

The Pros and Cons of Dry-Eye Technologies

A look at the advantages and disadvantages of time-honored methods as well as new techniques and devices.

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As we enter the dawn of dry-eye season and close the chapter on another year, it's an appropriate time to reflect on the current state of dry-eye diagnosis and treatment as well as the prospects for therapeutic development in the coming year and beyond. In August, we ran through a list of dry-eye diagnostic tests, and discussed the critical value of a thorough patient history and a comprehensive discussion between doctor and patient about the patient's ocular health. We also reviewed the standard clinical tests, namely fluorescein, rose bengal or lissamine green staining, tear-film breakup time, Schirmer's tests and fluorophotometry, that are the current diagnostics used in formulating a dry-eye diagnosis. While these tests provide the clinician with clues for diagnosis, it's clear that there's room for improvement.

This month, we'll continue our earlier discussion of testing by reviewing newer technologies and approaches and discussing the pros and cons of this next generation of diagnostic tools.

A Closer Look at Tears

A major focus in dry eye in recent

years has been the role of tear composition and volume. For the past century, physicians have used German ophthalmologist Otto Schirmer's test to measure tear volume, and while 100 years may be enough for any test, it remains an important tool for assessing dry eye. Schirmer's is a simple, convenient test that involves placing a paper wick in contact with the ocular surface to measure tear production. Beyond the issue of reflex tearing, the main drawback with the test is that it's not predictive in terms of disease severity, which limits its value as a diagnostic.

What are the available alternatives to the Schirmer's test? One of the best methods for measuring tear volume in a non-invasive way is based on measuring tear meniscus height.¹ While this can be done by simple visual inspection, instrument-based methods have the ability to measure tear volume in a precise, objective way. A recent study took values for meniscus volumes measured by optical coherence tomography and compared them to the results from other established dry-eye metrics, and found both upper- and lower-lid volumes were significantly correlated with the degree of corneal

fluorescein staining in both Sjögren's syndrome and non-Sjögren's dry-eye patients.² This type of objective measure would be particularly important for studies of dry-eye drugs designed to increase tear flow, such as cyclosporine.

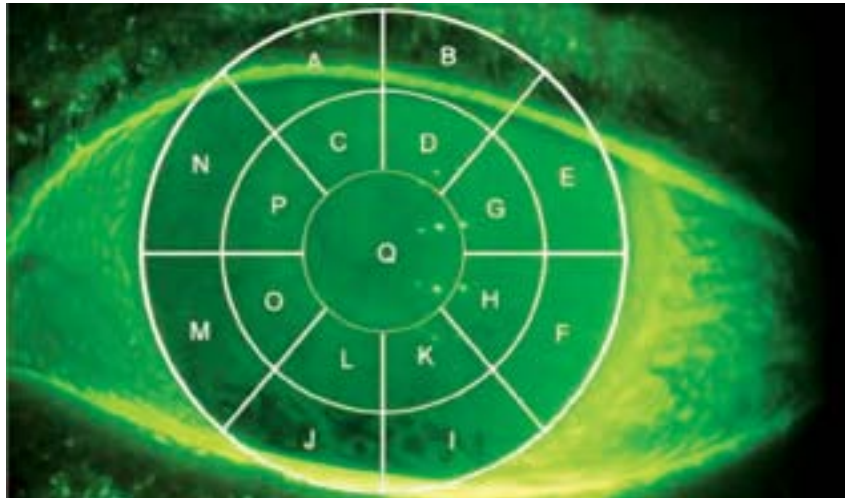
In addition to tear volume, tear osmolarity is also an important biomarker for dry-eye disease, as we discussed in Therapeutic Topics in July of this year. The 2007 International Dry Eye Workshop stated that part of the standard definition of dry eye is that it is "... accompanied by increased osmolarity of the tear film and inflammation of the ocular surface."³ The development of the TearLab osmometer (TearLab, San Diego) has addressed this important aspect of the disease and made it possible to conduct osmolarity measurements in a clinical setting. Despite this, the TearLab system is not a stand-alone diagnostic tool, and has yet to significantly impact the treatment of dry eye or the development of new therapeutics. According to the Food and Drug Administration, it's to be used "in conjunction with other methods of clinical evaluation,"⁴ which may be due to some inconsistencies in

osmolarity measures from the TearLab system. While some reports have confirmed the reliability of the device,⁵ another reported high variability between examiners. The same study suggested that osmolarity values measured with the TearLab device vary significantly depending on where precisely within the tear meniscus the tear film sample is collected. (*Wunderlich K, et al. IOVS 2011;52:ARVO E-Abstract 3797*) It's noteworthy that changes in osmolarity haven't been used as a clinical endpoint in any registered trials of new dry-eye therapeutics on the government website clinicaltrials.gov. Clearly, additional studies correlating accurate measures of osmolarity with other dry-eye signs and symptoms would be useful in developing a better understanding of the relationship between tear osmolarity and dry-eye disease.

New Tools and Technologies

What about other dry-eye diagnostics? Like the Schirmer's test, tear-film breakup time has been a standard dry-eye test for many years. TFBUT has traditionally been measured using fluorescein dye during a "forced-stare" protocol. The stability of the tear film is observable by the breakup of the fluorescent tear film coating the ocular surface (usually in about five to 15 seconds). While the measurements are both reliable and reproducible (dry-eye patients tend to have low TFBUTs), they often don't distinguish dry-eye sufferers from those without signs or symptoms of the disease. To address this, several recent studies have used video capture methods to accomplish two objectives: to measure breakup under more natural conditions than the forced stare; and to examine a related parameter of tear-film stability, tear-film breakup area, or BUA.^{6,7}

Studies of tear-film stability must also take the role of blinking into account. Blinking is the primary mechanism responsible for maintaining the integrity



Video images of corneal fluorescein staining can be manually scored with the aid of a transect grid such as this. However, automated methods of staining analysis are likely to obviate the need for such manual scoring in the near future.

of the ocular surface, since it facilitates the distribution and the formation of the tear film across the corneal surface. The relationship between successive blinks, called the inter-blink interval, and TFBUT define the integrity of the ocular surface. In an ideal system, the TFBUT would match or exceed the IBI, ensuring that the ocular surface would remain protected.

In 2008, we first described the idea of the Ocular Protection Index to quantify the interaction between TFBUT and IBI.⁸ While the use of the OPI provides a context for determining the clinical relevance of TFBUT, increased understanding of the complexities of blink physiology and tear-film breakup has prompted work on alternative methods for evaluation of ocular surface protection under natural visual conditions. The Video Capture Manual Analysis technique provides retrospective analysis of video data of fluorescein-stained eyes while a subject watches television.⁹ A key feature of the VCMA method is that it allows for the simultaneous capture of TFBUT, IBI and tear-film BUA while the subject blinks normally. The VCMA was able to successfully distinguish between dry eye and normal subjects, and therefore provides a clinically relevant analysis of tear-film

stability measured in the context of a natural blink pattern.

Another parameter that's often part of clinical evaluation of dry eye is conjunctival hyperemia. Historically, this evaluation has been done subjectively by a clinical grader using a pre-existing scale. For our own part, researchers here at Ora recently developed objective measures of redness using video capture in combination with software algorithms designed to identify and quantify redness patterns and intensities. This should allow for greater sensitivity and reproducibility of redness grading scores.

The same strategy for automated analysis can be used to improve upon the VCMA approach to studies of tear-film dynamics. Several recent studies (*Griffin J, et al. IOVS 2011;52:ARVO E-Abstract 384; Lafond A, et al. IOVS 2011;52:ARVO E-Abstract 3845; Contractor M, et al. IOVS 2011;52:ARVO E-Abstract 3830*) described the addition of automated analysis to VCMA data in a method designated OPI 2.0. This system, which is designed to automate the process of BUA analysis, has the same features as the VCMA (simultaneous measurement of TFBUT, IBI and BUA) while providing a more precise metric for BUA. This

approach also reduces the human error inherent in the manual analysis while increasing the speed of the overall data assessment process. The OPI 2.0, first described at this year's meeting of the Association for Research in Vision and Ophthalmology, should have a significant impact on the process of dry-eye therapeutic development.

A Better Image of the Surface

For those focused on retinal disease, confocal microscopy has been a diagnostic mainstay for years. More recently, confocal devices have been developed for use in the anterior segment. Several case reports published this year provide specific examples of the ways in which confocal imaging—either traditional confocal or laser scanning confocal—can enhance our ability to quickly and accurately diagnose cases of keratitis or conjunctivitis.^{10,11} These devices are also proving their utility in chronic allergy or infection, where the extent of disease can be associated with the degree of immune cell infiltration or epithelial cell integrity.^{12,13} Increases in dendritic cell infiltration into the central cornea can readily be imaged, as can changes in density of nerve endings in the same tissue that are typical of dry-eye disease.¹³ The true value of these enhanced imaging techniques is their ability to objectively and non-invasively assess the physiological state of the tissues of the anterior segment, including the nerves, endothelium, epithelium and stroma.

How can we use improved imaging technologies to develop new treatments for dry eye? The cornea seems like a good place to start. Confocal techniques have been used in a handful of studies that track the level of corneal innervation as a function of dry-eye severity, duration or both.^{14,15} These studies confirm the notion that patients with dry eye can exhibit either an increase or a decrease in corneal sensitivity, and this is often visualized as an en-

hanced nerve tortuosity. It seems that a key advance that's still needed is a way to quantify these changes as a function of dry-eye disease severity; such objective criteria should pave the way for an acceleration in the pace of therapeutic development.

Recent imaging studies are also adding to our ability to diagnose disorders of meibomian gland function.^{16,17} These studies demonstrate how LSCM can identify critical features of MG health, including mucocutaneous cell density, acinar unit density, meibum gland orifice structure and MG inflammation. As with imaging studies of corneal innervation, a better understanding of meibomian gland disease is likely to impact future therapies for dry eye. We expect that application of LSCM imaging of the ocular surface will provide improved diagnostics for many conditions, and in doing so will make it possible to develop enhanced diagnostic endpoints in future clinical trials.

Putting the New Tools to Work

As we emphasized in the previous column on dry-eye diagnostics, nothing can or will eliminate the need for a good patient history and examination in the diagnosis of dry eye. Despite this, it's reasonable to presume—or, at least, hope—that among the technologies we've considered, at least one will emerge as an effective tool to aid in the early, accurate identification of the disease in all its various subtypes. In addition, defining patient subpopulations is also critical to therapeutic progress, and many studies now focus on those patients with aqueous tear-deficient dry eye or patients with dry eye due to Sjögren's syndrome. We see this combination of an improved ability to identify patient subgroups and the availability of an extended array of objective, quantifiable signs as keys to dry-eye treatments in the future.

There's a wealth of new dry-eye treatments in the pipeline, including thera-

pies from SARcode, Mimetogen and Regenerex. If past experience is any predictor, we fully expect that the new technologies we've described should jump-start development of these and other new dry-eye therapies in 2012 and beyond. **REVIEW**

Dr. Abelson, a clinical professor of ophthalmology at Harvard Medical School and a senior clinical scientist at the Schepens Eye Research Institute, consults in ophthalmic pharmaceuticals. He wishes to thank the medical communications staff at Ora Inc., who contributed to this report.

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Remembering Mitchell Friedlaender, MD

Mitchell "Mitch" Friedlaender—physician, researcher, author, editor, educator and cornea specialist—passed away earlier this year. Possessed of a warm smile, a voice always flavored by humor and gentleness that belied a razor-sharp intellect and wit, Mitch was a true renaissance man. A pianist, singer and writer, he was the quintessential quick study and clear thinker who had a unique ability to summarize his observations without sacrificing clarity. The premature passing of such a revered colleague was a great loss to all of us who worked with Mitch throughout his career. We share this sadness with Mitch's wife Deborah, their children, as well as Mitch's brother and sister.

Mitch was born in Chicago in 1946, with the practice of medicine already in his veins. His father, Dr. Sidney Friedlaender, was an internist and his mother, Dorothy Blum Friedlaender, a registered nurse. Mitch received his undergraduate and medical school education at the University of Michigan, where he graduated *cum laude*. From Ann Arbor, Mitch moved on to do postgraduate training at Harvard University; the University

of California, San Francisco; and Washington University in St. Louis. He subsequently trained in ophthalmology at the Massachusetts Eye and Ear Infirmary. As senior fellow, I found myself



doing battle on his behalf to assure his proper share of cornea transplants ... he was inherently non-confrontational. It was during this time he began what became a lifelong focus on the disorders and treatments associated with the ocular surface, publishing several studies on the effects of topically applied ocular decongestants and antihistamines.

As fellows and colleagues, I always respected his deep knowledge and understanding of immunology and how it might be applied to the eye. In an early synthesis of this field, Mitch wrote the first comprehensive book on ocular allergy, "Allergy and Immunology of the Eye," in 1979. Following his fellowship years, Mitch joined the faculty at UCSF, where he taught and conducted research in addition to maintaining his prac-

tice for more than a decade. He later moved to the Scripps Clinic, where he founded the laser vision center and was most recently head of the ophthalmology division. Mitch co-authored more than 250 scientific papers and six books, and served as editor on several journals, including serving as editor-in-chief of *International Ophthalmology Clinics*. He also made time to found and serve as administrator for two medical societies, the Aspen Corneal Society and the Pacific Ophthalmic Forum. He was a longtime member of the Association for Research and Vision in Ophthalmology and the American Academy of Ophthalmology, and was a recipient of the Senior Honor Award from the AAO. In recent years, Mitch often lectured and taught at universities around the world, primarily on the topics of ocular allergy, immunology and infectious diseases, as well as refractive laser surgery. Aside from these many accomplishments, Mitch was a calm, reassuring presence and a valuable advocate for his patients. We have lost a wise and gentle soul in the passing of Mitchell Friedlaender.

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