Glaucoma Testing

Aetna considers the following medically necessary for evaluation of primary open-angle glaucoma:

- Computerized visual field examination
- Gonioscopy
- Measurement of optic nerve head and retinal nerve fiber layer.

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
• 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)
• RETeval portable electroretinogram device for the detection of glaucoma
• Visual evoked potential (including isolated-check VEP, and multi-focal VEP) for the diagnosis and early detection of glaucomatous field defects.

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 intra-ocular 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 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 tonometry. 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 micron 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 receiver operating characteristic (HSROC) model using the METADAS macro in SAS software. After studies were selected, the authors decided to use 2 x 2 data at 0.95 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 cannot 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.

De Moraes et al (2012) examined the correlation between central corneal thickness (CCT) and corneal hysteresis (CH) and their relationship with the rate of visual field (VF) change. Glaucoma patients who underwent complete ophthalmic examination and tonometry using both the Goldmann applanation tonometer and the Ocular Response Analyzer (ORA) were prospectively enrolled. Only eyes with greater than or equal to 5 SITA Standard 24-2 VF tests were included. Automated point-wise linear regression analysis was used to determine VF progression. A total of 153 eyes (153 patients; mean age of 61.3 ± 14.0 years; mean number of VF, 8.5 ± 3.4; mean follow-up time of 5.3 ± 2.0 years) met the enrollment criteria. The mean global rate of VF change was -0.34 ± 0.7 dB/year; 25 eyes (16 %) reached a progression endpoint. Progressing eyes had lower CCT (525.0 ± 34.2 versus 542.3 ± 38.5 μm, p=0.04) and lower CH (7.5 ± 1.4 versus 9.0 ± 1.8 mm Hg, p < 0.01) compared with non-progressing eyes; CH and CCT correlated significantly (r = 0.33, p < 0.01). By multi-variate analysis, peak intra-ocular pressure (IOP) [odds ratio (OR) = 1.13 per mm Hg higher, p < 0.01], age (OR = 1.57 per decade older, p = 0.03), and CH (OR = 1.55 per mm Hg lower, p < 0.01) remained statistically significant. The authors concluded that corneal biomechanical and physical properties, such as CH and CCT, are highly correlated and associated with VF progression. They stated that as CH may describe corneal properties more completely than thickness alone, it may be a parameter that is better associated with progression.

In a retrospective study, Agarwal et al (2012) evaluated CH and intraocular pressure (IOP) before and after IOP lowering with prostaglandin analogue (PGA) therapy in medication-naive eyes. This trial included records from 57 consecutive patients with open angle glaucoma who were initiated on
PGA. Patients underwent ORA measurement with IOP assessment at baseline (untreated) and at follow-up (treated). Median follow-up time between IOP measurements was 1.4 (range of 0.4 to 13.5) months. IOP was reduced by 3.2 mm Hg (18.8 %) from 17.0 to 13.8 mm Hg (p < 0.001); CH increased by 0.5 mm Hg (5.2 %) from 9.7 to 10.2 mm Hg (p = 0.02). Baseline CH (but not baseline CCT) was a significant predictor of the magnitude of IOP reduction, with patients in the lowest quartile of CH (mean of 7.0 mm Hg) experiencing a 29.0 % reduction in IOP while those in the highest CH quartile (mean of 11.9 mm Hg) experienced a 7.6 % reduction in IOP (p = 0.006). A multi-variate analysis controlling for baseline IOP demonstrated that baseline CH independently predicted the magnitude of IOP reduction with PGA therapy in both percent ($\beta = 3.5$, $p = 0.01$) and absolute ($\beta = 0.6$, $p = 0.02$) terms. The authors concluded that although CH was influenced by IOP, baseline CH was independently associated with the magnitude of IOP reduction with PGA therapy. They stated that a prospective study with multiple treatment arms would be useful in better defining this relationship and clarifying its full implications for improving patient care.

The authors stated that this study had several drawbacks. The investigation was limited by its retrospective nature. Accordingly, these researchers were unable to draw conclusions about causality and the prospective impact of CH on IOP reduction. In addition, they chose to employ Goldmann-correlated IOP (IOPg) to measure IOP in this study. Since some prior studies have relied on other measurements of IOP, particularly Goldmann applanation tonometry (GAT), this may limit comparability across studies. Nevertheless, the authors believed that this was a minor point since the outcome of interest in this study was IOP change, not true IOP, so any reproducible method of IOP measurement should provide external validity. Finally, the study was limited by the lack of serial IOP measurements. The authors acknowledged the improved precision of serial IOP measurements; however, there was no reason to believe that
noise generated by a lack of serial measurements would bias
the study in a particular direction. Acquisition of multiple IOP
measurements was beyond the scope of the current study,
which was retrospective in nature and exploited extant data
from the standard clinical evaluation of patients.

In a prospective, longitudinal, observational cohort study,
Medeiros et al (2013) examined the role of CH as a risk factor
for the rate of VF progression in a cohort of patients with
glaucoma followed prospectively over time. This trial included
114 eyes of 68 patients with glaucoma followed for an average
of 4.0 ± 1.1 years; VFs were obtained with standard automated
perimetry. Included eyes had a median number of 7 (range of
5 to 12) tests during follow-up. The CH measurements were
acquired at baseline using the ORA (Reichert Instruments,
Depew, NY). Evaluation of rates of VF change during follow-
up was performed using the visual field index (VFI). Linear
mixed models were used to investigate the relationship
between rates of VF loss and baseline CH, baseline IOP, and
CCT, while adjusting for potentially confounding factors. An
interaction term between IOP and CH was included in the
model to examine if the effect of IOP on rates of progression
depended on the level of CH. Main outcome measures were
effects of CH, IOP, and CCT on rates of VFI loss over time.
The CH had a significant effect on rates of VF progression
over time. In the uni-variable model including only CH as a
predictive factor along with time and their interaction, each 1
mmHg lower CH was associated with a 0.25 %/year faster rate
of VFI decline over time (p < 0.001). The multi-variable model
showed that the effect of IOP on rates of progression
depended on CH. Eyes with high IOP and low CH were at
increased risk for having fast rates of disease progression.
The CH explained a larger proportion of the variation in slopes
of VFI change than CCT (17.4 % versus 5.2 %, respectively).
The authors concluded that the CH measurements were
significantly associated with risk of glaucoma progression.
Eyes with lower CH had faster rates of VF loss than those with
higher CH. They stated that the prospective longitudinal
design of this study supported the role of CH as an important factor to be considered in the assessment of the risk of progression in patients with glaucoma. Moreover, they stated that further studies should clarify the role of CH as a true independent risk factor for glaucoma progression by evaluating its role in multi-variable models including corneal independent IOP measurements. In addition, although these findings suggested that CH may be a more important risk factor than CCT, it would be important to perform external validation of predictive models that include CH, before this parameter can be fully incorporated into clinical practice.

The authors noted that this study had several drawbacks. These researchers assumed a linear rate of VF loss over time. Several studies have suggested that functional changes did not follow a linear course over the natural history of the disease, which might be related to the logarithmic scaling (decibel) of VF sensitivity data. Nevertheless, the assumption of linear change was probably a reasonable one for short and medium follow-up periods, as performed in clinical practice. These investigators used the VFI to assess rates of VF progression as it is the current standard method used in the Humphrey Field Analyzer. However, limitations of the VFI in assessing VF progression in early disease have been described. When the authors performed analyses using mean deviation instead of VFI, similar results were obtained in uni-variable and multi-variable models.

In a retrospective study, Park et al (2015) examined the clinical significance of corneal biomechanical properties assessed using an ORA in patients with progressing normal-tension glaucoma (NTG). This trial included 82 eyes of 82 NTG patients who had been receiving topical anti-glaucoma medications. Patients were allocated to 2 groups based on the mean value of CH and the status of progression. The assessment of progression was based on the trend analysis using mean deviation slope. Uni- and multi-variable logistic analyses were constructed to identify factors associated with
increased odds of progression, including CH, CCT, and retinal nerve fiber layer (RNFL) thickness; 46 eyes (56.1%) reached the progression criteria. Eyes with progression had lower CCT (530.2 ± 38.6 versus 549.4 ± 38.3 μm, p = 0.03), thinner average RNFL thickness (70.6 ± 16.1 versus 82.8 ± 17.4 μm, p < 0.01), lower CH (9.4 ± 1.3 versus 10.8 ± 1.4 mm Hg, p < 0.01), and lower corneal resistance factor (9.3 ± 1.3 versus 10.4 ± 1.8 mm Hg, p < 0.01) than eyes without progression; CH and CCT were significantly correlated (r = 0.44, p < 0.01). Upon multi-variable analysis, CH (β (B) = 0.32 per mm Hg lower, p < 0.01) and average RNFL thickness (β = 0.96 per μm lower, p = 0.04) remained statistically significant. The authors concluded that corneal biomechanical properties were correlated and associated with the progression of VF damage in NTG patients. They stated that these findings suggested that CH could be used as one of the prognostic factors for progression, independent of corneal thickness or IOP.

In a retrospective, cohort study, Deol et al (2015) evaluated the relationship between baseline CH and the change in IOP before and after cataract extraction in patients without glaucoma. Charts of consecutive patients who had phacoemulsification cataract extraction with posterior chamber intraocular lens implantation were analyzed. All included patients had pre-operative and post-operative measurements with the ORA 2 to 4 months and 10 to 12 months post-operatively. Data collected included age, baseline CH, baseline CCT, and IOP. A total of 39 (65 eyes) of the 230 patients met the inclusion criteria. The mean patient age was 70.8 years ± 8.6 (SD). The mean pre-operative, 2- to 4-month and 10- to 12- month post-operative IOP values were 14.8 ± 3.5 mm Hg, 11.9 ± 3.4 mm Hg, and 12.6 ± 3.1 mm Hg, respectively (p < 0.05 for comparisons with pre-operative IOP). The baseline CH was not predictive of the IOP reduction at 2 to 4 months (β = -0.3; 95% confidence interval [CI]: -0.7 to 0.01; p = 0.06). However, the baseline CH (but not the baseline CCT) was statistically associated with the magnitude of IOP reduction at 10 to 12 months when controlling for
patient age ($\beta = -0.5; 95 \% \ CI: -0.8 \ to \ -0.1; p = 0.01$). The authors concluded that a low baseline CH was associated with a larger magnitude of IOP reduction after cataract extraction. This study did not include patients with glaucoma.

In a cross-sectional study, Murphy et al (2017) compared CH measurements between patients with glaucoma, ocular hypertension (OHT), and glaucoma-like optic discs (GLD) -- defined as a cup to disc ratio greater than or equal to 0.6 with normal IOP and visual fields. The secondary aim was to examine if corneal resistance factor (CRF) and CCT differ between patient groups. This trial included a total of 123 patients (1 eye each); they were recruited from a glaucoma out-patient department to undergo ORA testing and ultrasound (US) pachymetry as well as clinical examination. A 1-way analysis of co-variance (ANCOVA) was conducted to evaluate the mean difference (MD) in CH between the 3 diagnostic groups (glaucoma, OHT and GLD) correcting for potential confounding factors, IOP and age. Analysis was repeated for CRF and CCT. There was a significant difference in mean CH across the 3 diagnosis groups; $F(2, 115) = 96.95; p < 0.001$.

Mean CH significantly higher for GLD compared to glaucoma (MD 1.83, $p < 0.001$), and significantly higher for OHT compared to glaucoma (MD 2.35, $p < 0.001$). Mean CH was slightly lower in patients with GLD than those with OHT; but this difference was not statistically significant. A similar pattern was seen when the analysis was repeated for CRF and CCT.

The authors concluded that higher CH in GLD and OHT compared to glaucoma suggested increased viscoelasticity of ocular tissues may have a protective role against glaucoma.

The authors stated that the drawbacks of this study included that patients were not followed-up over a period of time to assess CH as an independent risk factor in the emergence of disease in glaucoma suspects and OHT patients, as well as a potential risk factor in the disease progression of known glaucoma patients. Also HTG, PXFG and NTG were grouped together as glaucoma patients for the purpose of analysis.
whereas separate analysis of each of these groups could yield more accurate results. They stated that future research in the area of CH should focus on its role in other diseases characterized by altered tissue compliance such as diabetes and hypertension. These areas may reflect a further advantage for the addition of CH measurements into routine ophthalmological examinations.

In a prospective, observational cohort study, Susanna et al (2018) examined the role of CH as a risk factor for development of glaucoma. A total of 287 eyes of 199 patients suspected of having glaucoma were followed for an average of 3.9 ± 1.8 years. All eyes had normal VFs at baseline. Development of glaucoma was defined as occurrence of 3 consecutive abnormal standard automated perimetry tests during follow-up, defined as pattern standard deviation (PSD) of less than 5 %, and/or Glaucoma Hemifield Test outside normal limits. Measurements of CH were acquired at baseline using the ORA. Uni-variable and multi-variable Cox regression models were used to investigate baseline factors associated with development of VF loss over time; 54 (19 %) eyes developed repeatable VF defects during follow-up. Measurements of CH at baseline were significantly lower in patients who developed glaucoma versus those who did not (9.5 ± 1.5 mm Hg versus 10.2 ± 2.0 mm Hg; p = 0.012). Each 1-mm Hg lower CH was associated with an increase of 21 % in the risk of developing glaucoma during follow-up (95 % CI: 1.04 to 1.41; p = 0.013). In a multi-variable model adjusting for age, IOP, CCT, PSD, and treatment, CH was still predictive of development of glaucoma (HR = 1.20; 95 % CI: 1.01 to 1.42; p =0 .040). The authors concluded that baseline lower CH measurements were significantly associated with increased risk of developing glaucomatous VF defects over time. The prospective, longitudinal design of this study supported a role of CH as a risk factor for developing glaucoma.
Zareei et al (2018) stated that the correct estimation of IOP is the most important factor in the management of various types of glaucoma. Primary congenital glaucoma is a type of glaucoma that can cause blindness in the absence of control of the IOP. In this retrospective observational study, 95 eyes, including 48 healthy eyes and 47 eyes with primary congenital glaucomatous (PCG) were studied. Two groups were matched for age, gender, and Goldman Applanation Tonometry (GIOP); CH, Corneal Resistance Factor (CRF), and IOPg, and corneal compensated IOP (IOPcc) was measured for each patient using the ORA; CCT was measured by US pachymetry. For each patient, 1 eye was selected randomly. Student's t-test and analytical regression were used for statistical analysis. The 2 groups were matched for age (p = 0.34), gender (p = 0.47), and GIOP (p = 0.17); CH and CRF were significantly lower in PCG than in normal eyes (p < 0.0001), yet CCT was significantly thicker in PCG than normal eyes (p < 0.0001). The regression equation on the effect of CH, CRF, and CCT on GIOP in the PCG group showed that CH and CRF (p-value = 0.001 and p value < 0.0001) also had a significant effect yet CCT did not (p-value = 0.691). A significant decrease in CH and CRF was found in the PCG group compared to the normal controls. In the PCG group, the CCT was greater than normal. The authors concluded that these results showed the usefulness of biomechanical properties (CH, CRF) in order to interpret IOP measurements. Furthermore, GIOP measurement may not be confined to consideration of CCT alone. A low CH and CRF value could be responsible for under-estimation of GIOP in the PCG group, in comparison to the normal controls.

These researchers examined the biomechanical properties and CCT of normal and PCG children and compared these variables in the 2 groups. In the PCG group, CCT was greater than normal. A significant decrease in CH and CRF was found in the PCG group compared to normal controls. These results showed the usefulness of biomechanical properties (CH and
CRF) in order to interpret IOP measurements correctly. Moreover, they stated that certainly further studies in the future are needed to extend this information.

Park et al (2018) evaluated the relationships between corneal biomechanical properties and structural parameters in patients with newly diagnosed, untreated normal-tension glaucoma (NTG). All subjects were evaluated using an ORA measuring CH and the corneal resistance factor (CRF); CCT, GAT data, axial length, and the spherical equivalent (SE), were also measured. Confocal scanning laser ophthalmoscopy was performed with the aid of a Heidelberg retina tomograph (HRT III). These researchers sought correlations between HRT parameters and different variables including CCT, CH, and the CRF. Multiple linear regression analysis was performed to identify significant associations between corneal biomechanical properties and optic nerve head parameters. They enrolled 95 eyes of 95 NTG patients and 93 eyes of 93 normal subjects; CH and the CRF were significantly lower in more advanced glaucomatous eyes (p = 0.001, p = 0.008, respectively). The rim area, rim volume, linear cup-to-disc ratio (LCDR), and mean RNFL thickness were significantly worse in more advanced glaucomatous eyes (p < 0.001, P<0.001, p < 0.001, and p = 0.001); CH was directly associated with rim area, rim volume, and mean RNFL thickness (p=0.012, p = 0.028, and p = 0.043) and inversely associated with LCDR (p = 0.015), after adjusting for age, axial length, CCT, disc area, GAT data, and SE. However, in normal subjects, there were no significant associations between corneal biomechanical properties and HRT parameters. The authors concluded that they found that lower CH was associated with smaller rim area and volume, larger linear cup-to-disc ratio, and thinner mean RNFL thickness in newly diagnosed untreated NTG patients after adjustment for age, axial length, corneal thickness, disc size, IOP, and spherical equivalent. They stated that the results of this study highlighted the importance of corneal biomechanical properties on changes in the optic nerve head in NTG patients and may improve our
understandings of the pathophysiological mechanism(s) involved in the development of glaucomatous optic neuropathy.

The authors stated that this study had certain limitations. First, the sample size of the study population was relatively modest. Second, all subjects included in this study were Asian; the relationship between biomechanical properties of cornea and structural measures may differ in other populations because CH differs by ethnicity. Third, glaucoma severity was not assessed as an independent variable which may influence the impact of corneal biomechanical properties on HRT parameters. Fourth, the study was performed cross-sectionally. Thus, these investigators were unable to determine whether the relationship between CH and HRT parameter in patients with NTG reflects a cause or an effect.

Chen et al (2018) measured CH with the ORA in patients with IOP of less than 21 mmHg to investigate if a low CH would identify NTG in an Asian-based practice. The authors concluded that the findings of this study suggested considering measuring CH as a screening tool for NTG, especially in patients with risk factors.

In a review on "Corneal hysteresis and glaucoma", Liang et al (2019) concluded that CH is used as a predictor of glaucoma risk and may help to assess the effect of corneal thickness on IOP. The clinical significance of CH in the diagnosis and efficacy of glaucoma will become more explicit. In the future, CH can also play an important role in the diagnosis and treatment of glaucoma.

Furthermore, an UpToDate review on "Open-angle glaucoma: Epidemiology, clinical presentation, and diagnosis" (Jacobs, 2018) does not mention measurement of corneal hysteresis as a management tool.
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 BclI (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 BclI and N363S polymorphisms were screened using RT-PCR-restriction fragment length polymorphism (RFLP) analysis. Frequencies of the BclI and N363S polymorphisms were determined and compared using Fisher's exact test and the Chi-squared test. Only the BclI 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 BclI 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 BclI 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.

Zhou and colleagues (2017) noted that POAG and primary congenital glaucoma (PCG) with Mendelian inheritance are caused by mutations in at least 9 genes. Utilizing whole-exome sequencing (WES), these researchers examined the disease burden accounted for by these known Mendelian glaucoma genes in a cohort of individuals with advanced early-onset POAG. The cases exhibited advanced POAG with young age of diagnosis. Cases and examined local controls were subjected to WES. A total of 993 previously sequenced exomes of Australian controls were called jointly with the authors' dataset. Qualifying variants were selected based on predicted pathogenicity and rarity in public domain gene variant databases. Case-control mutational burdens were calculated for glaucoma-linked genes. A total of 218 unrelated POAG participants and 103 non-glaucomatous controls were included in addition to 993 unexamined controls; 58 participants (26.6 %) harbored rare potentially pathogenic variants in known glaucoma genes. Enrichment of qualifying variants toward glaucoma was present in all genes except WDR36, in which controls harbored more variants, and TBK1, in which no qualifying variants were detected in cases or controls. After multiple testing correction, only MYOC showed statistically significant enrichment of qualifying variants (OR = 16.62, p = 6.31×10-16). The authors concluded that rare, potentially disease-causing variants in Mendelian POAG genes that showed enrichment in the authors' dataset were found in 22.9 % of advanced early-onset POAG cases; MYOC variants represented the largest monogenic cause in POAG. These researchers stated that the association between
WDR36 and POAG was not supported, and the majority of POAG cases did not harbor a potentially disease-causing variant in the remaining Mendelian genes.

Khawaja and Viswanathan (2018) stated that following a dramatic reduction in the cost of genotyping technology in recent years, there have been significant advances in the understanding of the genetic basis of glaucoma. Glaucoma patients represent about 25% of all out-patient activity in the UK hospital eye service and are a huge burden for the National Health Service. A potential benefit of genetic testing is personalized glaucoma management, allowing direction of limited healthcare resources to the glaucoma patients who most need it. These investigators summarized recent discoveries in the field of glaucoma genetics and discussed their potential clinical utility. While genome-wide association studies have now identified over 10 genes associated with POAG, individually, variants in these genes are not predictive of POAG in populations. There are data suggesting some of these POAG variants are associated with conversion from ocular hypertension to POAG and visual field progression among POAG patients. However, these studies have not been replicated yet and such genetic testing is not currently justified in clinical care. In contrast, genetic testing for inherited early-onset disease in relatives of POAG patients with a known genetic mutation is of clear benefit; this can support either regular review to commence early treatment when the disease develops, or discharge from ophthalmology services of relatives who do not carry the mutation. The authors concluded that genetic testing for POAG at a population level is not currently justified.

Visual Evoked Potential

Multi-focal visual evoked potential (mfVEP) has been studied for the diagnosis and early detection of glaucomatous field defects. However, its effectiveness for this indication has not been established.
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.

Tai (2018) stated that visual evoked potentials (VEP) can be
used to assess the function of the visual system objectively.
Research on VEP testing as a method of glaucoma evaluation
has been performed for many years. Pattern VEP has shown
good specificity and sensitivity in the detection of glaucoma in
some studies, but other studies have not shown similar
efficacy; mfVEP can produce a topographical measure of glaucomatous damage and has been shown to be able to detect a similar number of defects in patients with glaucoma or ocular hypertension as compared with the visual field test. Despite promising data on these VEP test modalities in the assessment of glaucoma, multiple aspects of test administration make their routine use impractical in a clinical setting. New VEP testing modalities, such as short-duration transient VEP and isolated-check VEP, allow the test to be performed more quickly and easily. The authors concluded that further research on these more recent technologies may allow VEP to be used effectively in the diagnosis and management of glaucoma.

**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 (VFs) 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”.

Computerized Visual Field Examination, Gonioscopy, and Measurement of Optic Nerve Head and Retinal Nerve Fiber Layer

The American Academy of Ophthalmology (AAO) Preferred Practice Pattern Glaucoma Panel’s preferred practice pattern on “Primary open-angle glaucoma” (Prum et al, 2015) noted the following:

- Characteristic clinical features of POAG include an open angle on gonioscopy, and glaucomatous optic nerve head (ONH) and retinal nerve fiber layer (RNFL) changes that usually are associated with typical glaucomatous visual field defects.
- Adjusting computerized visual field programs (24-, 30-, and 10-degrees) and varying stimulus size for patients with advanced glaucoma aid in detecting and monitoring progressive visual field loss.
Evaluation of Lamina Cribrosa Defects for Determining Risk of Glaucoma Progression

Park and associates (2017) stated that the advent of OCT imaging allows identification of the structural contribution of the lamina cribrosa (LC) to glaucoma progression. These researchers examined the role of various LC features, such as the LC depth (LCD), LC thickness (LCT), and focal LC defects, on the future rate of progressive RNFL thinning in patients with glaucoma. A total of 118 patients with glaucoma who had undergone at least 4 OCT examinations were included. Features of LC, including the LCD, LCT, and presence of focal LC defects, from serial scan of the optic disc using the enhanced depth imaging of Spectralis OCT; were analyzed at baseline. Eyes were classified as those with or without progressive RNFL thinning using the guided progression analysis of Cirrus OCT. Factors associated with the rate of RNFL thinning (linear regression analysis against time for global average, inferior, and superior RNFL thicknesses, μm/year) were evaluated using a general linear model. Greater baseline LCD and thinner baseline LCT were significantly associated with the rate of superior RNFL thinning. Focal LC defects were significantly more frequent in eyes with progressive inferior RNFL thinning (93.8 %) and the location of the focal LC defect was only related to the location of progression RNFL thinning in the inferior region (p<0.001). A deeper and thinner LC was related to the rate of superior RNFL thinning, and the presence of focal LC defects was related to the rate of inferior RNFL thinning.

The authors stated that this study had several drawbacks. First, only patients from a single ethnic group with glaucoma who were treated medically were included. Therefore, these findings may not be generalizable to all patients with glaucoma. Second, the follow-up period was relatively short (mean of 4.18 years). These investigators stated that further investigation is needed to determine the long-term influence of LC features on glaucoma progression. Third, issues of the
poor visualization of the LC under the optic disc rim and vessels exist. It was possible that some LC alterations in areas with poor OCT penetration may have been missed. To reduce false-positive detection of focal LC defects, these researchers defined a LC defect as having a diameter of greater than or equal to 100 μm and a depth of greater than 30 μm. The LC defect also had to be present in 2 neighboring B-scans. The definition of LC defects was based on previous studies and may not be ideal. However, previous studies had mentioned that the definition used in this trial may exclude normal anatomical variations and artifacts.

Moghimi and colleagues (2019) noted that certain features of the LC may be associated with increased risk of glaucoma progression. In a longitudinal, cohort study, these investigators compared the rates of RNFL thinning in patients with OAG with or without LC defects and examined factors associated with the rate of glaucoma progression in eyes with LC defects. This trial was carried out at a tertiary glaucoma center in California; and included 51 eyes of 43 patients with LC defects and 83 eyes of 68 patients without LC defects; and subjects were followed-up for a mean (SD) of 3.5 (0.8) years. Focal LC defects were detected using swept-source OCT (SS-OCT) images. All subjects underwent visual field testing and spectral-domain OCT for RNFL thickness measurements every 6 months. Uni-variate and multi-variable random-effects models were used to compare the rate of local and global RNFL loss. The mean (95% CI) age at baseline for individuals with LC defects was 69.5 (65.4 to 73.6) years, and for those without LC defects, it was 69.6 (67.2 to 72.0) years; 18 individuals (41%) with LC defects and 35 individuals (51%) without LC defects were men; 6 individuals (14%) with LC defects and 17 individuals (25%) without were African American. The mean (95% CI) rate of global RNFL loss in eyes with LC defects was 2-fold faster than that in eyes without LC defects (-0.91 [-1.20 to -0.62] versus -0.48 [-0.65 to -0.31] μm/year; difference, -0.43 [-0.76 to -0.09] μm/year; p<0.01). The rate of RNFL thinning was faster in the LC defect
sectors than that in the unaffected sectors (difference, -0.90 [95 % CI: -1.68 to -0.12] μm/year, p = 0.02). Thinner corneal thickness was the only factor that was associated with a faster rate of RNFL loss in eyes with LC defects (β2 = -0.09 [95 % CI: -0.14 to -0.04], p = 0.001). No association was found between mean IOP during follow-up and the mean rate of RNFL thinning in eyes with LC defects (β2, -0.05 [95 % CI: -0.17 to 0.06], p = 0.36). The authors concluded that these findings suggested that LC defects were an independent risk factor for RNFL thinning and that glaucoma progression may correspond topographically to the LC defect location. Thinner corneal thickness in eyes with LC defects was associated with faster further glaucoma progression. In the management of open-angle glaucoma, LC findings may inform the likelihood and rate of glaucoma progression. Moreover, it is not yet known whether aggressive treatment to reduce the likelihood of glaucomatous progression is beneficial in eyes with LC defects.

The authors stated that one limitation of this study was that focal LC defects were based on subjective observation, and even with SS-OCT it can be challenging to visualize the deep optic nerve head structures and to identify an LC defect. However, this limitation was addressed at least in part by having 2 graders determined the presence of LC defects, and by the excellent inter-observer agreement in determining the presence of the LC defects (κ = 0.81). The definition of LC defect may also have contributed to the results. Defects were required to be at least 100 μm in diameter in the present study. The size criteria were chosen to minimize the risk of labeling normal LC pores as defects, (i.e., minimizing the number of false-positive classifications), to increase inter-observer agreement, and to allow for comparisons with previous reports. However, it was possible that small LC defects may have been over-looked. In a histologic study, Jonas et al (1991) reported that normal LC pores had a mean area of only 4 mm2. This suggested that LC defects could be much smaller than the criteria used in the present study. Even
though these researchers included 134 eyes with a mean follow-up of more than 3.5 years, a large proportion of the cases showed early glaucoma, and this follow-up period might not have been long enough to detect significant global VF deterioration in these subjects because high intra-individual variability of VF test results necessitated a large number of visits. Finally, these investigators did not exclude eyes with prior glaucoma surgery; such surgery can change the optic nerve head morphology, as anterior lamina depth and bowing had been shown to be affected by trabeculectomy. However, in the present study, the proportion of eyes with or without LC defects that had undergone glaucoma surgery was similar.

Isolated-Check Visual Evoked Potential for the Diagnosis and Early Detection of Glaucomatous Field Defects

Xu and colleagues (2017) examined the diagnostic accuracy, sensitivity and specificity of isolated-check VEP (icVEP) in POAG. A total of 90 POAG patients and 66 healthy controls were recruited consecutively. All subjects underwent icVEP and visual field testing. Swept icVEP response functions were obtained by increasing contrast in 6 stimulus steps, recording the electroencephalogram synchronized to the stimulus display's frame rate and calculating the corresponding signal-to-noise ratio (SNR) of the response at the fundamental frequency to evaluate visual function. Depth of modulation of the check luminance was increased as follows: 2, 4, 8, 14, 22 and 32 %, about an equal level of standing contrast, so that the pattern appeared and disappeared at a frequency of 10.0-Hz; SNR above 0.85 was deemed to be significant at the 0.1 level and SNR above 1 significant at the 0.05 level. The results showed that SNR was contrast-dependent. It significantly rose as contrast increased. The areas under receiver-operating-characteristic curves (AUCs) indicating classification accuracy for all POAG cases in comparison with normal subjects were 0.790 (sensitivity 91.1 %, specificity 69.7 %) with the cut-off SNR of 0.85, and 0.706 (sensitivity 95.6 %, specificity 51.5 %) with the cut-off SNR of 1. The AUC of early
glaucoma cases (EG) in comparison with normal subjects was 0.801 (sensitivity 93.3 %, specificity 69.7 %) with the cut-off SNR of 0.85, and 0.717 (sensitivity 97.8 %, specificity 51.5 %) with the cut-off SNR of 1. The authors concluded that icVEP had good diagnostic accuracy (high sensitivity and moderate specificity) in distinguishing early POAG patients from healthy subjects; it might be a promising device to use in conjunction with complementary functional and structural measures for early POAG detection.

Chen and Zhao (2017) compared the diagnostic performance of icVEP with that of retinal ganglion cell-inner plexiform layer (GCILP) analysis using OCT. A total of 45 patients were enrolled: 25 patients with OAG and 20 healthy patients. All patients underwent a complete ophthalmological examination. Moreover, the OCT examination was used to analyze the structures of the GCILP. The icVEP technique was used to detect the transmission function of the magnocellular pathway, which is mainly managed by the retinal ganglion cells. The quantitative and qualitative comparisons between the diagnostic power of GCILP analysis and that of icVEP were performed. The AUC of GCILP analysis and icVEP were compared using the Clarke-Pearson method. The sensitivity and specificity of the 2 techniques were analyzed and compared using the McNemar test. With the quantitative comparison, the AUC of icVEP (AUC = 0.892) was higher than that of GCILP analysis (AUC = 0.814). However, there was no statistical significance between the AUCs of icVEP and GCILP (p > 0.05). With the qualitative comparison, the sensitivity of icVEP was 80 %, and its specificity was 90 %. The sensitivity of GCILP analysis was 72 %, and its specificity was 85 %. There was no significant difference between the sensitivities or specificities of icVEP and GCILP analysis (p > 0.05). Moreover, 30 (66.67 %) eyes had similar results between icVEP and GCILP analysis, and 15 (33.33 %) eyes had different results (7 eyes had abnormal results with GCILP analysis but normal results with icVEP, and 8 eyes had normal results with GCILP analysis but abnormal results with icVEP).
The authors concluded that the diagnostic power of icVEP was close to that of GCIPL analysis whether the comparison was based on the qualitative or quantitative data.

The authors stated that this study had several drawbacks. The patients assigned to the glaucoma group all had eyes with early stage glaucoma (the mean deviation of visual field was less than or equal to 6 dB). Therefore, the diagnostic performance of these 2 techniques would change if the patients with more serious stage glaucoma were enrolled in this study. Another drawback was that the small sample size (n = 25 for OAG) in the current study did not provide strong evidence for the results, which were based on the quantitative and qualitative comparisons between icVEP and OCT. Finally, peripheral visual function is known to be preferentially affected in the mild stage of glaucoma. However, icVEP was designed to detect the central visual abnormalities of glaucoma. These researchers stated that further studies are needed to determine which examination is better in the diagnosis of early glaucoma: icVEP or techniques that were designed to identify the peripheral visual function, such as standard automated perimetry and mfVEP.

Fan and colleagues (2018) noted that standard automated perimetry does not sufficiently detect early OAG in the clinic; thus, new visual function tests for early glaucoma damage are needed. In a cross-sectional study, these researchers examined if icVEP could be used to detect visual function abnormalities in early-stage OAG and to examine potential related factors. A total of 37 OAG patients with early-stage visual field loss (mean deviation greater than or equal to -6.00 dB) detected by the Humphrey Field Analyzer (30-2 SITA program) and 26 controls were included in this study; OCT was used to detect RNFL defects. The icVEP preferentially evaluated the magnocellular-ON pathway. VEPs were recorded and SNRs were derived based on multi-variate analysis. Eyes that yielded an SNR of less than or equal to 1 were considered abnormal; ROC curve analysis was used to
estimate the accuracy of group classification. Correlations between SNRs and related factors were analyzed. Based on an SNR criterion of 1, the icVEP had a sensitivity of 62.2% and a specificity of 92.3% for diagnosing early-stage OAG with 74.6% classification accuracy. The ROC curve analysis, however, suggested that an SNR criterion of 0.93 would produce the highest classification accuracy (77.3%). Both RNFL thinning in the temporal superior quadrant on OCT and number of abnormal test points in the central 11° visual field (pattern deviation, p < 0.5%) significantly correlated with the SNR (p < 0.05). The authors concluded that icVEP detected visual function abnormalities in approximately 3/5 of eyes with early-stage OAG with greater than 90% specificity; SNR correlated with both a decrease in RNFL thickness and severity of central visual field loss.

The authors stated that a drawback of this study was that the icVEP test required a best-corrected visual acuity (BCVA) of better than 0.3, spherical refraction within −6 to +3 diopters, and transparent ocular media, that is, the study only showed the usefulness of the icVEP for early-stage OAG eyes with better VA. Thus, further studies are needed to generate more discrete stimulations and determine better criteria for OAG eyes with poor VA, to determine if the icVEP might serve as a functional test to discriminate glaucoma suspects, pre-perimetical stage, and early-stage OAG, and to improve it for use in follow-up. Another drawback was that this was a cross-sectional study with a small sample (n = 37 for OAG patients) at a single center, therefore, further multi-center studies with a larger sample size are also needed to confirm the accuracy of this diagnostic test.

In a prospective, cross-sectional study, Kolomeyer and co-workers (2020) examined the utility of modified icVEP testing in detecting functional glaucomatous damage. Subjects who met pre-determined criteria of controls, glaucoma suspects, pre-perimetric glaucoma, or glaucoma were enrolled in this trial from a single tertiary-care center. Glaucoma patients
were further categorized as early, moderate, advanced, or severe on the basis of Hodapp-Anderson-Parrish criteria. icVEP testing was performed with 10 2-second runs per qualified eye using the EvokeDx testing software. Multi-variate statistics were used to calculate SNR and perform outlier analysis. A total of 140 eyes met criteria (mean ± SD; age of 63 ± 14 years; 49 % men; logMAR visual acuity, 0.11 ± 0.089). There was no significant difference in age, sex, or logMAR visual acuity among the groups. Controls had a significantly higher SNR than all other groups (p < 0.003), including patients with pre-perimetric glaucoma. Among those with glaucoma, the early glaucoma patients had significantly higher SNR than the moderate, advanced, or severe glaucoma cohorts (p < 0.04). The optimal SNR cut-off for differentiating between glaucomatous and non-glaucomatous eyes was 0.95, both with (sensitivity of 82 %, and specificity of 76 %) and without (sensitivity of 82 %, and specificity of 100 %) glaucoma suspects included in analysis. The authors concluded that the icVEP technology has the potential to complement standard achromatic perimetry in functional assessment of glaucomatous defects.

RETeval Portable Electroretinogram Device for the Detection of Glaucoma

Kita and colleagues (2020) noted that 4 parameters of the non-invasive, portable RETeval electroretinogram (ERG) device were found to correlate with visual field mean deviation and OCT thickness parameters, and may therefore be suitable for the detection of glaucoma. These investigators examined the RETeval full-field ERG parameters for accuracy of separating glaucoma and normal eyes, and correlation with glaucoma severity. A total of 62 eyes of 62 POAG patients [visual field mean deviation (MD) range of -0.44 to -31.15 dB] and 39 eyes of 39 healthy controls underwent one RETeval test (photopic negative response protocol), OCT imaging, and Humphrey 30-2 visual field testing. The glaucoma patients were divided into early (MD of greater than or equal to -6dB, n
and moderate-to-advanced (MD of less than -6 dB, n = 29) groups. Significant correlations were found between the best-performing 4 RETeval ERG parameters and the glaucoma severity measures (MD and OCT thickness parameters) for all eyes, all glaucoma eyes and the moderate-to-advanced glaucoma eyes [photopic negative response amplitude at 72 ms (PhNR 72) and MD: r = -0.333, -0.414, and -0.485, respectively, p ≤ 0.008; PhNR 72 and average circum-papillary RNFL thickness; r = -0.429, -0.450, and -0.542, respectively, p ≤ 0.002]. Except for P-ratio, there was no significant difference between the area under the receiver-operating characteristic (AUROC) values of the OCT thickness parameters (range of 0.927 to 0.938) and the 4 best-performing RETeval ERG parameters (range of 0.839 to 0.905) in the early glaucoma versus control separation. For differentiating the control and the moderate-to-advanced glaucoma eyes, the AUROC values of the 4 best-performing RETeval ERG parameters ranged between 0.924 and 0.958, and no significant difference was found between them and those of the OCT parameters. The authors concluded that the non-invasive, portable RETeval full-field ERG device may be useful to detect glaucoma in moderate-to-advanced stages. These findings need to be validated by well-designed studies.

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 "+":

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
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<tbody>
<tr>
<td>92020</td>
<td>Gonioscopy (separate procedure)</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>---------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>92081</td>
<td>Visual field examination, unilateral or bilateral, with interpretation and report; limited examination (eg, tangent screen, Autoplot, arc perimeter, or single stimulus level automated test, such as Octopus 3 or 7 equivalent)</td>
</tr>
<tr>
<td>92082</td>
<td>Intermediate examination (eg, at least 2 isopters on Goldmann perimeter, or semiquantitative, automated suprathreshold screening program, Humphrey suprathreshold automatic diagnostic test, Octopus program 33)</td>
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<tr>
<td>92083</td>
<td>Extended examination (eg, Goldmann visual fields with at least 3 isopters plotted and static determination within the central 30 deg, or quantitative, automated threshold perimetry, Octopus program G-1, 32 or 42, Humphrey visual field analyzer full threshold programs 30-2, 24-2, or 30/60-2)</td>
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<tr>
<td>92133</td>
<td>Scanning computerized ophthalmic diagnostic imaging, posterior segment, with interpretation and report, unilateral or bilateral; optic nerve retina</td>
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CPT codes not covered for indications listed in the CPB:

**Multi-focal visual evoked potential, Provocative test, isolated-check visual evoked potential - no specific code**

<table>
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<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>0198T</td>
<td>Measurement of ocular blood flow by repetitive intraocular pressure sampling, with interpretation and report</td>
</tr>
<tr>
<td>0329T</td>
<td>Monitoring of intraocular pressure for 24 hours or longer, unilateral or bilateral, with interpretation and report</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
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<tr>
<td>0464T</td>
<td>Visual evoked potential, testing for glaucoma, with interpretation and report</td>
</tr>
<tr>
<td>0509T</td>
<td>Electroretinography (ERG) with interpretation and report, pattern (PERG)</td>
</tr>
<tr>
<td>92145</td>
<td>Corneal hysteresis determination, by air impulse stimulation, unilateral or bilateral, with interpretation and report</td>
</tr>
<tr>
<td>92273</td>
<td>Electroretinography (ERG), with interpretation and report; full field (ie, ffERG, flash ERG, Ganzfeld ERG)</td>
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<tr>
<td>92274</td>
<td>multifocal (mfERG)</td>
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ICD-10 codes covered if selection criteria are met:

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<tr>
<th>Code</th>
<th>Description</th>
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<tr>
<td>H40.1110 - H40.1194</td>
<td>Primary open-angle glaucoma</td>
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</table>

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

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<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>H40.001 - H40.10x4, H40.1210 - H42</td>
<td>Glaucoma [except primary open-angle glaucoma]</td>
</tr>
<tr>
<td>Z13.5</td>
<td>Encounter for screening for eye and ear disorders [screening for glaucoma]</td>
</tr>
</tbody>
</table>

The above policy is based on the following references:

1. Agarwal DR, Ehrlich JR, Shimmyo M, Radcliffe NM. The relationship between corneal hysteresis and the magnitude of intraocular pressure reduction with


27. Gemenetzi M, Yang Y, Lotery AJ. Current concepts on primary open-angle glaucoma genetics: A contribution


90. 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.

revised 09/09/2020

Proprietary