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CME ACTIVITY

OPHTHALMOLOGY UPDATE

New Approaches to Medical and Surgical Therapies

Ophthalmology Update

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STATEMENT OF NEED

As population changes lead to shifts in the prevalence of ocular disease, developments in ophthalmic pharmaceuticals and new medical device technologies continue to change the treatment strategies available to general ophthalmologists and ophthalmic surgeons alike. As an example, Sean Ianchulev, MD, noted during the March 2010 Innovative Glaucoma Surgery Symposium that he had identified 548 ongoing clinical research studies, including 24 device studies and 198 studies in the active recruitment phase for the treatment of glaucoma.[1]

Likewise, new pharmaceutical and surgical treatment options continue to expand the knowledge base of ocular surface disease.[2] Coordinating the management of pre-, intra-, and postsurgical attention to the ocular surface can significantly affect cataract surgical patients' satisfaction. Improving the delivery of treatments for ocular surface disease requires expanding the diagnostic skills of practitioners as well as their awareness of patient symptoms and available treatment options. Additionally, in a review of past Dulaney Foundation medical education activity feedback, fewer than 40% of glaucoma specialists who responded were aware of the prevalence of ocular surface disease among glaucoma patients being treated with topical IOP-lowering medications.

Patient compliance with prescribed therapies remains a significant barrier to effective treatment in many areas of ocular disease, especially in glaucoma management, where failure can lead to the permanent loss of vision. In fact, new research published in *Ophthalmology* involving glaucoma medical therapy adherence and visual field defects demonstrated that patients "who were less than 80% adherent according to the [Medication Events Monitoring System] MEMS devices were significantly more likely to have worse defect severity." Clearly, the issue of medical therapy adherence is a key aspect of improving patients' outcomes in ocular disease.[3]

Addressing these gaps in education relative to the burden of ocular disease is an important part of improving both the delivery of effective care and the ocular health of the population. Due to the increased attention given to the medical needs of America's aging population, the efforts to contain increasing medical costs, and the need to improve the efficient delivery of care, we continue to learn more about the current and future burden of ocular disease.

According to several key papers published in 2004 by the Eye Diseases Prevalence Research Group, the number of persons in the United States with cataract is projected to rise dramatically by the year 2020 to more than 30 million, and the number of open-angle glaucoma cases will increase by 50%.[4,5] Glaucoma is the leading cause of preventable blindness in the United States, and at least 3 million Americans have the disease, according to the American Glaucoma Society.[6] Given the rapid increase in the aging American population, as well as increases in groups at high risk for glaucoma, the burden of disease related to this condition becomes more significant each year.[7] The Centers for Medicare & Medicaid Services (CMS) recognizes the following as high-risk groups for glaucoma.[8]

- Individuals with diabetes mellitus
- Individuals with a family history of glaucoma
- African Americans aged 50 and older
- Hispanic Americans aged 65 and older

Ocular surface disease continues to increase in significance for many patients, especially older individuals who may have additional needs for ocular surgery for cataracts or retinal degenerative disease.[9]

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4. Congdon N, Vingerling JR, Klein BE, et al; Eye Diseases Prevalence Research Group. Prevalence of cataract and pseudophakia/aphakia among adults in the United States. *Arch Ophthalmol*. 2004;122(4):487-494.

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6. American Glaucoma Society. Available at: http://www.glaucomaweb.org/displaycommon.cfm?an=1&subarticlenbr=12

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TARGET AUDIENCE

This certified CME activity is designed for anterior segment ophthalmic surgeons, glaucoma specialists, and general ophthalmologists involved in the management of patients with glaucoma and/or ocular surface disease.

LEARNING OBJECTIVES

Upon completion of this activity, the participant should be able to:

1. Properly diagnose external infectious and inflammatory eye disease
2. Discuss lid disease therapies and perioperative treatment strategies
3. Assess chronic conditions such as ocular surface disease
4. Describe effective perioperative management of ocular surface disease
5. Interpret glaucoma diagnostic techniques
6. Incorporate current glaucoma therapeutics and address patient compliance
7. Explain effective combined surgical and medical glaucoma management

METHOD OF INSTRUCTION

Participants should read the CME activity in its entirety. After reviewing the material, please complete the self assessment test, which consists of a series of multiple-choice questions. To answer these questions online and receive real-time results, please visit http://www.dulaneyfoundation.org and click "Online Courses." Upon completing the activity and achieving a passing score of over 70% on the self-assessment test, you may print out a CME credit letter awarding 1 *AMA PRA Category 1 Credit.*™ The estimated time to complete this activity is 1 hour.

ACCREDITATION AND DESIGNATION

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the Dulaney Foundation and *Advanced Ocular Care*. The Dulaney Foundation is accredited by the ACCME to provide continuing education for physicians. The Dulaney Foundation designates this enduring material for a maximum of 1 *AMA PRA Category 1 Credit.*™ Physicians should claim only the credit commensurate with the extent of their participation in the activity.

DISCLOSURE

In accordance with the disclosure policies of the Dulaney Foundation and to conform with ACCME and US Food and Drug Administration guidelines, anyone in a position to affect the content of a CME activity is required to disclose to the activity participants (1) the existence of any financial interest or other relationships with the manufacturers of any commercial products/devices or providers of commercial services and (2) identification of a commercial product/device that is unlabeled for use or an investigational use of a product/device not yet approved.

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FACULTY/STAFF DISCLOSURE DECLARATIONS

Dr. Haw states that he has no financial relationships to declare.

Dr. Medeiros states that he has received grant/research support from EY021818 of the National Eye Institute and Carl Zeiss Meditec, Inc.; and that he is a consultant to Alcon Laboratories, Inc., and Allergan, Inc.

Dr. Nouri-Mahdavi states that he has no financial relationships to declare.

Dr. Zangwill receives research support from Heidelberg Engineering, Inc., Carl Zeiss Meditec, Inc., Optovue, Inc., Nidek, Inc., and Topcon; and she provides reading center services for Optovue, Inc., Nidek, Inc., and Topcon.

All of those involved in the planning, editing, and peer review of this educational activity report no financial relationships with any company described herein. ■

Considerations in the Medical Treatment of Glaucoma

Advanced imaging and a new pharmacologic solution have changed the way we think about this condition.

BY KOUROS NOURI-MAHDAVI, MD

Medical therapy for glaucoma can be a highly effective means of reducing IOP so as to avoid the potential for vision loss. Several classes of glaucoma medications are available in the United Sates, and there are a variety of agents within each class. Given the plethora of choices for medical therapy, how these agents are used may be as important as which particular agent is selected. Additionally, because glaucoma therapy is a long-term commitment, careful consideration must be given as to the patient's health and when to initiate therapy.

The presentation of glaucoma is highly variable, and although the disease is often progressive, its rate of overall progression is slow on average. In the Early Manifest Glaucoma Trial,[1] the disease progressed slowly in untreated patients, with a loss of about 0.5 decibel per year (Table 1).[1] Considering the average glaucoma patient's lifespan (approximately 13 years per Quigley et al[2]), medical therapy can preserve vision in most patients.

GLAUCOMA THERAPY GOALS

Several studies have demonstrated the benefits of glaucoma treatments that are designed to lower IOP, both in patients with ocular hypertension[3-7] and in those with open-angle glaucoma.[1,8] Lowering IOP is the only proven method of slowing progression rates in glaucoma.[9] In addition to controlling pressure, however, surgeons must try to prescribe the smallest amount of medication prescribed to the patient, minimize any side effects, interfere with the patient's quality of life as little as possible, and to preserve the health of the ocular surface as much as possible.

In an ideal setting, any IOP-lowering treatment would provide all-day control so as to minimize the impact of fluctuations. IOP increases at night, in part because of the supine position, but also because of the influence of the dark/light cycle.[10] Additionally, blood pressure can decrease at night, which, when coupled with increasing IOP, can interfere with the control of glaucoma. Only certain glaucoma therapies are known to be effective for decreasing nocturnal IOP: prostaglandins, carbonic anhydrase inhibitors, and selective laser trabeculoplasty (SLT).[10]

All of the medications used in glaucoma come with appreciable safety concerns against which any potential benefit must be weighed. The cost of the medication and the potential for disrupting patients' quality of life are also not insignificant considerations. Prostaglandins, which work by increasing the uveoscleral outflow, have become the preferred first-line treatment in glaucoma since the introduction of latanoprost ophthalmic solution 0.005% (Xalatan; Pfizer, Inc.) in the mid 1990s. Although prostaglandins can be reasonably counted on to deliver 30% IOP reduction during the trough and the

TABLE 1. GLAUCOMA'S SLOW PROGRESSION

	Median (db/year)	Range (db/year)	Interquartile range
Normal-Tension Glaucoma (n=57)	-0.22	-4.9 to 1.8	0.65
High-Tension Glaucoma (n=46)	-0.46	-8.7 to 0.2	1.61
Pseudoexfoliation Glaucoma (n=15)	-1.13	-11.3 to -0.1	6.13

Table 1. A 6-year follow-up study to the Early Manifest Glaucoma Trial showed that the three most common types of glaucoma (ie, primary, high-, and normal-tension glaucoma) have a fairly slow yet variable rate of progression. Visual fields were tested every 3 months with the Humphrey 30-2 Full Threshold test program. (Data adapted from: Heijl A, Bengsston B, Hyman L, et al; Early Manifest Glaucoma Trial Group. Natural history of open-angle glaucoma. *Ophthalmology*. 2009;116(12):2271-2276.)

peak of IOP,[11-13] they are contraindicated during pregnancy or in patients with uveitis.[14]

The use of prostaglandins, especially bimatoprost ophthalmic solution 0.03% (Lumigan; Allergan, Inc.), has recently been associated with periorbitopathy, which is a combination of ptosis of the upper eyelid and deepening of the superior sulcus, and possible endophthalmos.[15] This condition is thought to be caused by prostaglandins' anti-adipose tissue characteristic. Generic latanoprost has been commercially available since March 2011, but there is evidence that it may not tolerate long periods of heat.[16] There is some suggestion that generic latanoprost may not be as effective as branded latanoprost solution,[17] but there is, overall, a dearth of quality information about generic medications used in glaucoma. A preservative-free prostaglandin (tafluprost ophthalmic solution 0.0015% [Zioptan]; Merck & Co., Inc.) was recently released and seems to be as effective as other prostaglandins, as well as timolol[18,19] with the added benefit of less adverse effects on the external eye.[20]

Beta-blockers are one of the oldest medications available for glaucoma therapy and are still a good first choice, but unfortunately, they have minimal effect at night. They are contraindicated in patients with asthma, bradycardia, and certain cardiac conditions. Patients on systemic beta-blockers may have a lesser response to the topical formulation.

Carbonic anhydrase inhibitors (CAIs), which suppress aqueous humor production, have been used for more than 50 years in glaucoma therapy. To achieve the desired effect, however, a nearly complete inhibition of carbonic anhydrase isoenzyme II activity in the ciliary body is required. This challenge may explain why the typical response is in the 15% to 20% range. It seems that the effect of topical CAIs are similar to that of oral CAIs.[21] There is some concern about using CAIs in patients with sulfonamide allergy, but there is really no evidence to support that.

Alpha-2 agonists work by suppressing the flow of aqueous humor and increasing the aqueous outflow. They are associated with some systemic side effects, especially with the generic version, which has a concentration of 0.2%. Dry mouth and drowsiness are not uncommon side effects, and alpha-2 agonists are contraindicated in patients younger than 12 years of age because of the risk of central nervous system depression. There is some evidence from the Low-Pressure Glaucoma Treatment Study that alpha-2 agonists are neuroprotective,[22] but the implications of that are unknown at this time.

Finally, miotics are rarely used to control IOP because of the significant side-effect profile associated with their use, especially dimming of vision and induced myopia.

More recently, fixed combinations of medications have become available. They are thought to be at least as effective as their ingredients used separately. Because they represent a simpler regimen, however, combination topical medications may improve compliance.[23] There is also less preservative exposure in a single-drop formulation compared with dosing two drops at the same time. In some cases, combination medications may cost less.

TARGET IOP

The effectiveness of glaucoma therapy is evaluated based on whether it achieves the desired level of IOP, or the target IOP. According to a recent World Glaucoma Association Consensus statement,[24] the target pressure is the IOP range at which the clinician judges that progressive disease is unlikely to affect the patient's quality of life. What this really means is that glaucoma will inevitably progress in almost all patients, and that clinicians should not aim to halt every bit of progression. Rather, it is implied that the goal is to maintain patients' ability to see as long as they are living.

Determining the target IOP should take into consideration the current severity of glaucomatous damage and the IOP at which that damage occurred; the rate of progression, if known; the cost and side effects of treatment; the patient's life expectancy and general health; as well as the status of the fellow eye and family history of severe glaucoma.

To effectively achieve a target IOP, it is beneficial to establish patients' baseline before initiating therapy. As mentioned earlier, prostaglandin analogs are the current preferred first-line therapy, but beta-blockers are a good alternative. A 20% reduction in IOP is a reasonable goal to keep a patient on a given medication, but if it is necessary to modify treatment, medications should be changed one by one. Unilateral medication trials have not proven to be helpful.[25,26]

ADJUNCTIVE AND ALTERNATIVE TREATMENTS

If a patient is started on a prostaglandin but does not achieve a significant response (<10% to 15%), an in-class switch might be the best choice before moving to other types of drugs.[27] There is limited benefit to adding additional medications in terms of achieving all-day control of IOP.[28]

More recently, studies have identified the benefit of SLT for 24-hour control of IOP.[29] SLT is repeatable, unlike other iterations of laser trabeculoplasty, has a good safety profile, and is probably more effective when used earlier in the treatment course. Most importantly, SLT's effect is not influenced by compliance, which is a considerable obstacle to effective glaucoma management.

(Continued on page 13)

Estimating Glaucoma Progression in Clinical Practice

Evaluating both structure and function is necessary to accurately assess the disease's progression.

BY FELIPE MEDEIROS, MD, PHD

The fundamental purpose of glaucoma treatment is to prevent patients from developing functional impairment, that is, loss in quality of vision and quality of life. Recent studies have suggested that even relatively early changes in the visual field, as measured by standard automated perimetry (SAP) may already significantly impact an individual's quality of life. Based on questionnaires given to subjects in the Los Angeles Latino Eye Study,[1] researchers found a close relationship between visual field loss on SAP and patients' perception of their visual disability. In order to assess the risk for development of functional impairment, it becomes essential to estimate the rate of disease progression.

MONITORING VISUAL FIELD LOSS

Figure 1 shows a schematic plot of disease severity (vertical axis) versus time (horizontal axis), from age at diagnosis until death. It also shows a "disability zone," where the disease is severe enough to significantly affect the patient's quality of vision and the ability to perform daily activities, such as read, use a computer, or drive. If the disease progresses at a relatively fast rate, it may become severe enough during the individual's lifetime that he or she is likely to enter the disability zone. On the other hand, a disease that is progressing relatively slowly may never reach a point in which it would significantly impact quality of vision. From Figure 1, we can see that both an early diagnosis as well as a relatively slow rate of change will have to be achieved in order to prevent patients from reaching the disability zone.

MEASURING THE RATE OF VISUAL CHANGE CLINICALLY

Rates of visual field loss can be measured using SAP in clinical practice, as shown in Figure 2. However, is it enough to simply measure the rate of functional change over time in order to estimate the risk of functional

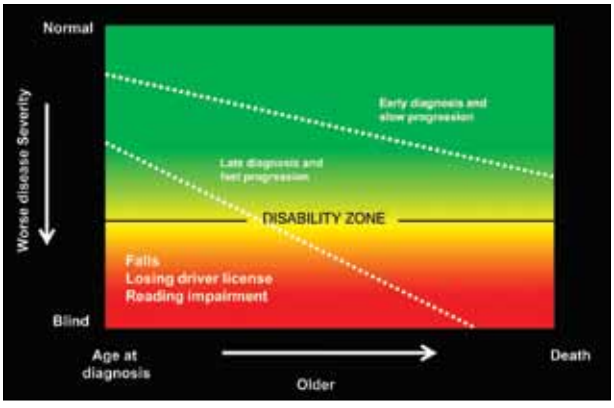

Figure 1. The relationship between the severity of glaucoma and the time from the disease's diagnosis until a patient's death. In order to prevent patients from developing functional impairment (falling into the "disability zone"), glaucoma must be diagnosed at an early stage and maintained at a relatively slow rate of change over time.

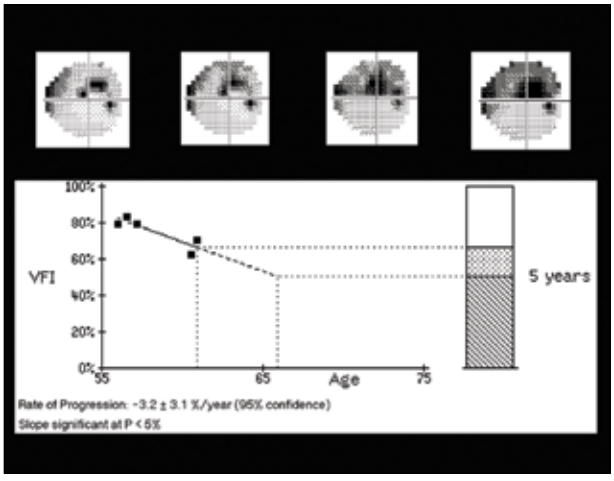

Figure 2. An example of the rate of functional change for a glaucomatous eye as measured by standard automated perimetry.

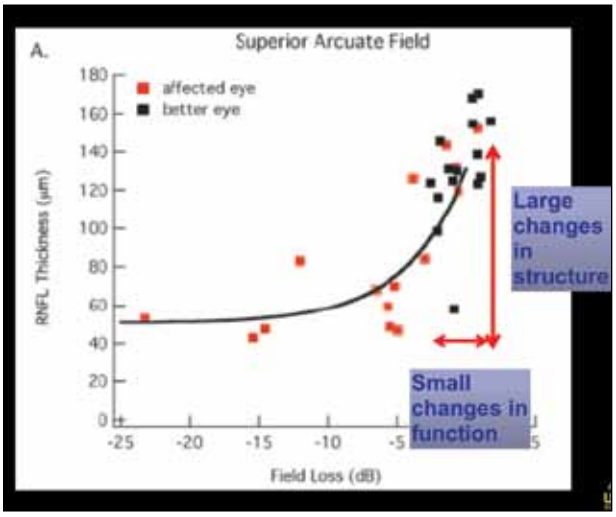

Figure 3. Curvilinear relationship between structure and function. At early stages of disease, large changes in structure (ie, fast rates of neural losses) may correspond to relatively small changes in visual function. (Reprinted with persmission from Hood DC, Anderson SC, Wall M, Kardon RH. Structure versus function in glaucoma: an application of a linear model. *Invest Ophthalmol Vis Sci.* 2007;48(8):3662-3668. Investigative ophthalmology & visual science by Association for Research in Vision and Ophthalmology Copyright 2012 Reproduced with permission of Investigative Ophthalmology & Visual Science.)

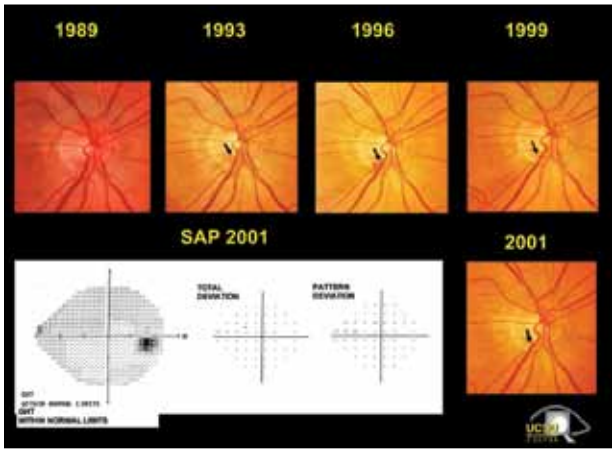

Figure 4. An eye can experience progressive damage to the optic nerve with no correlating visual field loss.

impairment? Recent research has improved our understanding of the relationship between functional and structural changes in glaucoma and has helped us answer this question. Figure 3 illustrates the relationship between functional defects, as measured by SAP, and structural damage, as measured by the thickness of the retinal nerve fiber layer (RNFL) with optical coherence tomography.[2] Note that the relationship has a curvilinear shape; that is, in the early stages of the disease, large changes in RNFL thickness will correspond to only relatively small detectable changes in function. In contrast, in the late stages of disease, large changes in function will correspond to only relatively small detectable changes in structure. This curvilinear relationship seems to be mostly explained by the logarithmic scaling of visual field sensitivity data. The analysis of the structure-function relationship has an obvious implication, which has been widely confirmed by many studies in this area: SAP in general will perform relatively poorly for detection of early glaucomatous damage.[3] Another implication, which has received far less attention but which may be even more important, is that not only may SAP fail in diagnosing early damage, but it may also underestimate the rate of the disease's progression in its early stages. That is, when measured by SAP,

(Continued on page 14)

TABLE 1. MEASURING THE RATES OF CHANGE IN STRUCTURE

Imaging Technology	Study	Parameter	Mean Rates Of Change	
			Progressors	Nonprogressors
CSLO	Alencar et al.	Rim area	-0.0058	-0.0073
	Poli et al.	Rim area	-0.0123	NA
	See et al.	Rim area	-0.0053	-0.0012
GDx-ECC	Medeiros et al.	RNFL thickness	-1.24	-0.34
	Grewal et al.	RNFL thickness	-1.11	-0.14
GDx-VCC	Medeiros et al.	RNFL thickness	-0.70	-0.14
Stratus OCT	Medeiros et al.	RNFL thickness	-0.72	-0.14
	Leung et al.	RNFL thickness	-3.30	NA

The Evolving Role of Imaging in Glaucoma Diagnosis

OCT imaging, combined with clinical features, should aid clinicians with diagnosing glaucoma.

BY LINDA M. ZANGWILL, PHD

Advances in imaging capabilities within ophthalmology have evolved rapidly over the past 2 decades. Confocal scanning laser opthalmoscopy was commercialized around 1992, and for a short time, it was the industry standard until time-domain optical coherence tomography (TD OCT) was introduced in 1996. Just one decade later, in 2007, the release of spectral-domain (SD) OCT again changed the ability to appreciate microscopic and, perhaps, subclinical retinal architectural changes.

Whereas 20 years ago, it was revolutionary to be able to view surface topography of the optic disc with artificial or arbitrary reference planes, it is now standard to directly measure the nerve fiber layer (NFL) and obtain an automated disc-margin outline of the optic nerve head with SD OCT. This technology, which is tantamount to 3D virtual histology, allows for segmentation of the macula and ganglion cell layer. It is capable of high reproducibility, better quality control than previous iterations of OCT, and new software permits automated progression analysis.

IMAGING IN CLINICAL PRACTICE

The principle advantage of SD OCT is that the clinician can visualize subtle changes in the macula and NFL that might not be detectable on photograph (Figures 1 and 2). In terms of measuring the NFL, SD OCT images are equally as diagnostic as TD OCT.[1-4] The faster image capture inherent to SD OCT becomes relevant in analyzing the ganglion cell complex in conjunction with measurements of the NFL. Regardless of the severity of the disease, measurements of both the ganglion cell complex and the NFL are equally predictive of glaucoma,[5-9] whereas measurements of the rim area tend to have poor predictive power.[7,10,11]

There are several SD OCT devices available on the US market with varying degrees of axial resolution, acquisition rates, and other features. For instance, while the RNFL is measured in a 3.4-mm diameter circle centered on the disc on the Spectralis (Heidelberg Engineering, Inc.), Cirrus (Carl Zeiss Meditec, Inc.), and on the RTVue (Optovue, Inc.), research that my colleagues and I conducted showed that the RTVue yields an NFL measurement that is approximately 10 µm thicker than that of the Cirrus and Spectralis.[12] However, in terms of diagnostic accuracy of RNFL measurements for differentiating between glaucoma and healthy eyes, the area under the receiver operator characteristic curve is virtually identical among these devices.[12] Moreover, compared to their internal normative databases, each device will likely display NFL thinning to a similar extent (Figure 3). In contrast, SD OCT instruments vary in how they measure the ganglion cell complex from macular scans, with some instruments such as the Cirrus measuring it by including two layers, the ganglion cell layer and the inner plexiform layer. Other instruments, such as the RTVue, include three layers: the ganglion cell layer, inner plexiform layer, and nerve fiber layer.

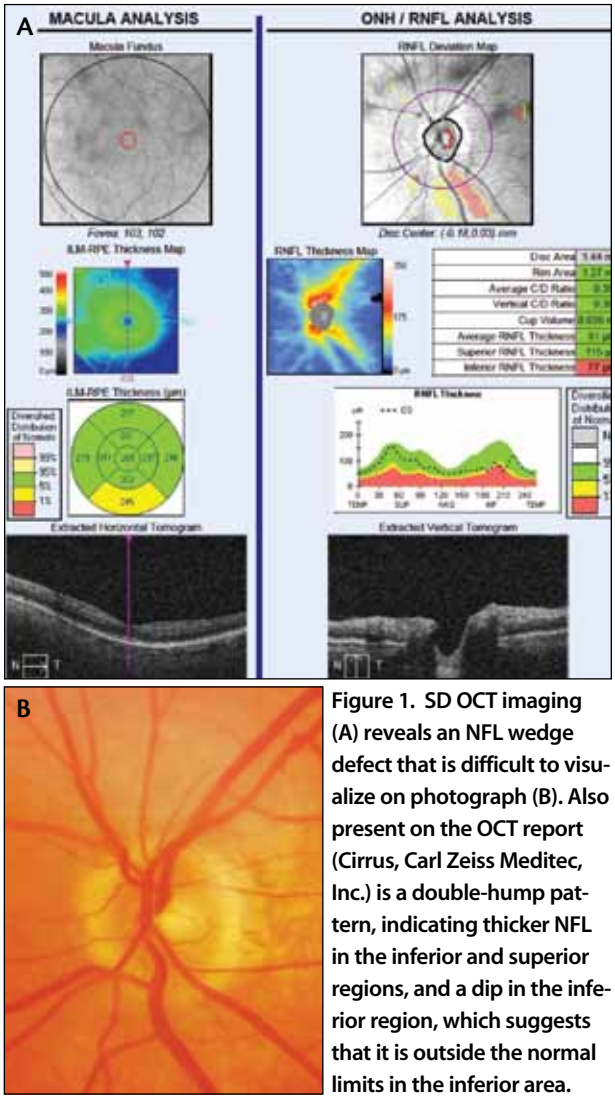

Figure 1. SD OCT imaging (A) reveals an NFL wedge defect that is difficult to visualize on photograph (B). Also present on the OCT report (Cirrus, Carl Zeiss Meditec, Inc.) is a double-hump pattern, indicating thicker NFL in the inferior and superior regions, and a dip in the inferior region, which suggests that it is outside the normal limits in the inferior area.

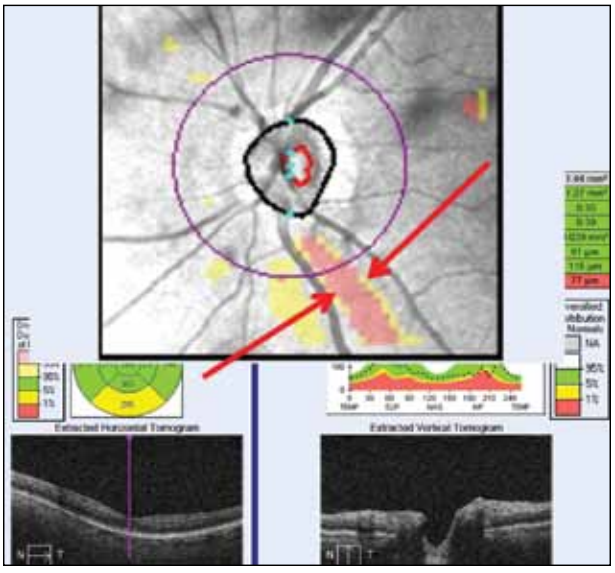

Figure 2. A close-up of the NFL map shows areas of thinning compared with healthy eyes.

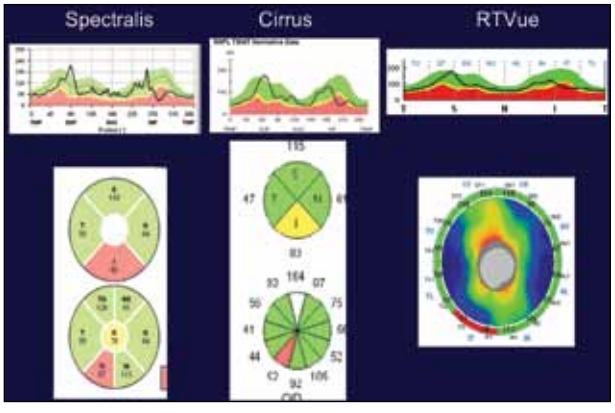

Figure 3. In an eye with early glaucoma, thinning of the NFL in the inferior region is visualized differently on printouts from Spectralis, Cirus, and RTVue devices. Regardless, the pattern of thinning is similar on all three.

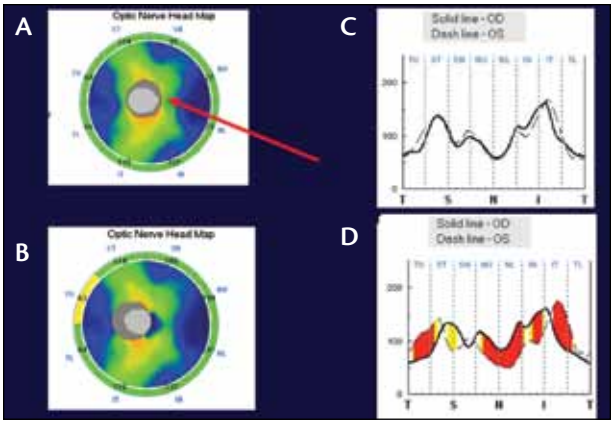

Figure 4. The difference between a correct disc margin location (A) and an incorrect one (B) can yield the difference between an eye with symmetrical results (C) and asymmetric findings (D).

CAVEATS TO USING OCT IMAGING

Regardless of the particular SD OCT device used, clinicians and their staffs must be mindful of the limitations of this imaging technology. In the same way that a poor-quality photograph may provide little information for clinical decision making, so too are image capture devices capable of returning poor-quality scans that muddle the clinical assessment.

Something to be cognizant of when reviewing OCT-generated reports is whether the device performed as desired. For example, it is possible for OCT devices to misalign the disc margin and yield an image with potentially confusing information (Figure 4). All of the OCT devices have indicators of the signal strength as a way to predict the image's quality. However, these automated quality measures do not identify every possible imaging problem (such as inappropriate placement of the disc margin), so it is still incumbent upon the clinician to carefully evaluate an image.

CONCLUSION

SD OCT technology offers higher scanning speed and increased reproducibility compared with TD OCT, while newer software offered with current devices adds higher resolution. Taken together, these characteristics help capture detailed images of the NFL, ganglion cell complex, and optic nerve head that can help the clinician assess the health of an eye well before visual changes take place. Evidence suggests that measurements of the NFL and ganglion cell complex have better diagnostic accuracy than analysis of the optic nerve head for detecting glaucoma. Although there is limited evidence from longitudinal studies, these metrics will likely help determine architectural changes earlier in the disease course, and they may also be useful for tracking the progression of this chronic disease. Despite all of the worthy information available from SD OCT devices, they are not intended as standalone tools, and results should be evaluated in the context of other clinical data including assessment of visual function. ■

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Redefining the Dry Eye Treatment Strategy

Treatment of this disease must keep pace with clinical research findings.

BY WELDON HAW, MD

Dry eye disease is highly prevalent in the United States. It is often underdiagnosed, underappreciated, and undertreated. Several studies indicate that dry eye disease is an immense public health burden. It is estimated that more than 3 million women and 1 million men over the age of 50 have dry eye syndrome.[1] In 2002, it accounted for approximately $540 million in sales of artificial tears, and contributed to more than $5,000 in lost productivity per year per patient.[2] The disease's impact will continue to increase as the American population ages; the number of patients over the age of 75 is expected to nearly triple by the year 2050.[1,3]

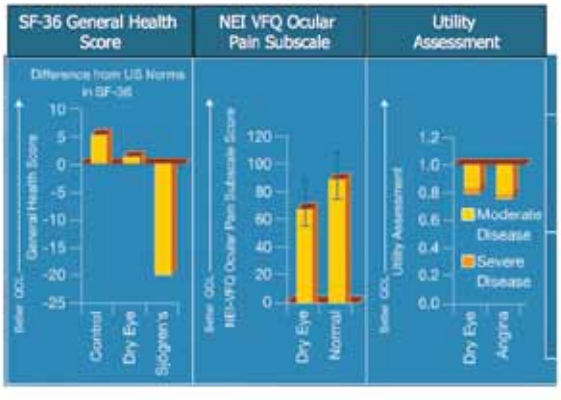
Figures such as these indicate that dry eye disease is not as easily understood and treated as previously thought. In order to manage this condition successfully and improve ophthalmic patients' quality of life, practitioners must reconsider their treatment strategies in favor of more individualized attention.

CONTRIBUTING FACTORS AND VISUAL IMPACT

A number of factors can contribute to the onset of dry eye disease: systemic medications, alcohol intake, inherited conditions, windy environments, pollutants in the air, and visual tasks such as prolonged computer use. The two predominant risk factors, however, are uncontrollable: advancing age and female gender.[4,5] Menopausal hormonal therapy, particularly estrogen therapy, has been associated with dry eye disease.[6] So too is the average American diet, because it is deficient in omega-3 fatty acids,[7] which may be protective.

The Ocular Surface Disease Index (OSDI) and other FDA-valid patient questionnaires (the Short Form 36,[8] the NEI-VFQ Visual Function Questionnaire,[9] and the Utility Assessment[10]) have confirmed that patients with dry eye have compromised visual function, which may significantly adversely impact a patient's quality of life (Figure 1).[11] On the Utility Assessment, dry eye's impact on quality of life ranked on par with moderate-to-severe angina, because a compromised ocular surface affects patients' visual performance. Patients with dry eye disease can have monocular diplopia, glare and halos around lights, and significantly diminished contrast. In addition, dry eye syndrome is an often-overlooked cause of unhappiness in our postoperative cataract[12] and refractive surgical patients. We surgeons must not forget that the ocular surface and the tear film are really the "first" refractive surface.

A



B

Quality-of-Life Measure	Dry Eye Impact
Short Form-36 (SF-36)	Lower pain, vitality, and general health scores than normal individuals
National Eye Institute Visual Function Questionnaire (NEI-VFQ)*	Worse ocular pain (dry eye, 78.6 ± 17.8 units; normal, 90 ± 15 units)
Utility Assessment	Impact comparable to angina (mean utility: dry eye, 0.72 to 0.78; angina, 0.71 to 0.75; normal: 1.0)

*Lower scores indicate more symptoms and quality of life, respectively.

Figure 1. Dry eye compromises patients' visual function (A and B). (Data adapted from: 1. Mangione CM, Lee PP, Pitts J, et al. Psychometric properties of the National Eye Institute Visual Function Questionnaire (NEI-VFQ). *Arch Ophthalmol.* 1198;116:1496-1504. 2. Schiffman RM, Walt JG, Jacobsen G, et al. Utility assessment among patients with dry eye disease. *Ophthalmology*. 2003;110:1412-1419. 3. Nichols KK, Smith JA. Association of clinical diagnostic tests and dry eye surveys: the NEI-VFQ-25 and the OSDI. *Adv Exp Med Biol.* 2002;506(Pt B):1177-1181.)

THE EVOLVING ETIOLOGY OF DRY EYE

The healthy tear film consists of a mucin layer, an aqueous layer, and a lipid layer.[13,14] The mucin layer is produced by the goblet cells in the conjunctiva and ensures uniform wetting over the ocular surface; it protects the ocular surface during blinking. The lacrimal glands produce the aqueous layer, which maintains an appropriate

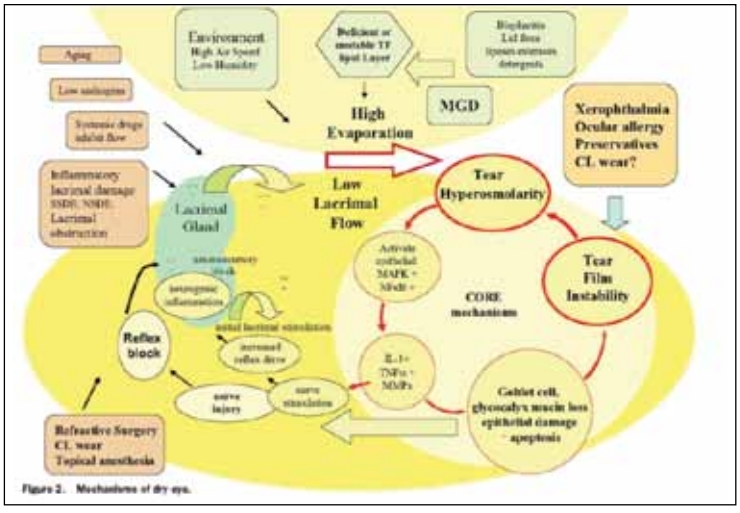


Figure 2. This chart from the 2007 DEWS report shows an updated understanding of the mechanisms of dry eye. (Reprinted with permission from the 2007 Report of the International Dry Eye Workshop. 2007;5(2):25.)

environment of proteins, electrolytes, and cytokines. The third component, the lipid layer, is produced by the meibomian glands and minimizes tear evaporation.

Ten to 15 years ago, the understanding of dry eye pathogenesis was incomplete. Since that time, we have learned that significant dysfunction in the meibomian glands can result in highly evaporative conditions that exacerbate dry eye disease. Factors such as age and androgen levels primarily impact the lacrimal glands. Neurogenic blockade from the cornea to the lacrimal gland can compromise the ocular surface. Central to the development of dry eye disease is the hyperosmolarity environment, in which inflammatory cytokines proliferate and adversely impact the ocular surface. This surface inflammation produces several anatomical changes, including degradation of the epithelial barrier, and over the long-term, it may cause an eventual reduction in goblet cell density. All of these factors cause dry eye to worsen. Thus, an updated definition of dry eye disease should reflect its multifactorial nature as well as identify osmolarity and inflammation as key components of the disease's development (Figure 2).

DIAGNOSIS

Today, we ophthalmologists have a number of tools available to assist us with assessing ocular surface disease, starting with the patient's history and symptoms, testing the tear film's quantity and quality, and ocular surface staining.[15,16] We can also perform more specialized tests such as serology or rheumatology evaluations. In my opinion, the patient's history of symptoms is one of the most important pieces of information, because ocular dryness is a symptoms-based disease. Talking with the patient and/or having him or her complete an OSDI questionnaire provides insights into the severity of symptoms of the disease.

Although diagnostic tests are important as far as confirming the signs of the disease and grading its severity, the results often correlate poorly with the symptoms. Osmolarity tests have the highest degree of accuracy in terms of positive predictive value and specificity (Table 1), but many practitioners do not have the ability to perform this test in the office. The Schirmer test has moderately specificity but low sensitivity. Staining of the ocular surface can produce variable results—fluorescein dye stains frank corneal epithelial defects, and specialized staining such as rose Bengal and lissamine green are good for identifying devitalized conjunctival epithelial cells and perhaps are more sensitive indicators.[17,18] Corneal staining has satisfactory sensitivity and better specificity. Tear breakup time, which measures the quality of the tear film, is a hallmark of dry eye disease;[17] a breakup time of less than 10 seconds is usually considered abnormal.[19] This test, however, has good sensitivity but poor specificity (Table 2).

PRACTICE GUIDELINES

A number of entities have attempted to characterize, stratify, and provide guidelines for the treatment of dry eye disease, from the American Optometric Association in 2002,[20] to the American Academy of Ophthalmology with its published *Preferred Practice Patterns* in 2003,[21] to

TABLE 1. TESTS WITH HIGHEST LEVEL OF ACCURACY

Test	Refer.	Cut-Off Value	Sensitivity (%)	FPR (%)	Specificity (%)	PPV
Sch + Osmol	†Farris	<1mm/min; >312	25	0	100	100
Lacto + Osmol	†Farris	>90; >312	35	0	100	100
TTR + Evap + Osmol	†Khanal	<12%; >33; >317	38	0	100	100

Specificity is proportion of normal population with negative result.
PPV is the probability of truly having Dry Eye Disease with a positive result.
(Adapted from the 2007 Report of the International Dry Eye Workshop. 2007;5(2):113.)

Dry Eye Testing Method	Sensitivity	Specificity
Schirmer Tear Test	42%	76%
Tear Break Up Time	92%	17%
Corneal Staining	63%	89%
Questionnaire	89%	72%

Table 2. Dry Eye Testing Method. (Data adapted from Versura P, Frigato M, Cellini M, et al. Diagnostic performance of tear function test in Sjogren's syndrome patients. *Eye* (Lond). 2007;21:229-237.)

the International Task Force (ITF) in 2006, which served as the foundation for the DEWS Report in 2007.[22]

The ITF categorized dry eye in terms of *episodic* and *chronic*. It identified episodic patients as those with intermittent, mild symptoms that usually related to environmental conditions; these patients, according to the ITF, can be managed with artificial tears alone. On the other hand, the ITF recommended that patients with dry eye symptoms that are always present or are moderate-to-severe in presentation could potentially benefit from additional therapy, such as topical cyclosporine.

The DEWS Report classified patients based on the severity of their symptoms, again with diagnostic tests playing more of a secondary role. The key symptoms in this classification are: use of artificial tears, ocular discomfort, ocular fatigue, and visual disturbance. This report also classified dry eye into four severity ratings based on the frequency of the occurrence and the impact on the patient's quality of life.

TREATMENT CONSIDERATIONS

Categorizing Treatment

In managing dry eye, the first step is to treat the treatable. Mechanical defects such as exposure keratopathy, lagophthalmos, and ectropion should be treated as necessary.

The DEWS Report proposed several specific guidelines for treating dry eye. For mild, episodic dry eye disease, the first step is patient education about environmental factors and augmenting the tear film with artificial tears.

For patients with more moderate dry eye disease—episodic, chronic, or stress-induced—topical cyclosporine ophthalmic emulsion is used, which is safe as a long-term topical anti-inflammatory. It is also beneficial to use topical steroids concomitantly as a short-term pulse therapy to improve the ocular surface. If punctal plugs will be used, it is recommended to first control any corneal inflammation and/or initiate a short course of pulsed steroids prior to placing the plugs. Additionally, doxycycline and the tetracyclines can be useful therapies to control inflammation and improve the quality of the tear film.

For patients with more severe or frequent dry eye disease, strategies such as autologous serum, specialty contact lenses, or permanent punctal occlusion are useful. Individuals with grade IV dry eye syndrome require oral anti-inflammatory medications, such as cyclosporine, and/or surgery, such as tarsorrhaphy or amniotic membrane transplantation.

IS THERE A ROLE FOR NUTRITIONAL SUPPLEMENTS?

Is there benefit to prescribing dietary changes, such as incorporating omega-3 fatty acids? Humans cannot synthesize essential fatty acids, and we must therefore absorb them from dietary sources. Omega-6 fatty acids are the precursors of proinflammatory mediators, the so-called "bad" omega fatty acids that are overabundant in the standard American diet. Omega-3 fatty acids inhibit the synthesis of inflammatory mediators. Used alone as a dietary supplement, omega-3 fatty acids may improve ocular surface irritation and staining.[23] These fatty acids are available in oral supplements or from certain types of fatty fishes, such as salmon and mackerels, as well as walnuts and flax seeds.

TOPICAL THERAPIES

Doxycycline and the macrolides (minocycline and azithromycin) inhibit lipase production and nonspecific matrix metalloproteinases. Doxycycline is useful to start at 100 mg twice per day and can be titrated to the clinical response to as low as 20 mg once per day.[24] Azithromycin 1% ophthalmic solution has also been reported to help improve the quality of the tear film.[25] Artificial tears are falling out of favor for patients with more than moderate dry eye disease, because they do not directly impact the cause or inflammation of the condition,[26-28] nor do they prevent its progression.[29] A testament to artificial tears' lack of efficacy is that many patients report having tried three or more brands on average before seeking an opinion from an eye care professional.[30]

CYCLOSPORINE

New data suggest that topical cyclosporine may alter the natural course of dry eye disease. The recent Dry Eye Progression Study[32] enrolled 74 patients with moderate-to-severe dry eye disease (grade II or III) who were randomized to receive either topical cyclosporine ophthalmic emulsion or an artificial tear vehicle. After 1 year, those in the cyclosporine group showed statistically significant improvements in their Schirmer scores, tear break-up time, and goblet cell density, whereas those who received artificial tears showed a decline in all these markers. Most telling, however, was that the patients in the cyclosporine group were less likely to exhibit progression of the disease, and some patients in that group had even experienced an arrest of the disease.

NEW TREATMENT APPROACH

Given the new information we have learned about dry eye disease in the past few years, what is the best way to

approach its treatment? It is no longer enough to simply hand patients artificial tears until they return for something stronger. If we view dry eye disease as a potentially progressive condition, where treatment with artificial tears alone progresses the disease, we are doing a disservice to our patients. Furthermore, if we wait until patients have progressed to level 4 of the disease, when the lacrimal glands are replaced with scar tissue, the effective window of treatment with topical cyclosporine, the strongest medication we have available today, will already have been lost.

I believe the best approach to treating dry eye disease now is a risk assessment approach that identifies risk factors for the progression of the disease and classifies patients according to their severity level. With that information, we can then tailor the treatment to the individual and their potential risk for the development of severe and progressive dry eye disease. ■

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CONCLUSION

Research and development efforts in glaucoma offer several promising alternatives to currently available treatments, including preservative-free formulations, new classes of drugs, new delivery methods, and new targets in therapy (ie, neuroprotection). Until these new modalities are available, there are a wide variety of effective and safe medical and therapeutic options. How a given treatment option is used may be equally as important as the choice of therapy itself. ■

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patients may appear to be progressing relatively slowly, when in fact they may be losing nerve tissue at relatively fast and dangerous rates. (Figure 4).

Although photographs can help detect progressive changes to the optic disc, they have several limitations, such as the need for subjective assessment and pupil dilation. Most importantly, they do not provide us with objective and quantitative measures of the rate of structural loss over time. To address this problem, we can use imaging devices that can provide objective and reproducible measurements of structural damage to the optic disc and RNFL. A number of studies have been conducted measuring rates of glaucomatous damage using various imaging modalities, such as scanning laser polarimetry, confocal scanning laser ophthalmoscope, and optical coherence tomography. These studies have consistently shown that these technologies can provide objective measurements of rates of glaucomatous damage over time. (Table 1).[4] These instruments may be used to assess the rate of the disease's deterioration, especially at relatively early stages of damage, thus giving us an indication of the velocity of neural losses and helping us to determine the risk of development of functional impairment in the disease.

STRUCTURE AND FUNCTION SHOULD NOT NECESSARILY AGREE

From the curvilinear relationship shown in Figure 3, it should be clear that structural and functional losses relating to glaucoma over time may not necessarily agree. Relatively fast rates of structural damage may be present in the early stages of the disease and be associated with no detectable rates of functional loss. In contrast, in late stages of damage, structural measurements seem to become less sensitive to change and, therefore, fast rates of functional deterioration may be present despite the absence of detectable structural losses as measured by currently available technologies. This observation highlights the importance of applying strategies to combine structural and functional measurements in order to better detect rates of disease deterioration in clinical practice.[5-8]

CONCLUSIONS

Glaucoma management should be directed toward preventing a decrease in patients' quality of vision during their lifetimes. The measurement of the rate of glaucoma progression is an essential component of both the diagnosis as well as the management of the disease. Due to the limitations of currently available technologies, it is essential to evaluate the rates of both structural and functional changes over time. Strategies to combine structural and functional measurements may result in a significant improvement in our ability to diagnose glaucoma and measure its rate of change. In addition, incorporating risk factors into strategies that combine structure and function may result in even further improvement in our ability to predict and prevent the development of functional impairment from this disease.[6-8] ■

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Name _____ ❑ MD participant ❑ non-MD participant

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CME QUESTIONS

1. What are the two most predominant risk factors for dry eye disease?

a. environmental pollutants and prolonged computer use

b. systemic medications and alcohol consumption

c. windy environments and inherited medical conditions

d. female gender and advancing age

2. What are the two key components of the etiology of dry eye disease?

a. age and androgen levels

b. osmolarity and inflammation

c. evaporative conditions

d. none of the above

3. What type of testing offers the greatest degree of accuracy for dry eye disease?

a. osmoloarity tests

b. Schirmer's

c. ocular surface staining

4. With which type of glaucoma is disc hemorrhage most often associated?

a. low tension

b. open-angle

c. high tension

d. all types

5. Disc hemorrhages usually occur adjacent to or within the retinal nerve fiber layer.

a. true

b. false

6. Measurements of the ganglion cell complex tend to be more predictive of glaucoma than measurements of the NFL.

a. true

b. false

7. Which type of imaging device is better for viewing the NFL?

a. TD OCT

b. SD OCT

c. They are equally diagnostic

8. In the Early Manifest Glaucoma Trial, what was the yearly progression of glaucoma in the average untreated patient?

a. 0.1 decibels

b. 0.3 decibel

c. 0.5 decibel

d. 1.0 decibel

9. Studies have found what type of relationship between nerve fiber layer thickness and visual field loss?

a. curvilinear

b. positive

c. negative

d. none

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Would you recommend this program to a colleague? ❒ Yes ❒ No

Do you feel the information presented will change your patient care? ❒ Yes ❒ No
If yes, please specify. We will contact you by e-mail in 1 to 2 months to see if you have made this change.

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If no, please identify the barriers to change.

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