP monitoring and repeated NPi assessment with the NPi-200® pupillometer. These investigators examined NPi trends over time (4 consecutive measurements over intervals of 6 hours) prior to sustained elevated ICP of greater than 20 mmHg. They further analyzed the relationship of cumulative abnormal NPi burden (%NPi values of less than 3 during total ICP monitoring time) with intra-cranial hypertension (ICHT)-categorized as refractory (ICHT-r; requiring surgical decompression) versus non-refractory (ICHT-nr; responsive to medical therapy)-and with the 6-month Glasgow Outcome Score (GOS). A total of 54 patients were studied (mean age of 54 ± 21 years, 74 % with focal injuries on CT), of whom 32 (59 %) had ICHT. Among subjects with
ICHT, episodes of sustained elevated ICP (n = 43, 172 matched ICP-NPi samples; baseline ICP [T-6 hours] 14±5 mmHg versus ICPmax [T0 hour] 30 ± 9 mmHg) were associated with a concomitant decrease of the NPi (baseline 4.2 ± 0.5 versus 2.8 ± 1.6, p < 0.0001 ANOVA for repeated measures). Abnormal NPi values were more frequent in patients with ICHT-r (n = 17; 38 [3 to 96] % of monitored time versus 1 [0 to 9] % in patients with ICHT-nr [n = 15] and 0.5 [0 to 10] % in those without ICHT [n = 22]; p = 0.007) and were associated with an unfavorable 6-month outcome (15 [1 to 80] % in GOS 1 to 3 versus 0 [0 to 7] % in GOS 4 to 5 patients; p(0.02) The authors concluded that in patients with severe TBI and abnormal intra-cranial CT lesions at risk for secondary intra-cranial hypertension, sustained elevated ICP was associated with impaired NPi, which in turn may recover to normal values upon ICP treatment with osmotherapy.

Sustained abnormalities of the NPi were more frequently observed in patients with refractory ICP requiring decompressive hemi-cranieectomy and were associated with a worse 6-month outcome. These researchers stated that these findings suggested that adding non-invasive NPi to invasive ICP monitoring provided important supplementary diagnostic, therapeutic, and prognostic information to guide the management of severe TBI patients.

The authors stated that this study had several drawbacks. It was a single-centered trial, and included a relatively limited sample size of patients (n = 54) with severe TBI monitored with ICP who were at high risk for ICHT. TBI injury subtype was also predominantly focal and included a cohort with a relatively advanced age, thus limiting the generalizability of these findings. However, the inclusion of a selected and homogeneous TBI cohort also had advantages, as it identified a potential group of severely head-injured patients, in whom the addition of the NPi monitoring could be of particular value and may be helpful for individualized ICP care; and future larger, multi-centered confirmatory studies using combined ICP and NPi monitoring may be warranted. Additional studies
also may help to better refine the role of the NPi as a monitoring tool, its place in ICP management algorithms, and potential role in future guidelines for TBI care. Episodes of sustained elevated ICP were retained for the analysis based on 3 main criteria: ICP max greater than 20 mmHg for at least 10 mins; at least 3 repeated consecutive NPi measurements during the 6 hours preceding ICP max (and respectively following ICP osmotherapy); and a maximum of 3 episodes per patient. While this increased data quality (particularly, by avoiding skewing of data) and thus the robustness of the statistical analysis, it may have introduced selection biases. The NPi data reported during episodes of elevated ICP may not necessarily be representative of average patient NPi during the entire intensive care unit (ICU) stay. Although all patients had NPi readings taken at least every 2 hours, NPi measurements were more frequent during elevated ICP episodes (at least every hour), and in this case, the lower values were considered for the matching analysis of NPi with ICP. Finally, there was no important change in the infusion rates of sedatives during analyzed ICP episodes, however, additional sedative boluses were given, and thus (albeit unlikely), these investigators could not completely rule out that this may have at least partly affected the NPi.

**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 25th to 75th 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.

Oddo and Friberg (2017) stated that delayed awakening after targeted temperature management (TTM) and sedation is frequent among cardiac arrest patients. Differentiating between prolonged coma and irreversible cerebral damage can be challenging, thus, the utilization of a multi-modal approach is recommended by international guidelines. These investigators discussed indications and advantages/disadvantages of available modalities for coma prognostication and described new tools to improve the accuracy for outcome prediction. Studies from the TTM era confirmed that combining neurological examination with electrophysiological assessment [electroencephalography (EEG) and somato-sensory evoked potentials (SSEP)] greatly improved coma prognostication. This combination is recognized as the most useful by many clinicians and appeared widely applicable as part of initial patient assessment. Additional tests (serum neuron specific enolase and neuroimaging) may be most useful to orient clinical
decisions in patients with prolonged coma. Advanced analysis of EEG and SSEP recordings and the emergence of quantitative pupillometry hold great promise.

Pupillography for Age-Related Macular Degeneration

Takayama and colleagues (2016) (i) evaluated, using pupillography, the difference between eyes affected by age-related macular degeneration (ARMD) and their contralateral normal eyes with regard to the mean relative afferent pupillary defect (RAPD) score, and (ii) determined any correlations between this difference in RAPD score and differences in visual acuity (VA) or ARMD dimensions. Measurements were made using the RAPDx pupillographer (Konan Medical, Nishinomiya, Japan), which analyzed pupil response to light stimulation. Both best corrected VA (BCVA; converted to logMAR) and greatest linear dimension (GLD; calculated on the basis of fluorescence angiography [FA] images) were measured. The correlations between RAPD difference and logMAR difference, and GLD difference were then analyzed. The study included 32 patients (18 men, 14 women; mean age of 74.8±9.7 years) who had ARMD in 1 eye and a normal fundus in the contralateral eye. Mean resting pupil diameter, mean latency onset of constriction, mean constriction velocity (VC), and recovery were not significantly different in ARMD eyes compared with normal eyes. The mean amplitude of constriction was smaller (p = 0.028), and the mean latency of maximum constriction was shorter (p=0.0013) in ARMD eyes than in normal eyes. Regarding RAPD scores, there was a significant correlation between VA difference and RAPD score differences of both amplitude (p<001, r = 0.53) and latency (p = 0.034, r = 0.33); GLD difference was also significantly correlated with differences in both amplitude (p = 0.021, r = 0.36) and latency (p = 0.033, r = 0.33) scores; RAPD outcomes were correlated with VA and ARMD dimension. The authors concluded that automated pupillography may be a useful tool in monitoring the progression of ARMD and assessing changes in retinal...
function that result from novel interventions. Moreover, they stated that longitudinal studies are needed to identify more correlations between retinal function and RAPD.

The drawbacks of this study included its small sample size (n = 32), the use of only 30° light stimulation, and the lack of corroborating focal macular electroretinogram (ERG) measurement or scotoma caused by ARMD. The RAPDx can be freely modified in terms of range and patterns of stimulation. Conversely, the focal macular ERG can only be modified in terms of an area of 5°, 10°, 15°, and 30° within the measured area of focal retinal function. Thus, future studies can be expected to detect focal retinal function and photoreceptor function in asymmetry with a greater degree of accuracy.

**Pupillography for Alzheimer's Disease / Parkinson Disease**

Chang and colleagues (2017) noted that clinical assessment of pupil appearance and PLR may inform us the integrity of the ANS. Current clinical pupil assessment is limited to qualitative examination, and relies on clinical judgment. Infra-red (IR) video pupillography combined with image processing software offer the possibility of recording quantitative parameters. In this study these researchers described an IR video pupillography set-up intended for human and animal testing. As part of the validation, resting pupil diameter was measured in human subjects using the NeurOptics (Irvine, CA) pupillometer, to compare against that measured by IR video pupillography set-up, and PLR was assessed in guinea pigs. The set-up consisted of a smart phone with a light-emitting diode (LED) strobe light (0.2 s light-ON, 5 s light-OFF cycles) as the stimulus and an IR camera to record pupil kinetics. The consensual response was recorded, and the video-recording was processed using a custom MATLAB program. The parameters assessed were resting pupil diameter (D1), CV, percentage constriction ratio, re-dilation velocity (DV) and...
percentage re-dilation ratio. We report that the IR video pupillography set-up provided comparable results as the NeurOptics pupillometer in human subjects, and was able to detect larger resting pupil size in juvenile male guinea pigs compared to juvenile female guinea pigs. At juvenile age, male guinea pigs also had stronger pupil kinetics for both pupil constriction and dilation. The authors concluded that their IR video pupillography set-up can be applied to clinical research in human, as well as in animal models of Alzheimer’s disease and Parkinson disease that are known to have cholinergic deficits. They noted that PLR is becoming an increasingly popular tool in neurological and eye research, contributing to the examination of the ANS, and the retina and optic nerve of the eye. They stated that the experimental set-up described in this study may provide a foundation for further development of a more integrated system, which can be used in research as well as in ophthalmological assessments in the clinical setting.

Quantitative Pupillometry in Isolated Third Nerve Palsy

In a retrospective, observational, case-series study, Kim and colleagues (2018) evaluated pupillary involvement according to various etiologies of acquired isolated third nerve palsy using automated pupillometry, and examined the efficacy of digital pupillometry in discriminating compressive lesions from microvascular ischemic 2rd nerve palsy. A total of 171 subjects were included in this study, consisting of 60 subjects with presumed microvascular ischemic third nerve palsy, 51 with non-ischemic third nerve palsy, and 60 controls whose pupillary light responses were measured using a dynamic automated pupillometer. Subjects with non-ischemic third nerve palsy were divided into subgroups according to their etiology: inflammatory and compressive groups including tumor and aneurysm. Pupillometry parameters including minimum and maximum pupil diameters, constriction latency and ratio, maximum and average constriction velocities and
dilation velocity were noted. The diagnostic ability of pupillometry parameters for discriminating compressive versus microvascular ischemic third nerve palsy was evaluated. The inter-eye difference of the involved eye and the uninvolved fellow eye was calculated to adjust for individual variability. Among all parameters, reduced pupillary constriction ratio was the most specific parameter for detecting non-ischemic third nerve palsy, as a large inter-eye difference beyond the normative range of controls was found in 0 % of ischemic, 20 % of inflammatory and 60 % of compressive third nerve palsy. With the diagnostic criteria using inter-eye differences of minimum pupil diameter of greater than 0.45 mm, or pupillary constriction ratio of less than -7.5 % compared to the fellow eye, the sensitivity and specificity for diagnosing compressive third nerve palsy were 95 % and 88 %, respectively. In the compressive group, positive correlations were found between the degree of external ophthalmoplegia and constriction ratio ($r = 0.615, p < 0.001$), average constriction velocity ($r = 0.591, p = 0.001$) and maximum constriction velocity ($r = 0.582, p = 0.001$). The authors concluded that abnormal pupillary constriction ratio was highly specific for detecting compressive third nerve palsy, although the sensitivity was not high. These researchers stated that digital pupillometry demonstrated relatively good performance for discriminating compressive lesions from microvascular ischemic third nerve palsy.

The authors stated that this study had several drawbacks. This trial was retrospective and there was not enough number of patients within the compressive group for a meaningful comparison between different etiologies. These researchers excluded 6 patients with mid-brain stroke, to exclude central lesions that might interrupt pupillary light responses in both eyes. They stated that further studies with a larger number of subjects are needed to better analyze the pupillometry data among different etiologies of acquired third nerve palsies. Furthermore, all subjects were Korean, and thus, these findings may not be generalizable to other populations. Lastly, as a major proportion of compressive and inflammatory cases
did not show pupil involvement, the sensitivity of dynamic pupillometry was low for predicting non-microvascular etiologies of third nerve palsy.

Detection of Impaired Cerebral Autoregulation in Critically Ill Persons

Cornejo and colleagues (2020) noted that critically ill patients are at high risk of developing neurological complications. Among all the potential etiologies, brain hypoperfusion has been advocated as one of the potential mechanisms. Impairment of cerebral autoregulation (CAR) can result in brain hypoperfusion. However, assessment of CAR is difficult at bedside. In a retrospective, observational study, these researchers examined if the automated pupillometer might be able to detect impaired CAR in critically ill patients. This trial included 92 patients; 52 were septic. CAR was assessed using the Mxa index, which is the correlation index between continuous recording of cerebral blood flow (CBF) velocities using the transcranial Doppler and invasive arterial blood pressure (BP) over 8 ± 2 mins. Impaired CAR was defined as an Mxa of greater than 0.3. Automated pupillometer (Neuroptics, Irvine, CA) was used to evaluate the pupillary light reflex concomitantly to the CAR assessment. The median Mxa was 0.33 in the whole cohort (0.33 in septic patients and 0.31 in the non-septic patients; p = 0.77). A total of 51 (55 %) patients showed impaired CAR, 28 (54 %) in the septic group and 23 (58 %) in the non-septic group. These investigators found a statistically significant although weak correlation between Mxa and the Neurologic Pupil Index \( r^2 = 0.04; p = 0.048 \) in the whole cohort as in septic patients \( r^2 = 0.11; p = 0.026 \); no correlation was observed in non-septic patients and for other pupillometry-derived variables. The authors concluded that automated pupillometry could not predict CAR indices such as Mxa in a heterogeneous population of critically ill patients.

Neuromonitoring of Delirium in Sedated Mechanically
Ventilated Critically Ill Persons

Farve and colleagues (2020) noted that ICU delirium is a frequent secondary neurological complication in critically ill patients undergoing prolonged mechanical ventilation. Quantitative pupillometry is an emerging modality for the neuromonitoring of primary acute brain injury, but its potential utility in patients at risk of ICU delirium is unknown. This was an observational cohort study of medical-surgical ICU patients, without acute or known primary brain injury, who underwent sedation and mechanical ventilation for at least 48 hours. Starting at day 3, automated IR pupillometry-blinded to ICU caregivers-was used for repeated measurement of the pupillary function, including quantitative pupillary light reflex (q-PLR, expressed as % pupil constriction to a standardized light stimulus) and constriction velocity (CV, mm/s). The relationship between delirium, using the CAM-ICU score, and quantitative pupillary variables was examined. A total of 59/100 patients had ICU delirium, diagnosed at a median 8 (5 to 13) days from admission. Compared to non-delirious patients, subjects with ICU delirium had lower values of q-PLR (25 [19 to 31] versus 20 [15 to 28] %) and CV (2.5 [1.7 to 2.8] versus 1.7 [1.4 to 2.4] mm/s) at day 3, and at all additional time-points tested (p < 0.05). After adjusting for the Sequential Organ Failure Assessment (SOFA) score and the cumulative dose of analgesia and sedation, lower q-PLR was associated with an increased risk of ICU delirium (odds ratio [OR] 1.057 [1.007 to 1.113] at day 3; p = 0.03). The authors concluded that sustained abnormalities of quantitative pupillary variables at the early ICU phase correlated with delirium and preceded clinical diagnosis by a median 5 days. These researchers stated that these findings suggested a potential utility of quantitative pupillometry in sedated mechanically ventilated ICU patients at high risk of delirium. They stated that these findings are hypotheses-generating; thus, additional larger, ideally multi-center studies are needed to confirm these
findings and more precisely examine the value of low q-PLR in predicting ICU delirium, and identify precise prognostic cut-offs in this setting.

The authors stated that this study had several drawbacks. The study was single-center and employed a convenience sample size, without formal sample size calculation, thereby implying a potential risk of biases. The cohort was selected to be representative of a high-risk ICU delirium population, undergoing mechanically ventilation for at least 48 hours or more, i.e., a setting where neuromonitoring may be of greatest potential utility. However, pupillometry was not started early on ICU admission in all patients expected to be on mechanical ventilation for at least 48 hours, but rather was restricted to patients who were actually still mechanically ventilated after 48 hours. Thus, it remained to be examined if very early pupillometry assessment may provide even earlier evidence for risk of delirium. The duration of the delirium was not available in all patients, which was an additional drawback. While neuroimaging was not systematically carried out, these investigators excluded all patients admitted for a primary acute brain injury or with a previous known neurological disease thereby limiting as much as possible intrinsic brain factors that may potentially alter pupillometry assessment. In addition, pupillometry measurements were carried out by an experienced research ICU physician or nurse, thus guaranteeing data reliability and quality, and the pupillometry data were blinded to clinicians involved in patient care. These researchers did not adjust for ambient light conditions, which may at least in part affect q-PLR. However, the pupillometer used in this study (AlgiScan device) has a black rubber that completely covers the eye, thereby ensuring homogeneous dark conditions during pupillary constriction measurements. The average absolute difference in pupil constriction between delirious and non-delirious patients was relatively low — ranging from 0.2 to 0.3 m — which approached the limits of inter-rater variability for the device. Furthermore, additional
computed variables such as the Neurological Pupil index (NPI) were not available in this study, but warrants further investigation.

**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(2)/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 a cross-sectional study, Najjar and colleagues (2018) assessed the ability of chromatic pupillometry to reveal abnormal pupillary responses to light in patients with early-stage POAG and to examined if the degree of pupillometric impairment correlated with structural hallmarks of optic nerve damage in the disease. A total of 46 patients with early-stage POAG (63.4 ± 8.3 years, 63 % men, 87 % ethnic-Chinese) and 90 age-matched healthy controls (61.4 ± 8.6 years, 34 % men, 89 % ethnic-Chinese). Patients with POAG had a visual field mean deviation (VFMD) of -6 decibels or better on automated perimetry. Each subject underwent a monocular 2-min exposure to blue light (462 nm) followed by another 2-min exposure to red light (638 nm) using a modified Ganzfeld dome equipped with a light-emitting diode lighting system. The light stimuli intensity was increased logarithmically to evaluate the combined extrinsic and intrinsic response of intrinsically photosensitive retinal ganglion cells (ipRGCs). Light-induced changes in horizontal pupil diameter were assessed monocularly using IR pupillography. Baseline-adjusted, light-induced pupillary constriction amplitudes were calculated, and individual irradiance-response curves were constructed for each stimulus. Pupillary constriction
amplitudes were compared between groups and across light intensities using a linear mixed model analysis. The linear relationship between pupillometric parameters and different structural and functional features of glaucoma was assessed using Pearson’s correlation analysis. Light-induced pupillary constriction was reduced in patients with early-stage POAG compared with controls at moderate to high irradiances (greater than or equal to 11 Log photons/cm²/s) of blue (p = 0.003) and red (p < 0.001) light. Maximal pupillary constriction amplitude was correlated with retinal nerve fiber layer thickness (RNFL) thickness (blue: r = 0.51, p < 0.001; red: r = 0.45, p = 0.002) in patients with POAG but not in controls. Conversely, pupillometric parameters were not correlated with visual field scores in patients with early-stage POAG. The authors concluded that this study showed that early-stage POAG was associated with altered pupillary responses to ramping-up full-field light stimulations. These wavelength-independent deficits in pupillary constriction to high irradiances of light correlated with subtle changes in RNFL thickness and were indicative of ipRGC dysfunction or loss early in the disease. These findings also added to the body of evidence supporting chromatic pupillometry as an objective, functional, and fast method that does not require clinical expertise to evaluate retinal integrity in ophthalmic diseases such as glaucoma. Moreover, these researchers stated that although these pupillometric findings showed promise for detecting POAG, further improvements are needed to render this approach more viable in a clinical setting. They noted that with modern technologic advancements, pupillometry-based methods could potentially be refined and adapted into reliable population-based ocular screening tools for early POAG detection.

The authors stated that this study had several drawbacks. First, because subjects were only briefly (approximately 2 mins) dark-adapted before blue light exposure, these researchers assumed that rhodopsin was not fully regenerated to optimally capture light and rods’ contribution to the pupillary
responses to light may have been sub-optimal. Thus, they could not exclude that a reduction in pupil constriction to dimmer irradiances of blue light or an increased threshold of constriction to this wavelength of light could be observed in patients with POAG after being fully dark adapted. A dark adaptation of 30 to 45 mins is usually needed to fully regenerate rhodopsin. Such a procedure is cumbersome in a clinical setting, but could be replaced by a partial dark adaptation period of at least 5 mins (approximately 50 % of regenerated rhodopsin). Second, these investigators acknowledged that their paradigm may not allow them to fully disentangle the disease-dependent pupil responses from direct pupillometric changes resulting from the lower retinal illumination induced by the gradual pupil constriction. In fact, these researchers likely under-estimated the pupillary response to both blue and red lights, especially in healthy controls, because subjects’ pupils were not dilated pharmacologically. Nevertheless, given the potential effect of anti-muscarinics on the physiologic properties of retinal ganglion cells, they believed that the use of such agents would generate greater uncertainty when testing retinal integrity. Conversely, adopting a Maxwellian view optical system may improve the control of retinal light exposure during the ramping-up light regimen and across age groups. Third, PIPR metrics (slope of re-dilation, amplitudes) were unconventional in this study. This could be due to the duration and pattern of the light exposure paradigm, in addition to the gradual constriction of the pupil and the reduction in the amount of light reaching the retina. Conventionally, optimal PIPR was induced by short bright stimulations to a dilated pupil and was reduced under blue background, or subsequently to blue light exposure. The dynamics of the light stimulation used in this study did not necessarily allow for a direct and isolated assessment of the melanopsin-based response and may have led to gradual light adaptation and to less discernible PIPRs under blue light. Although PIPR is a proxy to assess the integrity of the melanopsin-signaling pathway, melanopsin is not exclusively affected in glaucoma.
but rather the ipRGCs expressing the photopigment. In this study, the authors showed that the amplitudes of pupil constriction during a nonmydriatic full-field light stimulation delivered in a logarithmic ramping-up fashion can be used to detect ipRGC dysfunction in early-stage POAG. Further experiments in melanopsin knock-out animal models are needed to discern the melanopsin-dependent pupillometric component in the ramping-up paradigm. Finally, given that the pool of subjects included mainly ethnic Chinese individuals, it would also be important to examine if these findings are generalizable to other ethnic groups.

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

**Chromatic Pupillography for Hemianopia**

Maeda and colleagues (2017) noted that the pupil light reflex is considered to be a simple subcortical reflex. However, many studies have proven that patients with isolated occipital lesions with homonymous hemianopia show pupillary hemihypokinesia. These researchers hypothesized that the afferent pupillary system consists of 2 pathways: (i) one via intrinsically photosensitive retinal ganglion cells (ipRGCs), (ii) the other running through the normal RGCs via the visual cortex. The purpose of this study was to test the hypothesis of these 2 separate pupilometer pathways. A total of 12 patients (59.1 ± 18.8 years) with homonymous hemianopia due to post-geniculate lesions of the visual pathway and 20 normal controls (58.6 ± 12.9 years) were examined using chromatic pupillography: stimulus intensity was 28 lx corneal illumination, stimulus duration was 4.0 s, and the stimulus wavelengths were 420 ± 20 nm (blue) and 605 ± 20 nm (red), respectively. The examined parameters were baseline pupil diameter, latency, and relative amplitudes (absolute amplitudes compared to baseline), measured at maximal constriction, at 3 s after stimulus onset, at stimulus
offset, and at 3 s and 7 s after stimulus offset. The relative amplitudes for the red stimulus were significantly smaller for hemianopia patients compared to the normal controls [maximal constriction: 35.6 ± 5.9 % (hemianopia) to 42.3 ± 5.7 % (normal); p = 0.004; 3 s after stimulus onset: p = 0.004; stimulus offset: p = 0.001]. No significant differences in any parameter were found between the 2 groups using the blue stimulus. The authors concluded that these findings supported the hypothesis that the ipRGC pathway is mainly subcortical, whereas a second, non-ipRGC pathway via the occipital cortex exists.

Chromatic Pupillography for Optic Nerve Diseases and Retinitis Pigmentosa

In a cross-sectional study, Chibel and colleagues (2016) evaluated VF defects as well as retinal function in healthy subjects and patients with retinitis pigmentosa (RP) using a chromatic multi-focal pupillometer. The right eyes of 16 healthy participants and 13 RP patients were studied. Pupil responses to red and blue light (peak, 485 and 625 nm, respectively) presented by 76 LEDs, 1.8-mm spot size at different locations of a 16.2° VF were recorded. Subjective VFs of RP patients were determined using chromatic dark-adapted Goldmann VFs (CDA-GVFs); 6 healthy participants underwent 2 pupillometer examinations to determine test-retest reliability. Three parameters of pupil contraction were determined automatically: (i) percentage of change of pupil size (PPC), (ii) maximum contraction velocity (MCV; in pixels per second), and (iii) latency of MCV (LMCV; in seconds). The fraction of functional VF was determined by CDA-GVF. In healthy participants, higher PPC and MCV were measured in response to blue compared with red light. The LMCV in response to blue light was relatively constant throughout the VF. Healthy participants demonstrated higher PPC and MCV and shorter LMCV in central compared with peripheral test points in response to red light. Test-retest correlation coefficients were 0.7 for PPC and 0.5 for MCV. In RP patients,
test point in which the PPC and MCV were lower than 4 standard errors from the mean of healthy participants correlated with areas that were indicated as non-seeing by CDA-GVF. The mean absolute deviation in LMCV parameter in response to the red light between different test point was significantly higher in RP patients (range of 0.16 to 0.47) than in healthy participants (range of 0.02 to 0.16; p < 0.0001) and indicated its usefulness as a diagnostic tool with high sensitivity and specificity (AUC, 0.97, Mann-Whitney-Wilcoxon analysis). Randomly reducing the number of test points to a total of 15 points did not significantly reduce the AUC in RP diagnosis based on this parameter. The authors concluded that this study demonstrated the feasibility of using a chromatic multi-focal pupillometer for objective diagnosis of RP and assessment of VF defects. These preliminary findings need to be validated by well-designed studies.

In a prospective study, Richter and colleagues (2017) compared the chromatic PLR in healthy subjects with those from patients with diseases of the outer or inner retina under various stimulus conditions, and determined the parameters needed to optimally distinguish between disease and control groups. A total of 15 patients with RP, 19 patients with optic nerve disease (ON), and 16 healthy subjects were enrolled in this study; ON included optic neuritis (NNO) and non-arteritic anterior ischemic optic neuropathy (NAION). For each subject, the PLR was recorded, to red, yellow, green, and blue stimuli for durations of 4 and 12 s, and for stimulus intensities of 4 lx and 28 lx. Comparison between control and RP or ON patient results showed that responses after stimulus onset were significantly different for most stimulus conditions, but the post-stimulus amplitudes at 3 s and 7 s after light extinction were not. On the other hand, the difference between the ON and RP groups was significant only for post-stimu time-points and only for blue stimuli. Differences between responses to blue and red were significantly different, predominantly at post stimulus time-points. A ROC analysis revealed that the maximal constriction amplitudes to a 4 lx, 4 s yellow stimulus
were significantly different in ON versus RP patients, and the responses to a 4 s, 28 lx blue stimulus at 7 s post-stimulus were significantly different in controls versus ON versus RP patients with a high specificity. The authors concluded that pupillary light responses to blue light in healthy, RP, and ON subjects were significantly different from one another; the optimal stimuli for future protocols was found to be a 4 s blue stimulus at 28 lx, and a 4 s yellow stimulus at 4 lx. These preliminary findings need to be validated by well-designed studies.

Kelbsch and associates (2017) analyzed pupil responses to specific chromatic stimuli in patients with advanced RP to examine if chromatic pupillography can be used as an objective marker for residual retinal function. These investigators examined correlations between parameters of the pupil response and the perception threshold of electrically evoked phosphenes. Chromatic pupillography was performed in 40 patients with advanced RP (VA less than 0.02 or VF less than or equal to 5°, non-recordable ERGs) and 40 age-matched healthy subjects. Pupil responses to full-field red (605 nm) and blue (420 nm) stimuli of 28 lx corneal illumination were recorded and analyzed for 2 stimulus durations (1 and 4 seconds). The perception threshold of phosphenes to trans-corneal electrostimulation was ascertained and correlated to the pupil responses and VA. Patients with RP showed significantly reduced pupil responses to red and blue stimuli compared with the controls. With red stimuli, pupillary escape could be observed; blue stimuli resulted in a well-preserved post-illumination pupil response. Phosphene thresholds were significantly increased in patients with RP and correlated with the parameters of the pupil response if all subjects were considered. Within the RP group alone, this relationship was less pronounced and statistically not significant. The authors concluded that chromatic pupillography demonstrated a significant decrease in outer retinal photoreceptor responses but a persisting and disinhibited intrinsic photosensitive RGC function in advanced
RP. The authors concluded that these phenomena may be useful as an objective marker for the effectiveness of any interventional treatment for hereditary retinal diseases as well as for the selection of suitable patients for an electronic retinal implant.

Furthermore, UpToDate reviews on "Retinitis pigmentosa: Clinical presentation and diagnosis" (Givre and Garg, 2017) and "Nonarteritic anterior ischemic optic neuropathy: Clinical features and diagnosis" (Tamhankar and Volpe, 2017) do not mention pupillometry/pupillography as a diagnostic tool.

Chromatic Pupillography for Detection of Leber Congenital Amaurosis and Monitoring of Progression of Retinal and Optic Nerve Diseases or Recovery After Treatment

Rukmini and associates (2019) stated that the pupillary light reflex is mediated by melanopsin-containing intrinsically-photosensitive retinal ganglion cells (ipRGCs), which also receive input from rods and cones. Melanopsin-dependent pupillary light responses are short-wavelength sensitive, have a higher threshold of activation, and are much slower to activate and de-activate compared with rod/cone-mediated responses. Given that rod/cone photoreceptors and melanopsin differ in their response properties, light stimuli can be designed to stimulate preferentially each of the different photoreceptor types, providing a read-out of their function. This has given rise to chromatic pupillography methods that aim to examine the health of outer retinal photoreceptors and ipRGCs by measuring pupillary responses to blue or red light stimuli. These investigators reviewed different types of chromatic pupillography protocols that have been tested in patients with retinal or optic nerve disease, including approaches that use short-duration light exposures or continuous exposure to light. Across different protocols, patients with outer retinal disease (e.g., retinitis pigmentosa or Leber congenital amaurosis) showed reduced or absent
pupillary responses to dim blue-light stimuli used to examine rod function, and reduced responses to moderately-bright red-light stimuli used to evaluate cone function. By comparison, patients with optic nerve disease (e.g., glaucoma or ischemic optic neuropathy, but not mitochondrial disease) showed impaired pupillary responses during continuous exposure to bright blue-light stimuli, and a reduced post-illumination pupillary response after light offset, used to examine melanopsin function. These proof-of-concept studies showed that chromatic pupillometry methods can be used to evaluate damage to rod/cone photoreceptors and ipRGCs. In future studies, it will be important to examine if chromatic pupillometry methods could be used for screening and early detection of retinal and optic nerve diseases. Such methods may also prove useful for objectively assessing the degree of recovery to ipRGC function in blind patients who undergo gene therapy or other treatments to restore vision. These researchers stated that investigators are now in the position to exploit these research findings to examine prospectively the ability of chromatic pupillometry to detect abnormalities in ipRGC function. Future large-scale studies should focus on optimizing, standardizing, and adapting chromatic pupillometry protocols for early detection of retinal and optic nerve diseases, and for monitoring disease progression or recovery after treatment.

Suo and colleagues (2020) noted that computerized pupillary light reflex assessment devices (CPLRADs) may serve as an effective screening tool for glaucomatous optic neuropathy, since they can dynamically detect abnormal pupillary responses from a novel sequence of light stimuli and functionally-shaped stimuli. These researchers systematically examined the current state of advanced CPLRADs and accuracy of application in detecting glaucoma. They carried out an electronic literature search of PubMed, Medline, and Embase from data-base inception to December 2019. Studies that reported data on the use of computer-aided pupillometry with monocular and/or binocular monitoring in glaucoma
patients were included. Two review authors independently conducted the study selection and extracted study data. A total of 25 studies were included in this review; 8 with a total of 829 subjects were included in this meta-analysis. Data were pooled using a random-effect model, since the significant heterogeneity (p < 0.1, I² > 50 %). The meta-analysis of 8 studies showed reasonably high summary sensitivity and specificity estimates of 0.81 (95 % CI: 0.73 to 0.89) and 0.83 (95 % CI: 0.75 to 0.91), respectively. Simpler monochromatic devices, such as PupilmetrixTM PLR60, generally performed as well as or slightly better than more complex chromatic devices. The authors concluded that this review suggested that CPLRADs may facilitate direct clinical decision-making for glaucoma diagnosis and evaluation, and may provide a deeper understanding of the pathomechanism of glaucoma. These researchers stated that these findings revealed that the diagnostic abilities of even the best CPLRD parameters were only moderate in glaucoma. The diagnostic abilities of the CPLRAD measurements were significantly influenced by the inter-eye asymmetry and within-eye asymmetry in case of glaucomatous damage. They stated that further research on the mechanism of intrinsically photosensitive retinal ganglion cells (ipRGCs) in glaucoma should be deeply examined by chromatic pupillography to investigate other factors, such as sleep qualities in glaucoma patients.

The authors stated that this study had several drawbacks. First, the search strategy was limited to only those articles written in English. Second, none of the 25 studies, considered how to control the cognitive load and emotional factors that possibly altered both pupil size. Third, in some of the studies, the glaucomatous subjects were notably older than the control subjects. Fourth, some of the participants had systemic conditions, such as diabetes and hypertension and were on medications for these conditions. Moreover, many glaucoma patients were on glaucoma medications with unknown effects on the pupil light reflex (PLR). Furthermore, some other factors may have affected PLR, further limiting the accuracy of
the CPLRADs, including the presence of an abnormal pupil shape, previous ocular surgery or medications (topical and systemic). Fifth, these researchers did not examine other computer-aided PLR methods, such as pupil perimetry in glaucoma patients.

### CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

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<th>Code</th>
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<td>Quantitative pupillometry with interpretation and report, unilateral or bilateral</td>
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<td>T70.29x+</td>
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<td>Aftercare following organ transplant [liver transplantation]</td>
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The above policy is based on the following references:


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<td>Z76.82</td>
<td>Awaiting organ transplant status [liver transplantation]</td>
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11. Freedman N. Quantifying sleepiness. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed November 2013.


15. Hughes D. Gaucher disease: Pathogenesis, clinical manifestations, and diagnosis. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed August 2015a.


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

There are no amendments for Medicaid.

revised 12/11/2020