PERSPECTIVE
Advances in Understanding and Managing Dry Eye Disease

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• PURPOSE: To present evidence from the literature and scientific meetings to support fundamental changes in concepts regarding the prevalence, pathogenesis, definition, diagnosis, management of dry eye disease (DED) and the prospects for the development of new therapies.

• DESIGN: Analysis and clinical perspective of the literature and recent presentations.

• METHODS: Review and interpretation of literature.

• RESULTS: The tear film and ocular surface form an integrated physiologic unit linking the surface epithelia and secretory glands via a neural network. This sensory-driven network regulates secretory activity in quantity and composition, supporting the homeostasis of the system. The tear film forms a metastable covering between blinks, subserving clear vision, and maintains the health and turnover of the ocular surface cells. Disturbance of intrinsic factors such as increasing age; hormonal balance; systemic or local autoimmune disease, or both; systemic drugs or extrinsic factors including topical medications; environmental stress; contact lens wear; or refractive surgery result in a final common pathway of events at the tear film and ocular surface, resulting in DED. Diagnosis of DED and the design of clinical trials for new drugs have been hampered by a lack of correlation between signs and symptoms and flawed endpoints; successful new drug applications likely will require new approaches, such as the use of objective biomarkers for disease severity.

• CONCLUSIONS: Recent advances in our knowledge of the causation of DED open opportunities for improving diagnosis and disease management and for developing new, more effective therapies to manage this widely prevalent and debilitating disease state. (Am J Ophthalmol 2008;146:350–356. © 2008 by Elsevier Inc. All rights reserved.)

STRUCTURE AND FUNCTION OF THE TEAR FILM AND THE OCULAR SURFACE

OVER THE LAST TWO DECADES, SUBSTANTIAL progress has been made in understanding the structural elements of the tear film, ocular surface, and the associated tissues that form a single integrated unit termed the lacrimal functional unit.¹ This information has led to revised concepts about the way in which the tear film is formed and maintained and the pathophysiologic events operative in the development of dry eye. In addition, it has opened paths for new therapeutic interventions.

Traditionally, the tear film has been thought to consist of three discrete layers, with an innermost mucin layer covering the corneal and conjunctival epithelium, an intermediate aqueous layer produced by the lacrimal glands, and an outermost lipid layer, the product of the meibomian glands of the eyelids²; this concept has been revised substantially. The contemporary concept of the tear–ocular surface structure is that of a metastable tear film consisting of an aqueous gel with a gradient of mucin content decreasing from the ocular surface to the undersurface of the outermost lipid layer. The latter structure interacts with the underlying aqueous and mucin components, retarding evaporative loss of aqueous tears and contributing to the stability of the tear film between blinks.³

The tear film is formed by a blink, which distributes the tears over the ocular surface; immediately after the blink, the tear film starts to thin in an orderly fashion, maintaining a complete aqueous cover until the next blink occurs, reestablishing a thicker film, and the process repeats itself. At least three distinct types of mucin have been identified: transmembrane mucins produced by the corneal and conjunctival cells, gel-forming mucins from the conjunctival goblet cells, and soluble mucins primarily from the lacrimal glands.⁴ The transmembrane mucins contribute to the surface structure of the epithelial cells, interact with the gel-forming and soluble mucins of the tear film to stabilize the film, and provide a cleansing pathway for the ocular surface; lipid–mucin interactions support a relatively stable tear film between blinks.

Accepted for publication May 14, 2008.
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In addition to nourishing the ocular surface and providing for lubrication between the lids and the ocular surface, the tear film serves as the anterior refracting surface of the eye. Recent studies have demonstrated the profound effects on vision when the tear film becomes unstable in dry eye disease (DED; vide infra). All tissues of the ocular surface, secretory glands, eyelids and outflow channels of the nasolacrimal pathway are linked via a neural network (the lacrimal functional unit). Sensory receptors monitor conditions of the tears and cells, sending afferent signals to the central nervous system that, in turn, send efferent impulses to the secretory glands and cells, effecting changes in composition and volume to maintain homeostasis and to respond to stress and injury. Additional factors supporting the tear film–ocular surface complex include bioavailable hormones, primarily androgens, and an intact immune system. This exquisitely balanced system represents a highly complex unit providing our visual access to the external environment. Derangement of any one element leads to a breakdown in overall structure and function with significant clinical effects.

CHARACTERISTICS OF DRY EYE DISEASE

THERE ARE A NUMBER OF RECOGNIZED RISK FACTORS FOR the development of dry eye. These include: aging; female gender; hormonal changes; systemic autoimmune disease (most prominently Sjögren syndrome); decreased corneal sensation; refractive surgery in which the corneal nerves are either severed or ablated; blinking abnormalities; drug effects; viral infections such as human immunodeficiency virus, cytomegalovirus, and hepatitis C; diabetes mellitus; vitamin A deficiency; and graft-versus-host disease. Regardless of which of the initiating factors or groups of factors result in the presentation of dry eye, there is a common final pathway for expression of the disease at the tear film–ocular surface interface. Common features include: an unstable tear film between blinks, elevated electrolyte concentration in tears leading to hyperosmolarity and subsequent damage to the ocular surface, symptoms of discomfort, and a decrease in vision between blinks. Inflammation is a feature in dry eye associated in both Sjögren-associated and non–Sjögren-associated DED. It has been reported that allergy and other inflammatory conditions of the ocular surface can destabilize the tear film. Although the exact place of inflammation in the stream of events leading to ocular surface distress is not clear, its role is unmistakable.

DRY EYE AS A DISEASE

DRY EYE HAS A NUMBER OF NAMES ASSOCIATED WITH IT. These include: keratoconjunctivitis sicca, dry eye syndrome, and the more recently suggested dysfunctional tear syndrome. Dry eye develops in response to the presence of one or more risk factors listed above; in addition, environmental, workplace, or recreational stress—for example, arid atmosphere, constant wind currents, the presence of a contact lens, and prolonged use of video display screens—are factors that can initiate and exacerbate the disease process. The features of dry eye are those of a specific disease process, and dry eye is, therefore, a disease. The use of the term syndrome, which is a collection of presenting signs usually applied to multiple organ systems, tends to trivialize a discrete and debilitating disease.

The term dry eye has been criticized recently as not being fully descriptive of a process that, in some patients, may be characterized primarily by qualitative changes in the tear film, and the substitute dysfunctional tear syndrome (DTS) has been proposed. Although this term is arguably more descriptive, dry eye is embedded not only in the medical literature but also in lay writing and is used in other languages. At a recent large international dry eye workshop, DTS was rejected as a substitute, and the term dry eye disease was accepted and is used in the recently published Report of the International Dry Eye Workshop (DEWS).8

PREVALENCE OF DRY EYE DISEASE

IT HAS BEEN KNOWN FOR MANY YEARS THAT DED IS A common clinical problem. Only recently, however, have valid quantitative data appeared that document the extent of DED. Surveys over the last 20 years have estimated the prevalence of DED to be between 5% to more than 30% at various ages. Different definitions of the disease at use in various studies make comparison difficult. In a survey by the American Academy of Ophthalmology, respondents reported that approximately 30% of patients seeking treatment at an ophthalmologist’s office have symptoms consistent with DED. In several large studies, it is estimated that just fewer than 5 million Americans 50 years and older have moderate to severe DED. Other estimates, which include subjects reporting dry eye symptoms some of the time or in response to certain environmental, workplace, or recreational activities, range as high as 20% of the American population. It is thought that European and Asian populations have a similar or slightly higher prevalence. With the aging of populations in developed countries, it is likely that the numbers of subjects with DED will increase substantially. In younger subjects, the spread of refractive surgery in which the corneal nerves are either severed or ablated is associated with a high incidence of postoperative DED. Although there is some debate as to the extent to which this is true DED or a form of neurotrophic keratopathy, symptoms of DED occur in more than 50% of laser in situ keratomileusis patients. A
significant group has continuing symptoms for months to even years after surgery.14 Although irritation has been the primary symptom associated with DED, other limiting factors relating to vision loss have added to the impact on the quality of life of patients. This impact has been measured in a number of ways. Specific questionnaires measure effects of DED on activities of daily life such as reading, computer use, driving, pain and irritation, and general health and well-being.15,16 These have demonstrated a significant degradation in the quality of life in those with DED. Utility scores, another measure of impact on quality of life, have shown that patients with DED rate the severity of impact on their lives as similar to those patients with moderate angina.17 DED is increasingly recognized as one of the most commonly encountered diseases with a substantial effect on peoples' lives and sense of well-being that limits important daily activities and leads to a significantly reduced quality of life.

**DRY EYE DISEASE AND MICROBIAL INFECTION**

THE EXTERNAL EYE HAS A NUMBER OF DEFENSE MECHANISMS that protect the ocular surface against microbial infection.18 These include mechanical factors such as tearing and blinking, which remove noxious agents from contact with the ocular surface. In addition, immunity plays an important role. The immune system operating at the ocular surface is complex, involving both an immediate local innate system comprising cells and mechanisms that defend the host from infection by other organisms. Protective cells include Mast cells, neutrophils, macrophages, dendritic cells, basophils, and eosinophils. Access to systemic cells may be facilitated by local neurogenic inflammation.19 In addition, immunomodulating proteins, for example, lactoferrin, lysozyme, toll-like receptors, complement, neuropeptides, and many other of the more than 500 proteins contained within aqueous tears, form an adaptive immunity mediated by systemic responses (e.g., T cells). Although the relative roles of these two forms of immunity in the protection of the eye from noxious influences are, as yet, unclear, their effectiveness is clear.

It is commonly thought that patients with DED are more susceptible to microbial keratitis than the general population. This is, however, poorly documented in the literature.5 Most of the reports concern cases of patients with comorbid conditions, for example, systemic autoimmune disease, particularly rheumatoid arthritis, or other factors such as surgery, trauma, or contact lens wear. Ocular surface disease or keratopathy is mentioned as a predisposing factor, but no further characterization of the condition is provided.20,21 This has given rise to a misleading impression that even small amounts of surface disruption may predispose patients to microbial keratitis.

Although it is intuitive to think that interruption of the barrier function of the corneal epithelium manifest by corneal fluorescein staining would lead to a susceptibility to infection, my clinical experience is that microbial infections are quite rare in the absence of the comorbid factors mentioned above or other conditions such as exposure keratitis, graft-versus-host disease, or other systemic immunologic disorders.

The risk for microbial keratitis in DED without these other factors would seem to be of a very low order in that given the wide prevalence of the DED, there are a limited number of cases of microbial keratitis seen, and these are usually associated with the comorbid conditions mentioned above. Corneal staining itself, especially in the peripheral inferior cornea, commonly is seen in non-DED subjects and usually is a late sign in DED patients (vide infra).22 Were staining an indicator for risk for microbial keratitis in DED, there would be many more cases than practitioners encounter in practice. It is probable that the redundant defense mechanisms at play in defending the external eye against infection are effective even in dry eye patients, unless they are compromised by one or more of the additional risk factors mentioned.

**DRY EYE DISEASE AND ITS EFFECT ON VISION**

PATIENTS WITH SYMPTOMS OF OCULAR IRRITATION SUGGESTIVE of DED often also report more vague problems such as sensitivity to light, a decrease in reading, night driving difficulties, or ocular fatigue. Only in the past several years has it been recognized that these symptoms can be attributed to the effects of DED on vision. It is a common clinical experience that standard visual acuity (VA) testing with Snellen or Early Treatment Diabetic Retinopathy Study (ETDRS) charts seldom reveals a significant drop in vision in DED patients until they exhibit moderate to severe staining of the central cornea. Early in the course of development of DED, however, the tear film becomes unstable between blinks.23 An initial compensatory response to this is rapid blinking to reestablish momentarily a continuous tear film necessary for clear vision; this allows a patient to read the eye chart quickly. What is now known, however, is that the tear film quickly breaks up after blinking, resulting in a substantial interblink degradation of vision. Japanese studies have documented that, unlike normal eyes, within 3 to 4 seconds after a blink, the VA in dry eye patients can decrease to 20/40 to 20/60, leading to serious problems in reading and driving.24 These experiences are difficult for the patient to describe, but their effects on important activities of life can be appreciated more fully now. Continual attempts to compensate for this phenomenon with rapid blinking lead to ocular fatigue.
CURRENT CHALLENGES IN THE DIAGNOSIS AND MANAGEMENT OF DRY EYE DISEASE

IT IS A COMMONLY HELD OPINION THAT DED CAN BE diagnosed largely on the basis of patient symptoms. Recently, a number of studies have called this impression into question. Only a small percent of patients with DED have been diagnosed. It has been documented that symptoms of DED do not necessarily reflect the severity of the disease. Clinicians have long known that many patients without clinical evidence of DED, such as staining of the ocular surface and decreased Schirmer test scores, are highly symptomatic. Conversely, there is a subset of patients with severe damage to the ocular surface with few subjective symptoms. This lack of concordance between signs and symptoms presents a problem not only in the diagnosis of the disease, but also in assessment of severity and in the design of clinical trials to evaluate the clinical efficacy of drugs.

Recent studies on corneal sensitivity may add some light on these perplexing observations. Both animal and human studies on the response to nerve damage to the corneal have revealed that injured nerve endings respond by developing microneuromas that may alter transducing signals leading in dry eye states to an autonomous-like discomfort. This may account for patient symptoms of discomfort in the early stages of DED development in which patients’ symptoms are out of proportion to observed tissue damage. Paradoxically, it has been observed that inflammatory changes characteristic of a more severe form of DED may result in decreased nerve sensitivity, explaining the paucity of symptoms. This disconnection between signs and symptoms is, as yet, not completely understood, but must be factored into diagnostic criteria and the design of clinical trials.

Standard objective tests for DED also have shortcomings. The Schirmer test, which has been in widespread clinical use for more than a century, has been criticized for its variability and its tendency to exhibit wide intrasubject, day-to-day, and visit-to-visit variation. As tear secretion decreases in more advanced disease, the results become more reproducible. In mild to moderate disease, however, it has limited usefulness. Other standard tests in wide use include the use of vital dyes to assess damage to the cornea and conjunctiva. Those in general use are fluorescein for the cornea and either rose Bengal or lissamine green for the conjunctiva. Vital staining of the ocular surface, although a measure of damage to the ocular surface is not specific for DED, occurs in a substantial percentage of normal subjects and is present in a minority of patients with mild to moderate DED. In addition, reproducibility in patients with DED and no change in treatment has been reported as being relatively poor. This calls into question its usefulness as a primary efficacy measure in clinical trials for DED and suggests that its presence and degree may reflect short-term environmental influences as much or more than underlying disease or effects of therapy.

Several classification schemas for DED have been developed. On a mechanistic basis, one distinguishing between aqueous tear deficiency and evaporative dry eye has been in use for more than a decade. Although this is an important clinical tool, particularly in looking for evidence of meibomian gland dysfunction of the lids, the most common form of evaporative dry eye, increasingly it is recognized that most cases of DED involve both types of mechanisms. In creating a treatment plan, assessment of severity of the disease is playing a more important role. In the recent DEWS report, a severity scale has been introduced (Table 1). Based on the earlier Delphi panel article, it provides a useful clinical schema to aid in assessing severity of disease; an accompanying set of guidelines for treatment should prove useful for the clinician in making practical decisions in the management of patients (Table 2).

Although treatment options have been limited largely to over-the-counter tear substitutes and 1 Food and Drug Administration (FDA)-approved therapeutic agent, cyclosporine A (Restasis; Allergan Inc, Irvine, California, USA) several newer tear substitutes with therapeutic properties have been marketed. These properties include stabilization of the tear film, protection of the corneal and conjunctival cells, reduction in evaporative tear loss by the introduction of lipids, enhanced wound healing, and enhanced lubrication between lids and the ocular surface. In addition, measures such as punctual plugs, environmental changes, autologous serum for severe disease, and other emerging strategies add to the spectrum of disease management tools. There has been great interest in the use of omega 3 fatty acids either from diet or in the form of nutraceuticals to treat DED. These compounds, which are present in fish and green leafy vegetables, have anti-inflammatory properties. There are a few small, well-designed studies in addition to anecdotal evidence to suggest their usefulness. Large-scale prospective clinical trials are being developed to document their effects.

In addition to the use of cyclosporine (Restasis) to modulate immune activity and to suppress inflammation in DED, there is increasing evidence that the use of topical corticosteroids as temporary or pulsed therapy can be useful in reducing the damaging effect of inflammation. The anti-inflammatory properties of doxycycline have been demonstrated in animal models; its benefits in the treatment of meibomian gland dysfunction are well known, and the anti-inflammatory effects of both systemic and topical use are becoming increasingly recognized.

Reference to the treatment guidelines should aid in making treatment selection. With the anticipated approval of more therapies directed to specific disease mechanisms in the coming years, the clinician will be called on to make increasingly complex decisions to manage DED effectively; it is probable that more than one therapeutic
agent will be required to provide optimal management of patients.

**CURRENT PROBLEMS AND FUTURE PROSPECTS IN THE DEVELOPMENT OF NEW THERAPIES**

ADVANCES IN UNDERSTANDING THE MECHANISMS OPERATIVE in forming and maintaining a normal tear film and the pathologic breakdowns that occur in DED have led to a variety of novel interventional strategies. These include: secretagogues of aqueous tears, mucins and lipids, anti-evaporative compounds, immunomodulating agents that have anti-inflammatory effects, corticosteroids, cellular protective formulations, and tear film stabilizers. Although most of the results of clinical trials are proprietary, published papers and abstracts presented at meetings suggest that more than 20 products have undergone clinical testing in the United States. As of this writing, only one drug formulation has received FDA approval for marketing as a therapeutic product for DED. It has been difficult for sponsors to generate data that will meet the FDA’s criteria of primary efficacy endpoints. These endpoints usually include improvement in at least one sign and one symptom and that these should be both statistically and clinically significant. Given the information previously discussed concerning the lack of concordance between signs and symptoms in DED, the hurdle for obtaining approval is high indeed. In fact, the basis for approval of Restasis was not on a primary efficacy endpoint but rather a secondary one, that is, improvement in the Schirmer test results and a correlated improvement in a symptom in a subset of patients. As increasing evidence is appearing in the literature about the difficulties of using standard primary endpoints such as vital dye staining, investigators have been looking to other endpoints. This is a rapidly evolving field in which design of clinical trials largely is proprietary and, therefore, such information is not available for general scrutiny. A number of trends, however, are apparent and are discussed in the recently published DEWS report.5

A principal problem encountered in all clinical trials is the placebo effect of artificial tears on outcomes.22 This refers to the observation that patients receiving a placebo or drop with no active ingredients display notable improvements in most trials. The suggested reasons for this include greater compliance in patients participating in clinical trials, the lubrication effects of drops, and a regression to the mean in subjects recruited on the basis of findings that may be variable over time. The DEWS report suggests that substituting a no treatment arm for a placebo arm may be indicated.5

One innovative approach that attempts to harness the short-term environmental effects on surface staining has been the controlled adverse environment.32 In this experimental design, subjects preselected for prior clinical response, for example, staining in DED, are exposed to adverse conditions such as wind and dry climate in a

| TABLE 1. Dry Eye Disease Severity Grading Scheme |

<table>
<thead>
<tr>
<th>Dry Eye Severity Level</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discomfort, severity, and frequency</td>
<td>Mild and/or episodic; occurs under environmental stress</td>
<td>Moderate, episodic, or chronic; stress or no stress</td>
<td>Severe, frequent, or constant without stress</td>
<td>Severe and/or disabling and constant</td>
</tr>
<tr>
<td>Visual symptoms</td>
<td>None or episodic mild fatigue</td>
<td>Annoying and/or activity-limiting episodic</td>
<td>Annoying, chronic, and/or constant limiting activity</td>
<td>Constant and/or possibly disabling</td>
</tr>
<tr>
<td>Conjunctival injection</td>
<td>None to mild</td>
<td>None to mild</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Conjunctival staining</td>
<td>None to mild</td>
<td>Variable</td>
<td>Moderate to marked</td>
<td>Marked</td>
</tr>
<tr>
<td>Corneal staining (severity/location)</td>
<td>None to mild</td>
<td>Variable</td>
<td>Marked central</td>
<td>Severe punctate erosions</td>
</tr>
<tr>
<td>Corneal tear signs</td>
<td>None to mild</td>
<td>Mild debris, tear meniscus</td>
<td>Filamentary keratitis, mucus clumping, tear debris</td>
<td>Filamentary keratitis, mucus clumping, tear debris, ulceration</td>
</tr>
<tr>
<td>Lid/meibomian glands</td>
<td>MGD variably present</td>
<td>MGD variably present</td>
<td>Frequent</td>
<td>Trichiasis, keratinization, symblepharon</td>
</tr>
<tr>
<td>TSBUT (seconds)</td>
<td>Variable</td>
<td>≤ 10</td>
<td>≤ 5</td>
<td>Immediate</td>
</tr>
<tr>
<td>Schirmer score (mm/5 minutes)</td>
<td>Variable</td>
<td>≤ 10</td>
<td>≤ 5</td>
<td>≤ 2</td>
</tr>
</tbody>
</table>

MGD = meibomian gland disease; TSBUT = tear film break-up time.

*Must have signs and symptoms.

TABLE 2. Dry Eye Disease Treatment Guidelines Based on Disease Severity

<table>
<thead>
<tr>
<th>Severity Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Education and environmental/dietary modifications; elimination of offending systemic medications; artificial tear substitutes, gels/ointments; eye lid therapy</td>
</tr>
<tr>
<td>2</td>
<td>If level 1 treatments are inadequate, add: antiinflammatories, e.g., cyclosporine A, topical corticosteroids; tetracyclines (for meibomianitis, rosacea); punctal plugs; secretagogues; moisture chamber spectacles</td>
</tr>
<tr>
<td>3</td>
<td>If level 2 treatments are inadequate, add: serum; contact lenses; permanent punctal occlusion</td>
</tr>
<tr>
<td>4</td>
<td>If level 3 treatments are inadequate, add: systemic antiinflammatory agents, e.g., cyclosporine A, prednisolone, methotrexate, infliximab; surgery (lid surgery, tarsorrhaphy, mucus membrane, salivary gland, amniotic membrane transplantation)</td>
</tr>
</tbody>
</table>

Modified from the International Task Force Guidelines for Dry Eye, and reprinted from the 2007 Report of the International Dry Eye Workshop (DEWS) with permission from Ethis Communications.

specially designed temperature and humidity controlled chamber while performing visual tasks requiring open eyes. They are pretreated with either test drug or placebo and are examined for response. This approach should be able to determine pharmacologic effect in a short period. There is a limited literature on this technology, and results of drug trials generally are proprietary. As of this writing, no dry eye drug approval using this approach has been announced. A possible limitation of the use of preselected responders is the lack of generalizability to the entire DED population. Nonetheless, this novel approach undoubtedly will undergo further development and refinement.

Alternatively, others have tried to refine traditional endpoints such as staining to specific areas, for example, the central cornea, which has an effect on vision. In addition, there are attempts to study variability in the general population and that of DED patients to document variation in presentation and variability over time. Another approach would be to identify target groups most likely to respond to specific therapies, that is, those with reduced but still measurable Schirmer test results in the testing of a putative lacrimal secretagogue. The use of such responder groups should increase the likelihood of demonstrating efficacy.

The DEWS report recommends that future trials using surrogate markers for DED be considered. A surrogate marker is a test that correlates with clinical evidence of severity of disease. Tear osmolarity is one candidate discussed in the DEWS report. It is considered an established marker and is considered “the central mechanism causing ocular surface inflammation, damage and symptoms and the initiation of compensatory events in dry eye.” Other suggestions of the report for new efficacy endpoints include: an objective measure of functional VA, tear cytokines, more precise measures of tear stability, and altered ocular staining schema allowing for minimal peripheral corneal stain as seen in many normal subjects. Surrogate markers will have to be validated to reflect disease severity before they are suitable for clinical trials, but they represent a promising approach that circumvents the problems of conventional endpoints such as ocular staining.

CONCLUSIONS

WHAT IS NOT KNOWN IS HOW EFFECTIVE THE NEW AGENTS are that have undergone clinical trials; what is known is that the methodology used to evaluate them is flawed. As new information becomes available, designs for clinical trials undoubtedly will undergo further evolution. This is critical to surmount the regulatory barriers to successful development of new, more efficacious treatment options for patients with DED. As new products become available, there will be a greater challenge to the clinician to diagnose the disease more accurately and to establish more effective treatment regimens for the different stages of the disease. This augurs well for an improved outlook for patients and greater professional satisfaction for clinicians.

THE AUTHOR INDICATES NO FINANCIAL SUPPORT OR FINANCIAL CONFLICT OF INTEREST. THE AUTHOR IS AN OFFICER IN Ocusense Inc, a company that has developed a tear osmometer. The author was involved in the design and conduct of study; data collection; analysis and interpretation of data; and the preparation and review of the manuscript.

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Biosketch

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