Aetna considers the following procedures experimental and investigational for glaucoma testing (not an all-inclusive list) because of insufficient evidence of their effectiveness:

- Continuous monitoring of intra-ocular pressure (IOP) for management of glaucoma and other indications
- Genotyping for the screening, diagnosis and monitoring of glaucoma
- Measurement of corneal hysteresis for the screening, diagnosis and monitoring of glaucoma and for all other indications
- Multi-focal visual evoked potential for the diagnosis and early detection of glaucomatous field defects
- Ocular blood flow analyzer (BFA) for screening, diagnosis and monitoring of glaucoma and for all other indications.
- Ocular blood flow tonometer, which has been used in the screening, diagnosis, and monitoring of glaucoma
- Provocative tests (e.g., dark room provocation test and pharmacological tests)
Background

Glaucoma is a leading cause of blindness, affecting over 60 million people worldwide. Open-angle glaucoma, the most common subtype of the disease, affects over 2.5 million people in the United States. On behalf of the American Academy of Ophthalmology, Jampel et al (2011) reviewed the published literature to summarize and evaluate the effectiveness of visual function tests in diagnosing glaucoma and in monitoring progression. Literature searches of the PubMed and Cochrane Library databases were conducted last on May 7, 2010, and were restricted to citations published on or after January 1, 1994. The search yielded 1,063 unique citations. The first author reviewed the titles and abstracts of these articles and selected 185 of possible clinical relevance for further review. The panel members reviewed the full text of these articles and determined that 85 met inclusion criteria. They conducted data abstraction of the 85 studies, and the panel methodologist assigned a level of evidence to each of the selected articles. One study was rated as level I evidence. The remaining articles were classified broadly as providing level II evidence. Studies deemed to provide level III evidence were not included in the assessment. Standard white-on-white automated perimetry remains the most commonly performed test for assessing the visual field, with the Swedish interactive threshold algorithm (SITA) largely replacing full-threshold testing strategies. Frequency-doubling technology and its refinement into Matrix perimetry, as well as short-wavelength automated perimetry, now available with SITA, have been evaluated extensively. Machine learning classifiers seem to be ready for incorporation into software to help distinguish glaucomatous from non-glaucomatous fields. Other technologies, such as multi-focal visual-evoked potential and electro-retinography, which were designed as objective measures of visual function, provide testing free of patient input, but issues prevent their adoption for glaucoma management. The authors concluded that advances in technology and analytic tools over the past decade have provided us with more rapid and varied ways of assessing visual function in glaucoma, but they have yet to produce definitive guidance on the diagnosis of glaucoma or its progression over time. They stated that further research on an objective measure of visual function is needed.

An Agency for Healthcare Research and Quality review on "Screening for Glaucoma: Comparative Effectiveness" (Ervin et al, 2012) summarized evidence linking glaucoma screening to health
outcomes. It found insufficient evidence to address whether glaucoma screening is effective in improving vision-related outcomes and concluded that more research is needed to address the association between screening and quality of life outcomes.

**Ocular Blood Flow Tonometer:**

The ocular blood flow (OBF) tonometer measures not only intraocular pressure (IOP) but also pulsatile OBF. According to the manufacturer, taking the IOP and OBF test results together increases the detection rate for glaucoma when compared to traditional tonometry, which measures only average IOP. In addition, the manufacturer claims that the OBF tonometer can be used to provide ongoing analysis of the effectiveness of glaucoma treatment. The manufacturer explains that the OBF applanation tonometer has a resolution of 0.01 mm Hg, and automatically takes 200 readings per second, continuously analyzing the pulsatile variations in IOP. These data are analyzed by a computer, which calculates the OBF. The OBF tonometer records the complete IOP waveform and prints out of the average, maximum, and minimum values in a group of chosen pulses.

To date, the OBF tonometer has been studied primarily as a research tool. The evidence published to date on the OBF tonometer provides comparisons of IOP measurements to standard tonometers. There are no prospective clinical studies, however, demonstrating that measurement of waveforms and calculation of pulsatile OBF improves the management of glaucoma patients or glaucoma suspects, such that clinical outcomes are improved.

Neither the American Academy of Ophthalmology's Preferred Practice Patterns on Glaucoma nor the American Optometric Association's Clinical Practice Guidelines on Glaucoma mention any role for the OBF tonometer in the evaluation and management of patients with glaucoma.

There is no adequate evidence that OBF tonometers offer any clinically significant benefits over conventional applanation or indentation tonometers for screening, diagnosing or monitoring glaucoma.

Bhan et al (2003) examined the repeatability of OBF pneumotonometry and its agreement with Goldmann
Intra-ocular pressure was measured by 1 experienced ophthalmologist in both eyes of 10 healthy female subjects on 10 different occasions at the same time of day. The 2 methods were performed by alternate allocation, and laterality was chosen by random order. The authors concluded that the repeatability of the OBF pneumotonometer was worse than that of the Goldmann tonometer. This casts doubt on the value of the OBF pneumotonometer as a tool for measuring IOP. The agreement plots indicate that the OBF pneumotonometer may produce significant numbers of false-positive results in screening programs.

Furthermore, pulsatile OBF assessment is used to measure the choroidal circulation and provides diagnostic value to certain ocular diseases such as glaucoma. This technique assumes a constant ocular rigidity and is influenced by axial length, diurnal variation, and age. Lam et al (2003) investigated the effect of age on pulsatile OBF, with consideration of the above factors (n = 118). Ocular blood supply in the ophthalmic artery was also determined using color Doppler ultrasonography. These investigators found that the reduction in pulsatile OBF with age was significant. Although aging affects scleral rigidity and systemic blood pressure, multiple regression analysis indicates that the most influential factor affecting pulsatile OBF is aging.

Also, Gunvant et al (2004) ascertained the effect of central corneal thickness and corneal curvature on IOP measurements using the pulsatile OBF tonograph and the Goldmann applanation tonometer, and assessed the agreement between the pulsatile OBF tonograph and the Goldmann applanation tonometer in IOP measurement (n = 479). The IOP measurements obtained with both the Goldmann applanation tonometer and the pulsatile OBF tonograph varied with central corneal thickness and mean keratometric reading. IOP measured using the Goldmann applanation tonometer increased by 0.027 mm Hg per micron increase in central corneal thickness. IOP measured using the pulsatile OBF tonograph increased by 0.048 mm Hg per microm increase in central corneal thickness. For an increase of 1 mm of mean corneal curvature there was rise in IOP of 1.14 mm Hg measured by the Goldmann applanation tonometer and of 2.6 mm Hg measured by the pulsatile OBF. When compared to the Goldmann applanation tonometer, the pulsatile OBF tonograph
under-estimated at low IOP and over-estimated at higher IOP. The authors concluded that central corneal thickness and corneal curvature affected measurements obtained with the pulsatile OBF tonograph more than they affected measurements obtained with the Goldmann applanation tonometer.

Tonnu et al (2005) compared the inter-method agreement in IOP measurements made with 4 different tonometric methods: (i) the Goldmann applanation tonometer (GAT), (ii) Tono-Pen XL, (iii) OBF tonograph, and (iv) Canon TX-10 non-contact tonometer (NCT) in a randomized order in 1 eye of each of 105 patients with ocular hypertension or glaucoma. A total of 3 measurements were made with each method, and by each of 2 independent GAT observers. GAT inter-observer and tonometer inter-method agreement was assessed by the Bland-Altman method. The outcome measures were 95% limits of agreement for IOP measurements between GAT observers and between tonometric methods, and 95% confidence intervals for intra-session repeated measurements. The authors reported that there was good inter-observer agreement with the GAT and moderate agreement between the NCT and GAT. The differences between the GAT and OBF tonograph and between the GAT and Tono-Pen probably preclude the OBF tomography and Tono-Pen from routine clinical use as objective methods to measure IOP in normal adult eyes.

The ocular Blood Flow Analyzer (BFA) (Paradigm Medical Industries, Inc., Salt Lake City, UT) is an electronic pneumotonometer that measures IOP 200 times per second over a period of 5 to 15 seconds and automatically measures OBF. Ocular pressure rises and falls with each heartbeat and a pressure waveform is created when the bolus of blood from each heartbeat passes through the ocular choroid. The systolic increase and diastolic decrease in IOP caused by the pulsatile OBF is recorded by the BFA. The data are then analyzed by an on board computer in real time and a resultant OBF is calculated. Six test parameters are taken per eye with a calculated average mean value in microliters/second. Measurements for each pulse with a calculated average are given for IOP (tonometry) and pneumoplethysmographic vascular activity including: pressure, pulse amplitude, systole and diastole duration, pulse rate, and OBF rate. The BFA is fundamentally an OBF tonometer, using a pneumatic mode of operation.
Resch and colleagues (2011) stated that little information is available regarding the relationship between glaucomatous visual field defects, morphological changes of the optic disc and OBF. In this study, OBF parameters were correlated with parameters of optic nerve head (ONH) morphology and visual field performance in a cross-sectional study. A total of 103 patients with primary open angle glaucoma were included. Choroidal and ONH blood flow was assessed using laser Doppler flowmetry. Retinal blood velocities and retinal vessel diameters were measured with laser Doppler velocimetry and a Retinal Vessel Analyzer, respectively. To evaluate the ONH morphology, fundus photographs were taken and confocal laser scanning tomography was performed. Among all measured ocular hemodynamic parameters, the ONH blood flow was most strongly correlated to structural parameters of ONH damage and visual field loss. Reduced retinal vessel diameters were only slightly correlated with the degree of glaucomatous damage. The authors concluded that reduced blood flow in the ONH was associated with increasing amount of visual field defect and morphological changes of the ONH. Retinal vessel diameters were only marginally associated with glaucomatous optic nerve damage. Based on retinal vessel diameter determination alone, it is not possible to evaluate if reduced retinal blood flow is causative or secondary in glaucoma.

In a case-control study, Hwang et al (2012) examined the relationship among visual field, neural structural, and blood flow measurements in glaucoma. A total of 47 eyes of 42 patients with perimetric glaucoma were age-matched with 27 normal eyes of 27 patients. All patients underwent Doppler Fourier-domain optical coherence tomography to measure retinal blood flow and standard glaucoma evaluation with visual field testing and quantitative structural imaging. Linear regression analysis was performed to analyze the relationship among visual field, blood flow, and structure, after all variables were converted to logarithmic decibel scale. Retinal blood flow was reduced in glaucoma eyes compared to normal eyes (p < 0.001). Visual field loss was correlated with both reduced retinal blood flow and structural loss of rim area and retinal nerve fiber layer (RNFL). There was no correlation or paradoxical correlation between blood flow and structure. Multi-variate regression analysis revealed that reduced blood flow and structural loss are independent predictors of visual field loss. Each dB decrease in blood flow was associated with at least 1.62 dB loss in mean deviation (p ≤ 0.001), whereas each dB decrease in rim area and
RNFL was associated with 1.15 dB and 2.56 dB loss in mean deviation, respectively (p ≤ 0.03). The authors concluded that there is a close link between reduced retinal blood flow and visual field loss in glaucoma that is largely independent of structural loss. They stated that further studies are needed to elucidate the causes of the vascular dysfunction and potential avenues for therapeutic intervention. Blood flow measurement may be useful as an independent assessment of glaucoma severity.

Michelessi and colleagues (2015) stated that the diagnosis of glaucoma is traditionally based on the finding of ONH damage assessed subjectively by ophthalmoscopy or photography or by corresponding damage to the visual field assessed by automated perimetry, or both. Diagnostic assessments are usually required when ophthalmologists or primary eye care professionals find elevated IOP or a suspect appearance of the ONH. Imaging tests such as confocal scanning laser ophthalmoscopy (HRT), optical coherence tomography (OCT) and scanning laser polarimetry (SLP, as used by the GDx instrument), provide an objective measure of the structural changes of RNFL thickness and ONH parameters occurring in glaucoma. In a Cochrane review, these investigators determined the diagnostic accuracy of HRT, OCT and GDx for diagnosing manifest glaucoma by detecting ONH and RNFL damage. They searched several databases for this review; the most recent searches were on February 19, 2015. These researchers included prospective and retrospective cohort studies and case-control studies that evaluated the accuracy of OCT, HRT or the GDx for diagnosing glaucoma. They excluded population-based screening studies, since they planned to consider studies on self-referred people or participants in whom a risk factor for glaucoma had already been identified in primary care, such as elevated IOP or a family history of glaucoma. The authors only considered recent commercial versions of the tests: spectral domain OCT, HRT III and GDx VCC or ECC. They adopted standard Cochrane methods; and fitted a hierarchical summary ROC (HSROC) model using the METADAS macro in SAS software. After studies were selected, the authors decided to use 2 x 2 data at 1.95 specificity or closer in meta-analyses, since this was the most commonly-reported level. These researchers included 106 studies in this review, which analyzed 16,260 eyes (8,353 cases, 7,907 controls) in total; 40 studies (5,574 participants) assessed GDx, 18 studies (3,550 participants) HRT, and 63 (9,390 participants) OCT, with 12 of these studies comparing 2 or 3 tests.
Regarding study quality, a case-control design in 103 studies raised concerns as it can over-estimate accuracy and reduce the applicability of the results to daily practice; 24 studies were sponsored by the manufacturer, and in 15 the potential conflict of interest was unclear. Comparisons made within each test were more reliable than those between tests, as they were mostly based on direct comparisons within each study. The Nerve Fiber Indicator yielded the highest accuracy (estimate, 95% confidence interval (CI)) among GDx parameters (sensitivity: 0.67, 0.55 to 0.77; specificity: 0.94, 0.92 to 0.95). For HRT measures, the Vertical Cup/Disc (C/D) ratio (sensitivity: 0.72, 0.60 to 0.68; specificity: 0.94, 0.92 to 0.95) was no different from other parameters. With OCT, the accuracy of average RNFL thickness was similar to the inferior sector (0.72, 0.65 to 0.77; specificity: 0.93, 0.92 to 0.95) and, in different studies, to the vertical C/D ratio. Comparing the parameters with the highest diagnostic odds ratio (DOR) for each device in a single HSROC model, the performance of GDx, HRT and OCT was remarkably similar. At a sensitivity of 0.70 and a high specificity close to 0.95 as in most of these studies, in 1,000 people referred by primary eye care, of whom 200 have manifest glaucoma, such as in those who have already undergone some functional or anatomic testing by optometrists, the best measures of GDx, HRT and OCT would miss about 60 cases out of the 200 patients with glaucoma, and would incorrectly refer 50 out of 800 patients without glaucoma. If prevalence were 5% (e.g., such as in people referred only because of family history of glaucoma), the corresponding figures would be 15 patients missed out of 50 with manifest glaucoma, avoiding referral of about 890 out of 950 non-glaucomatous people. Heterogeneity investigations found that sensitivity estimate was higher for studies with more severe glaucoma, expressed as worse average mean deviation (MD): 0.79 (0.74 to 0.83) for MD less than -6 db versus 0.64 (0.60 to 0.69) for MD greater than or equal to -6 db, at a similar summary specificity (0.93, 95% CI: 0.92 to 0.94 and, respectively, 0.94; 95% CI: 0.93 to 0.95; p < 0.0001 for the difference in relative DOR). The authors concluded that the accuracy of imaging tests for detecting manifest glaucoma was variable across studies, but overall similar for different devices. Accuracy may have been over-estimated due to the case-control design, which is a serious limitation of the current evidence base. The authors recommended that further diagnostic accuracy studies should be performed in patients selected consecutively at a defined step of the clinical pathway, providing a description of risk factors leading...
to referral and bearing in mind the consequences of false positives and false negatives in the setting in which the diagnostic question is made. Moreover, they stated that future research should report accuracy for each threshold of these continuous measures, or publish raw data.

**Ocular Response Analyzer for Corneal Hysteresis:**

Central corneal thickness has become an important biometric factor and is an essential part of the evaluation of glaucoma. Goldmann applanation tonometry is the most widely used method of measuring IOP, but it is well known that corneal parameters affect the accuracy of this instrument (Herndon, 2006). Corneal pachymetry is used to measure central corneal thickness, and is an adjunct to applanation tonometry for screening and diagnosis of glaucoma. In addition to central corneal thickness, there are probably further biomechanical properties that play a role in IOP measurement (Hager et al, 2007).

A new measure of corneal biomechanics, called corneal hysteresis, assesses corneal resistance to deformation. The Ocular Response Analyzer (ORA, Reichert Ophthalmic Instruments, Depew, NY) is a new instrument that measures corneal hysteresis, the corneal biomechanical response to rapid indentation by an air jet (Kotecha et al, 2006). Corneal hysteresis is the difference in applanation pressures between the rising and falling phases of the air jet.

Current evidence for measurement of corneal hysteresis has focused on its potential use in glaucoma, and has focused on correlations between corneal hysteresis and IOP, corneal thickness, and other ocular measurements. There are no studies demonstrating that measurement of corneal hysteresis alters clinical management such that clinical outcomes are improved.

Kotecha (2007) stated that current evidence suggests that the importance of corneal biomechanics to the glaucoma clinician rests primarily with its effects on IOP measurement. However, the possibility that corneal biomechanics may give an indication of the structural integrity of the optic nerve head can not be completely excluded. The author noted that further population and longitudinal studies are needed to clarify whether current in vivo measures of corneal biomechanical properties, including
corneal hysteresis, prove to be independent predictors of glaucoma susceptibility.

Nongpiur and colleagues (2015) investigated the association between corneal hysteresis (CH) and corneal resistance factor (CRF) with glaucoma severity in primary angle closure glaucoma (PACG). These investigators recruited 204 subjects with PACG. Each subject underwent CH and CRF measurements using the ORA, ONH topography measurement using scanning laser ophthalmoscopy, and visual field assessment. Glaucoma severity was based on the visual field mean deviation (MD) and classified as mild (71), moderate (55), and severe (78). The mean age ± SD of study subjects was 68.7 ± 8.9 years, with most being Chinese (n = 186; 91.2 %). Corneal hysteresis and CRF were lowest in the severe PACG group (9.32 ± 1.86 and 9.50 ± 1.67 mm Hg) followed by moderate PACG (9.38 ± 1.88 and 9.73 ± 1.88 mm Hg) and mild PACG (9.47 ± 1.90 and 9.85 ± 1.75 mm Hg) respectively, but the differences were not significant (p = 0.89 and p = 0.46, respectively). There was a significant positive correlation between CH and central corneal thickness (CCT) (correlation coefficient [r] = 0.26, p < 0.001), CRF and CCT (r = 0.43, p < 0.001), and negative correlation between CRF and vertical cup-disc ratio (VCDR; r = -0.20, p = 0.004), and CRF with cup-disc area (r = -0.14, p = 0.04). Corneal hysteresis and CRF were not correlated with MD (r = 0.01 for CH, r = 0.1 for CRF). After multi-variate analyses, adjusting for age, sex, CCT, axial length, IOP, and number of glaucoma medication, no significant associations were noted between CH and CRF with MD, VCDR, disc area, rim area, or cup area. The authors concluded that corneal biomechanical parameters measured by the ORA are not associated with severity of glaucoma in PACG.

Genotyping for Glaucoma:

Gibson et al (2012) stated that primary open angle glaucoma (POAG) is a characteristic optic neuropathy which progresses to irreversible vision loss. Few genes have been detected that influence POAG susceptibility and other genes are therefore likely to be involved. These researchers analyzed carefully characterized POAG cases in a genome-wide association study (GWAS). They performed a GWAS in 387 POAG cases using public control data (WTCCC2). They also investigated the quantitative phenotypes, cup:disc ratio (CDR), CCT, and intra-ocular pressure (IOP). Promising single nucleotide polymorphisms (SNPs), based
on various prioritization criteria, were genotyped in a cohort of 294 further POAG cases and controls. These investigators found 2 GWAS significant results in the discovery stage for association, one of which had multiple evidence in the gene neural precursor cell expressed, developmentally down-regulated 9' (NEDD9; rs11961171, \( p = 8.55E-13 \)) and the second on chromosome 16 with no supporting evidence. Taking into account all the evidence from risk and quantitative trait ocular phenotypes these researchers chose 86 SNPs for replication in an independent sample. Their most significant SNP was not replicated \( (p = 0.59) \). They found 4 nominally significant results in the replication cohort, but none passed correction for multiple testing. Two of these, for phenotypes CDR (rs4385494, discovery \( p = 4.51x10^{-5} \), replication \( p = 0.029 \)) and CCT (rs17128941, discovery \( p = 5.52x10^{-6} \), replication = 0.027), show the consistent direction of effects between the discovery and replication data. These investigators also assessed evidence for previously associated known genes and found evidence for the genes 'transmembrane and coiled-coil domains 1' (TMCO1) and 'cyclin-dependent kinase inhibitor 2B' (CDKN2B). The authors concluded that although they were unable to replicate any novel results for POAG risk, they did replicate 2 SNPs with consistent effects for CDR and CCT, though they do not withstand correction for multiple testing.

There has been a range of publications in the last couple of years identifying POAG risk genes and genes involved in POAG related ocular traits. The authors found evidence for 3 known genes (TMCO1, CDKN2B, and S1 RNA binding domain 1 [SRBD1]) in this study. Novel rare variants, not detectable by GWAS, but by new methods such as exome sequencing (also known as targeted exome capture) may hold the key to unraveling the remaining contribution of genetics to complex diseases such as POAG.

Ulmer et al (2012) noted that central corneal thickness (CCT) is associated with POAG. Using SNP data from the GLAUGEN and NEIGHBOR consortia, these researchers investigated the effects of CCT-associated variants on POAG risk. They performed a replication analysis of previously reported CCT SNPs in their CCT dataset \( (n = 1,117) \) and tested these SNPs for association with POAG using the full dataset \( (n = 6,470) \). They performed a CCT GWAS, selected top SNPs from this analysis, and tested these for association with POAG. They generated cDNA libraries from fetal and adult brain and ocular tissue samples for candidate gene expression analysis. They replicated association with 1 of 20 previously published CCT SNPs: rs12447690, near the ZNF469
gene (p = 0.001; beta = -5.08 microns/allele). None of these SNPs was significantly associated with POAG. In the CCT GWAS, no SNPs reached genome-wide significance. After testing 50 candidate SNPs for association with POAG these investigators identified rs7481514 within the NTM gene that was significantly associated with POAG in a low tension subset (p = 0.00099; OR = 1.28). Additionally, SNPs in the CNTNAP4 gene showed suggestive association with POAG (top SNP = rs1428758; p = 0.018; OR = 0.84). They found evidence of NTM and CNTNAP4 gene expression in ocular tissues. The authors concluded that these findings suggested that previously reported CCT loci are not significantly associated with POAG susceptibility. By performing a quantitative analysis of CCT and a subsequent analysis of POAG, they identified SNPs in 2 cell adhesion molecules, NTM and CNTNAP4, which may increase POAG susceptibility in a subset of cases.

Gemenetzi et al (2012) noted that most of the molecular mechanisms leading to POAG development are still unknown. Gene mutations in various populations have been identified by genetic studies and a genetic basis for glaucoma pathogenesis has been established. Linkage analysis and association studies are genetic approaches in the investigation of the genetic basis of POAG. Genome-wide association studies are more powerful compared with linkage analysis in discovering genes of small effect that might contribute to the development of the disease. POAG links to at least 20 genetic loci, but only 2 genes identified in these loci, myocilin and optineurin, are considered as well-established glaucoma-causing genes, whereas the role of other loci, genes, and variants implicated in the development of POAG remains controversial. Gene mutations associated with POAG result in retinal ganglion cell death, which is the common outcome of pathogenetic mechanisms in glaucoma. The authors stated that if the sensitivity and specificity of genotyping increases, it may be possible to screen individuals routinely for disease susceptibility.

Guidelines from the Australian National Health and Medical Research Council (2010) state that mutations in transcription factor genes have been found to be responsible for developmental disorders associated with childhood glaucoma. The guidelines list the following genetic syndromes associated with childhood glaucoma: Nail Patella Syndrome with the LMX1B gene, Axenfeld Rieger Syndrome/Anterior segment dysgenesis.
with the PITX2 and FOXC1 genes and Aniridia with the PAX6 gene. Patients with these syndromes or mutations are usually followed closely for glaucoma. The guidelines note that there is some evidence that adult-onset POAG is linked to mutations in the same genes. The guidelines state that the situation is complex and it is likely that multiple mutations in more than one gene may be involved, given that POAG is likely to be inherited as a complex trait. The guidelines note that current research has identified more than 30 mutations of the myocilin gene alone, with connections to POAG in different ethnic groups. The guidelines conclude that there is "evolving evidence" for genetic screening for glaucoma.

Zacharaki et al (2014) investigated plasma homocysteine levels and polymorphisms in genes encoding enzymes in the metabolic pathway of homocysteine in association with POAG and pseudoexfoliation glaucoma (PXFG). A total of 156 glaucoma patients (76 with POAG and 80 with PXFG) and 135 controls matched for age and sex were enrolled in this study. Plasma homocysteine levels were measured using a commercially available enzyme-linked immunosorbent assay kit. DNA was extracted from peripheral blood leukocytes and real-time polymerase chain reaction (RT-PCR) was performed for genotyping of the samples. Patients were genotyped using pre-designed TaqMan(®) SNP genotyping assays for 2 exon variations (rs1801131, rs1801133) in the 5,10-methylenetetrahydrofolate reductase (MTHFR) gene and 1 intron variation (rs8006686) in the methylenetetrahydrofolate dehydrogenase (MTHFD1) gene. Homocysteine levels were slightly higher in the patient group (POAG and PXFG) compared with controls, but the difference did not reach statistical significance. The minor alleles of the MTHFR single nucleotide polymorphisms showed a protective effect for POAG and showed an increased risk for PXFG, but none of these associations reached statistical significance (p > 0.05). The minor allele of MTHFD1 rs8006686 showed a trend for increased risk of both POAG and PXFG (p > 0.05). No statistically significant interaction was seen between the genetic variants and homocysteine levels (p > 0.05). The authors concluded that the findings of this study showed that neither the examined SNP from genes involved in the pathway of homocysteine metabolism nor the measured homocysteine levels were associated with POAG or PXFG in this study cohort.

Wang et al (2015) stated that to avoid the side effects of ocular
hypertension of glucocorticoid (GC) usage in eye, one must identify susceptible individuals, which exists in about 1/3 of all population. Further, the majority of all POAG patients show this phenotype. Glucocorticoid receptor (GR) regulates C responsiveness in trabecular meshwork (TM) cells. In this study, SNP genotyping was used to determine whether there are differences in the Bcll (rs41423247) and N363S (rs6195) polymorphisms of the GR gene in healthy and POAG patients, and glucocorticoid-induced ocular hypertension (GIOH) populations. A total of 327 unrelated Chinese adults, including 111 normal controls, 117 GIOH subjects and 99 POAG patients, were recruited. DNA samples were prepared and the Bcll and N363S polymorphisms were screened using RT-PCR-restriction fragment length polymorphism (RFLP) analysis. Frequencies of the Bcll and N363S polymorphisms were determined and compared using Fisher’s exact test and the Chi-squared test. Only the Bcll polymorphism was identified in the Chinese Han population. The frequency of the G allele was 21.6 % in normal controls, 18.3 % in GIOH patients, and 13.64 % in the POAG patients. There was no significant difference in polymorphism or allele frequency in the 3 groups. Furthermore, no N363S polymorphism was found in the study subjects. The authors concluded that the Bcll polymorphisms in GR gene had no association with GIOH and POAG patients, and N363S polymorphism might not exist in the Chinese Han population. Therefore, the Bcll polymorphism might not be responsible for the development of GC-induced ocular hypertension or POAG.

Sit and Pruet (2016) stated that determining target IOP in glaucoma patients is multi-faceted, requiring attention to many different factors (e.g., glaucoma type, severity of disease, age, race, family history, corneal thickness and hysteresis, and initial IOP). Even with all these variables accounted for, there are still patients who have progression of the disease despite achieving target IOP. The authors noted that IOP variability has been identified as a potential independent risk factor for glaucoma progression; however, it is currently difficult to quantify in individual patients.

**Multi-Focal Visual Evoked Potential:**

Multi-focal visual evoked potential (mfEVP) has been studied for the diagnosis and early detection of glaucomatous field defects. However, its effectiveness for this indication has not been
The National Collaborating Center for Acute Care’s clinical guideline on “Glaucoma. Diagnosis and management of chronic open angle glaucoma and ocular hypertension” (2009) did not mention the use of mfVEP. The American Academy of Ophthalmology’s report on “Assessment of visual function in glaucoma” (Jampel et al, 2011) stated that technologies, such as mfVEP and electro-retinography, which were designed as objective measures of visual function, provide testing free of patient input, but issues prevent their adoption for glaucoma management. The U.S. Preventive Services Task Force’s recommendation statement on “Screening for glaucoma” (2013) listed tonometry, visual field measurement, dilated ophthalmoscopy and slit lamp examination as screening tests for POAG. The USPSTF statement noted that “Diagnosis of POAG is based on a combination of tests showing characteristic degenerative changes in the optic disc and defects in visual fields (often loss in peripheral vision). Although increased IOP was previously considered an important part of the definition of this condition, it is now known that many persons with POAG do not have increased IOP and not all persons with increased IOP have or will develop glaucoma. Therefore, screening with tonometry alone may be inadequate to detect all cases of POAG. Measurement of visual fields can be difficult. The reliability of a single measurement may be low; several consistent measurements are needed to establish the presence of defects. Specialists use dilated ophthalmoscopy or slit lamp examination to evaluate changes in the optic disc; however, even experts have varying ability to detect glaucomatous progression of the optic disc. In addition, no single standard exists to define and measure progression of visual field defects. Most tests that are available in a primary care setting do not have acceptable accuracy to detect glaucoma”.

Mousa et al (2014) stated that mfVEP is a newly introduced method used for objective visual field assessment. Several analysis protocols have been tested to identify early visual field losses in glaucoma patients using the mfVEP technique, some were successful in detection of field defects, which were comparable to the standard automated perimetry (SAP) visual field assessment, and others were not very informative and needed more adjustment and research work. These researchers
implemented a novel analysis approach and evaluated its validity and whether it could be used effectively for early detection of visual field defects in glaucoma. Three groups were tested in this study: (i) normal controls (38 eyes), (ii) glaucoma patients (36 eyes) and (iii) glaucoma suspect patients (38 eyes). All subjects had a 2 standard Humphrey field analyzer (HFA) test 24-2 and a single mfVEP test undertaken in 1 session. Analysis of the mfVEP results was done using the new analysis protocol; the hemifield sector analysis (HSA) protocol. Analysis of the HFA was done using the standard grading system. Analysis of mfVEP results showed that there was a statistically significant difference between the 3 groups in the mean signal-to-noise ratio (ANOVA test, p < 0.001 with a 95% confidence interval). The difference between superior and inferior hemispheres in all subjects were statistically significant in the glaucoma patient group in all 11 sectors (t-test, p < 0.001), partially significant in 5/11 (t-test, p < 0.01), and no statistical difference in most sectors of the normal group (1/11 sectors was significant, t-test, p < 0.9). Sensitivity and specificity of the HSA protocol in detecting glaucoma was 97% and 86%, respectively, and for glaucoma suspect patients the values were 89% and 79%, respectively. The authors concluded that the new HSA protocol used in the mfVEP testing can be applied to detect glaucomatous visual field defects in both glaucoma and glaucoma suspect patients. Using this protocol can provide information about focal visual field differences across the horizontal midline, which can be utilized to differentiate between glaucoma and normal subjects. They stated that sensitivity and specificity of the mfVEP test showed very promising results and correlated with other anatomical changes in glaucoma field loss. Well-designed studies are needed to establish the clinical value of mfVEP for the diagnosis of glaucoma.

Furthermore, UpToDate reviews on “Open-angle glaucoma: Epidemiology, clinical presentation, and diagnosis” (Jacobs, 2014) and “Angle-closure glaucoma” (Weizer, 2014) do not mention the use of mfVEP as a diagnostic tool.

Kanadani et al (2014) stated that the gold standard in functional glaucoma evaluation is SAP. However, SAP depends on the reliability of the patients' responses and other external factors; therefore, other technologies have been developed for earlier detection of visual field changes in glaucoma patients. The frequency-doubling perimetry (FDT) is believed to detect
glaucoma earlier than SAP. The mfVEP is an objective test for functional evaluation. These investigators evaluated the sensitivity and specificity of FDT and mfVEP tests in normal, suspect, and glaucomatous eyes and compared the monocular and interocular mfVEP. A total of 95 eyes from 95 individuals (23 controls, 33 glaucoma suspects, 39 glaucomatous) were enrolled. All participants underwent a full ophthalmic examination, followed by SAP, FDT, and mfVEP tests. The area under the curve for mean deviation and pattern standard deviation were 0.756 and 0.761, respectively, for FDT, 0.564 and 0.512 for signal and alpha for interocular mfVEP, and 0.568 and 0.538 for signal and alpha for monocular mfVEP. This difference between monocular and interocular mfVEP was not significant. The authors concluded that the FDT Matrix was superior to mfVEP in glaucoma detection. The difference between monocular and interocular mfVEP in the diagnosis of glaucoma was non-significant.

**Provocative Tests:**

Domínguez-Duenas and colleagues (2016) examined the diagnostic ability of the ibopamine provocative test for early glaucoma detection. A sample of 44 patients with suspicious optic discs was recruited and compared with 37 controls with normal optic discs and no ocular pathology. The ibopamine provocative test was performed in all patients who were then followed-up with diagnostic tests for glaucoma, visual fields, and spectral-domain OCT. Early glaucoma was diagnosed in 26 patients. The sensitivity of the ibopamine test to discriminate patients who had early glaucoma was 78.7 %, with a specificity of 71.6 %. In multi-variable analyses adjusted for demographic and clinical variables, subjects with a positive ibopamine test at baseline had an 8-fold higher risk of glaucoma compared with those who had a negative test; glaucoma risk was highest among
ibopamine-positive subjects with initial clinical diagnostic impression of glaucoma. The authors concluded that the ibopamine provocative test showed an adequate diagnostic performance to detect individuals at increased risk of glaucoma in a very early stage of the disease. They stated that while further studies are needed, the provocative ibopamine test for the diagnosis of early glaucoma is promising.

In a prospective, single-center, longitudinal observational study, Salvetat and associates (2016) assessed the ability of baseline clinical, morphological, and functional factors to predict the conversion to POAG in ocular hypertensive (OHT) patients. This trial included 116 eyes of 116 OHT patients followed for a 10-year period. All patients had IOP greater than or equal to 24 mm Hg in 1 eye and greater than 21 mm Hg in the other eye, normal visual fields (VF) and normal optic disc (OD) appearance in both eyes at baseline. All OHT patients were untreated at baseline with subsequent treatment upon need according to clinical judgment. Only 1 eye per subject was randomly selected. Patient age, gender, IOP, CCT, and ibopamine provocative test results were collected at baseline. All patients underwent standard automated perimetry, short-wavelength automated perimetry (SWAP), frequency-doubling technology, confocal scanning laser ophthalmoscopy (CSLO), and scanning laser polarimetry (SLP) at baseline and every 6 months thereafter. Main outcome measure was the conversion to POAG, defined as the development of reproducible VF and/or OD abnormalities attributable to glaucoma. Cox proportional hazards models were used to identify the baseline factors predictive of POAG conversion. During the 10-year follow-up, 25 % of eyes converted to POAG. In multi-variate Cox models, baseline factors that were significant predictors of POAG development included: older age (hazard ratio (HR) 1.0, 99 % CI: 1.0 to 1.2, per 1 year older); SWAP Glaucoma Hemifield test 'outside normal limits' (HR 4.3, 99 % CI: 1.2 to 17.9); greater SLP 'Inter-eye Symmetry' (HR 1.1, 99 % CI: 0.4 to 3.0, per 1 unit lower); lower CSLO Rim Volume (HR 1.1, 99 % CI: 0.3 to 3.2, per 0.1 mm(3) lower); and greater CSLO cup-to-disc ratio (HR 6.0, 99 % CI: 3.6 to 16.8, per 0.1 unit greater). The authors concluded that the baseline parameters that proved to be useful in assessing the likelihood of an OHT patient to develop
POAG included age, functional variables provided by SWAP, and structural variables provided by SLP and CSLO. In contrast, baseline IOP, CCT, and ibopamine provocative test results were not significant predictors of POAG conversion.

Furthermore, an UpToDate review on “Angle-closure glaucoma” (Weizer, 2017) states that “Provocative tests most often do not provide additional information beyond the clinical examination, and are not widely used because of their risks. In the dark room provocation test, a patient rests (awake) in a dark room for 30 minutes with his or her head in the prone position to encourage pupillary dilation and forward displacement of the lens. Angle-closure is suggested if the intraocular pressure rises significantly or if the angle appears more closed on gonioscopy. Clinical applicability is unknown. In pharmacological tests, the pupil is dilated with phenylephrine or parasympatholytic mydriatic eye drops and pilocarpine is instilled in an attempt to provoke an attack of angle-closure. This procedure involves risk and a negative result does not absolutely rule out angle-closure. Both eyes should not be tested simultaneously. We do not recommend this test”.

<table>
<thead>
<tr>
<th>CPT Codes / HCPCS Codes / ICD-10 Codes</th>
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<tbody>
<tr>
<td><em>Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by &quot;+&quot;:</em></td>
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<tr>
<td><strong>CPT codes not covered for indications listed in the CPB:</strong></td>
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<tr>
<td><strong>Multi-focal visual evoked potential:</strong></td>
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<tr>
<td>No specific code</td>
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<tr>
<td>0198T</td>
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<tr>
<td>0329T</td>
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<td>0464T</td>
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Corneal hysteresis determination, by air impulse stimulation, unilateral or bilateral, with interpretation and report

ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):

- H40.001 - Glaucoma
- H42
- Z13.5 Encounter for screening for eye and ear disorders [screening for glaucoma]

The above policy is based on the following references:


60. Gemenetzki M, Yang Y, Lotery AJ. Current concepts on


63. Jacobs DS. Open-angle glaucoma: Epidemiology, clinical presentation, and diagnosis. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed April 2014.

64. Weizer JS. Angle-closure glaucoma. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed April 2014.


Amendment to
Aetna Clinical Policy Bulletin Number: 0622 Glaucoma Testing

There are no amendments for Medicaid.