The Ultimate Guide to The C.DIAG® By Lumibird Medical

While “dry eye” symptoms are common and well known, accurately diagnosing and properly addressing the various conditions that constitute ocular surface disease can often be challenging. Now, a new aided diagnostic imaging platform makes that aspect of eye care more attainable.

Ocular surface disease (OSD) is an overarching clinical term that describes a wide variety of conditions affecting the collective ocular surface tissues, i.e., the cornea, conjunctiva, eyelids – with their respective glands and lashes – and the associated adnexal tissue. Within this broad disease category are many more specific diagnoses, including dry eye disease, ocular allergy, meibomian gland dysfunction (MGD), blepharitis, ocular rosacea, iatrogenic damage from chronic medications (e.g., topical glaucoma therapy) or surgery, chemical and thermal burns, and even ocular surface manifestations of autoimmune disease.

The actual prevalence of OSD is difficult to express. Most of the current literature regarding such statistics is limited to dry eye disease, which is itself a very common and multifactorial disorder of the tear film and ocular surface. A recent systematic review and meta-analysis using the broadest definition of dry eye disease and including MGD suggest that the pooled prevalence of these conditions is 17.4%, and further extrapolation to the overall US population suggests a number approaching 58 million Americans. This could be viewed as the lower limit of OSD prevalence in the United States.[1]

The pathophysiology of OSD is similarly difficult to describe. Because it involves numerous etiologies – allergic, autoimmune, infectious, inflammatory, mechanical, neurogenic, parasitic, senescent, etc. – one can hardly comment on a singular cause or disease process. In essence, any condition that compromises the integrity of the ocular surface tissues, whether it impacts one or more of the previously noted structures, can be a driver of ocular surface disease. OSD can manifest as a disorder limited solely to the eye, or it can involve the eye as an end organ in a wider systemic condition, such as rheumatoid arthritis. OSD can even occur as a result of prior ocular trauma, whether incidental or iatrogenic in nature.

One item that is not difficult to convey with regard to OSD is the symptomatology. The subjective complaints associated with these collective disorders are both well-known and well-documented, though unfortunately, they are not specific to any single underlying etiology. The most commonly reported symptoms in patients with OSD include feelings of grittiness, tearing/epiphora, photosensitivity, and transient visual disturbances such as intermittent blur that clears briefly after blinking.[2-4] Additionally, patients may report itching, burning, stinging, heaviness, and a host of other descriptive terms to describe their discomfort. The most commonly impacted activities of daily living, according to our patients, include such things as reading, use of computers or other digital devices, driving, and watching television.

Diagnostic Testing for OSD

Assessing symptoms

There are many tests that eye care practitioners (ECPs) may employ in the diagnosis of OSD. Validated questionnaires such as the Ocular Surface Disease Index (OSDI), the Dry Eye Questionnaire (DEQ)-5, and the Standard Patient Evaluation of Eye Dryness (SPEED) can provide an initial quantitative value that corresponds to the severity with which a patient is impacted by symptoms.[5-7] Other methods for evaluating symptom severity include a visual analog scale, where the patient is asked to rate their discomfort on a linear scale from 0 to 100, with 0 representing "no pain" and 100 representing "severe intolerable pain" **(Figure 1)**. While there is often disparity between symptoms and signs from one patient to another, assigning a value to symptom severity allows physicians to assess: (1) the degree to which a given patient is bothered or impacted by the disease state; and (2) the amount of improvement (or lack thereof) over time with regard to therapeutic intervention.

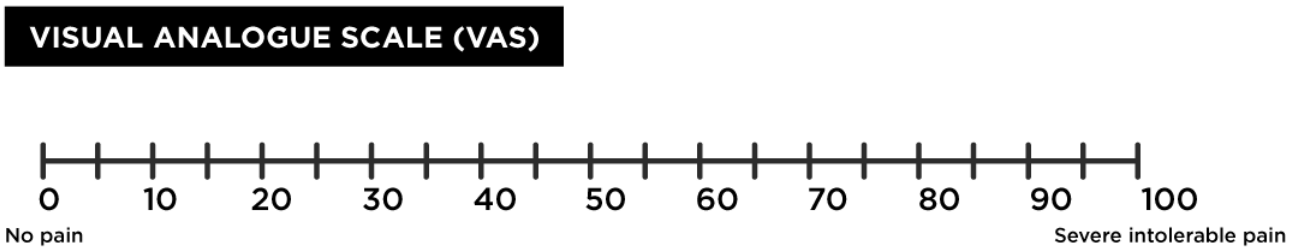

Figure 1. Visual analog scale for evaluation of symptoms severity in OSD

Tear volume

Another important metric for determining the underlying etiology of OSD is assessment of tear volume, which indirectly predicts the capacity of a patient to produce tears over time. Historically, the most common method for assessing tear volume is the Schirmer tear test, which utilizes a 35 mm by 5 mm strip of filter paper (Whatman #41) draped over the lower lid **(Figure 2)**.[8] The test works by capillary action, allowing the aqueous component

of the tears to travel along a strip's length as similar fluids do within a capillary tube; the travel rate is proportional to the tear production rate, and is typically measured over a period of 5 minutes.[9] Similar tests may be performed using alternative means, such as the phenol red thread test, which utilizes a 70 mm cotton thread impregnated with phenol red dye (a pH indicator) as a substitute for the filter paper. The advantage of phenol red thread is diminished patient discomfort and reflexive tearing, as well as a more rapid result, requiring just 15 seconds for a definitive result.[10]

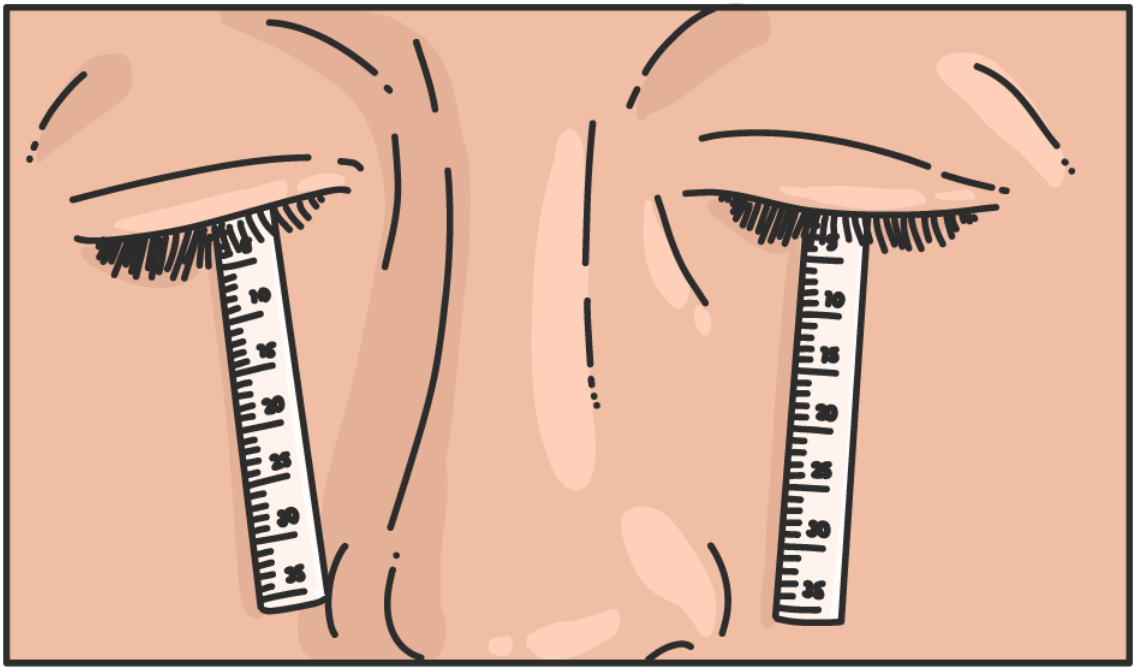

Figure 2. Schirmer test for measuring tear production

Vital dye staining

Perhaps the most important and clinically useful test in the evaluation of ocular surface disease is direct biomicroscopic evaluation of the cornea and conjunctival surface, aided by the use of vital dyes. These dyes permit evaluation of ocular surface regularity, integrity, and vitality. Corneal staining is typically conducted with the use of sodium fluorescein, which can help to delineate the stability of the tear film, but moreover collects and permeates the cornea in areas where cell-to-cell junctions have been compromised. The degree of "staining" corresponds to the severity of cellular disruption and damage, and hence the impact of the underlying condition.

Lissamine green dye is also sometimes used to assess the integrity of the conjunctival tissues in addition to the cornea. Lissamine green specifically stains ocular surface epithelial cells that are unprotected by mucin or glycocalyx, as well as cells that have been damaged or vitally compromised, findings which are often indicative of OSD.[11]

Inspecting the eyelids

One of the more crucial diagnostic tests in the differential diagnosis of OSD patients involves assessment of meibomian gland integrity, and the collective capacity of these glands to produce and secrete a viable lipid tear component. There are several methods by which ECPs may evaluate the meibomian glands; however, as with other critical ocular structures, assessment of both structure and function is necessary to determine the most

appropriate course of action. Meibography is the term used to describe imaging of the meibomian glands within the upper and/or lower lids; this can be accomplished using simple transillumination of the lid with biomicroscopic assessment, the use of infrared light to directly examine the palpebral conjunctival surface, or a combination of the two.[12] Over the past 10 years, numerous commercial devices have been introduced to the eye care market that specifically function to provide meibographic imaging, or incorporate meibography into their multiple testing capabilities.

Meibography is one of the most critical tests that we can perform in a comprehensive ocular surface health evaluation. The assessment of meibomian gland structure in OSD is akin to OCT evaluation of the optic nerve and retinal nerve fiber layer in glaucoma, displaying compromised areas that may coincide with altered function. Unfortunately, some early diagnostic devices were notorious for delivering "incomplete meibography", i.e., areas that were improperly imaged because of poor camera alignment or lid eversion technique. Newer devices that can incorporate retroillumination and deliver more consistent lid eversion provide more complete and accurate scans.

—Rolando Toyos, MD

While meibography can provide tremendous insight into the structure of the meibomian glands, including the degree to which they may be damaged or compromised, it generally cannot provide information about the quality or quantity of the meibum produced by those glands. For functional assessment, most clinicians rely on either manual expression of the glands – with subjective evaluation of meibum quality based upon visual inspection – or in vivo examination of the tear lipid components, typically aided by interferometry to reveal the characteristics and even the thickness of the lipid layer.[13,14]

External lid evaluation, including a detailed biomicroscopic evaluation of the lashes and eyelid margin, is another critical component of OSD diagnosis. The presence of anterior blepharitis is often readily apparent, demonstrating the characteristic debris along and within the eyelashes as well as thickening and hyperemia of the lid margins. Bacteria-associated (i.e., Staph) blepharitis, seborrheic blepharitis, and Demodex blepharitis **(Figure 3)** can each present similarly with regard to symptoms and gross appearance, but careful inspection of the debris under high magnification can often reveal characteristic differences that are pathognomonic to the underlying etiology.

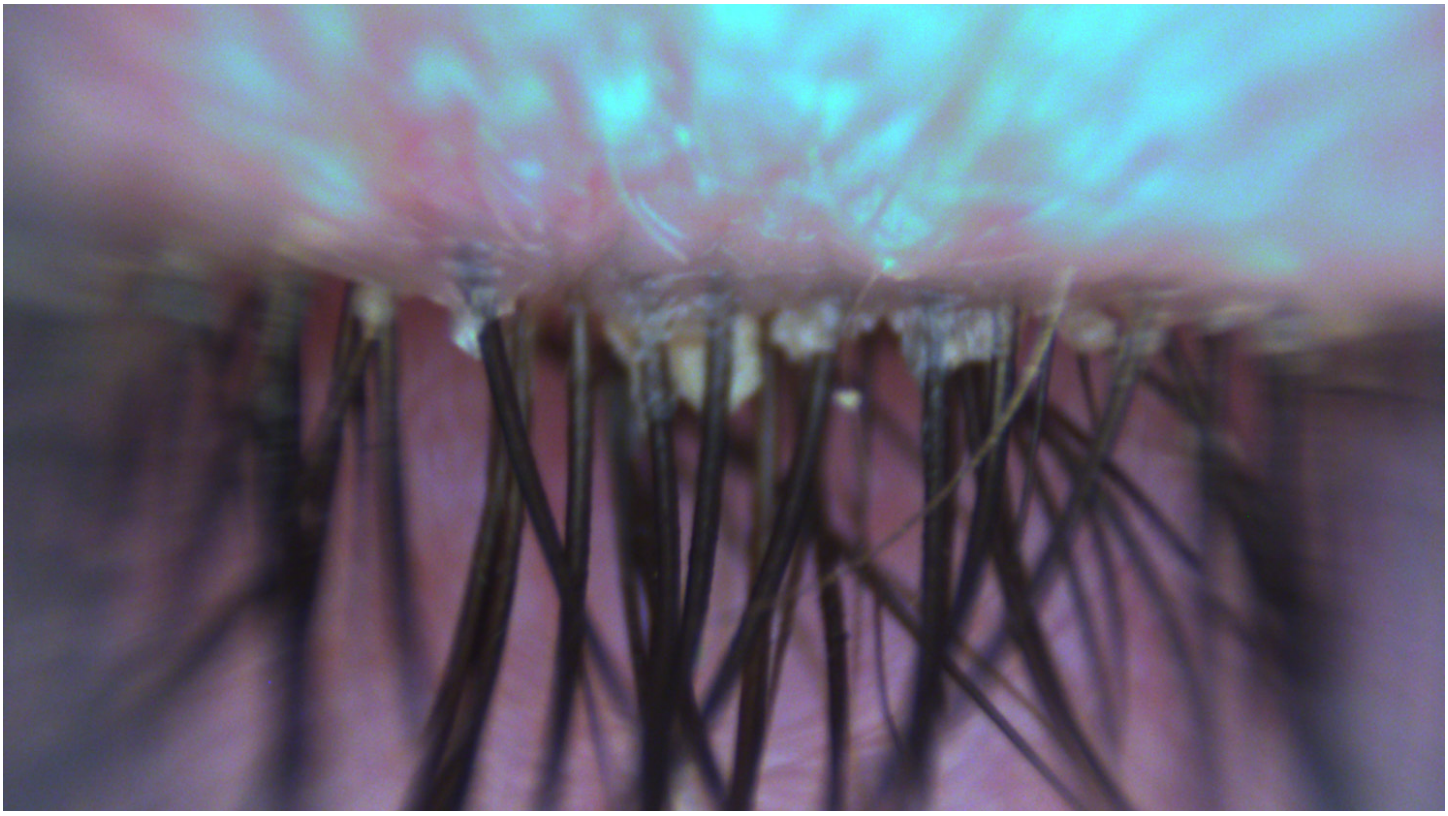

Figure 3. Demodex Blepharitis | Image courtesy of Lumibird Medical

Assessing blink dynamics is another important though often overlooked diagnostic element in the assessment of OSD. Evaluating the blink rate and the overall blink quality (i.e., whether there is partial or complete closure of the lids) can be challenging within the confines of a routine, comprehensive examination. However, with the advent of some recently developed diagnostic devices, it is possible to capture real-time video of the blink dynamics and artificial intelligence (AI) algorithms can differentiate between complete and partial blinks, helping to diagnose those individuals whose OSD may be related to poor lid function.

Some additional point-of-care tests are occasionally used by ECPs in their assessment of OSD patients. These can include:

- **Matrix metalloproteinase (MMP)-9 testing** - this 10-minute, in-office, CLIA-waived test detects the presence of MMP-9, an inflammatory biomarker that may be elevated in tears of patients with OSD. It utilizes a small tear sample collected from the palpebral conjunctiva along with a pre-packaged test kit and reagent to rapidly identify inflammation, helping to narrow the differential diagnosis and guide potential therapy.
- **Tear osmolarity** - osmolarity represents a biophysical measurement that reflects the concentration of salts in a solution – in this case, the tear film. Elevated tear osmolarity (>308 mOsm/L), has been shown to be consistent with aqueous tear deficiency and/or hyper-evaporative dry eye disease.[15,16] By evaluating tear osmolarity, we can more easily differentiate between dry eye disease and other forms of OSD.
- **Corneal sensitivity testing / aesthesiometry** - corneal sensitivity testing has long been held as the standard for identifying neurotrophic keratopathy (NK), an advanced degenerative condition affecting the cornea whereby damage to the trigeminal nerve (which is responsible for innervation of the cornea) results in impairment of

corneal sensitivity, leading to spontaneous epithelial disruption, poor corneal healing, and in severe cases, the development of corneal ulceration, melting, and perforation.[17] Such testing can be crucial in cases of advanced OSD, since NK often fails to respond to conventional therapies for similarly presenting conditions such as dry eye disease. Like OSD, NK has multiple potential etiologies, with the most common being prior herpetic ocular infection, prior corneal surgery (i.e., iatrogenic causes), diabetes, or neurological conditions affecting the central nervous system.[18]

Diagnostic devices for OSD

For a number of years, manufacturers have attempted to create diagnostic devices and platforms that can aid ECPs in evaluating the cornea and ocular surface for a variety of assessments, from keratometry and corneal topography to meibography and tear film assessment. Corneal topography – a non-invasive imaging technique that serves to create a map of the corneal surface – helps to identify distortions or irregularities in curvature, which can be indicative of numerous corneal disorders including OSD. Topography is essential in the preoperative planning of keratorefractive surgeries, and can also provide crucial information for the fitting of medically necessary contact lenses; hence, most cataract and refractive surgeons, and many other ophthalmologists and optometrists own and use corneal topographers routinely. Naturally, incorporating some of the previously discussed diagnostic elements into these existing topography platforms was the way in which several, bundled testing capabilities were leveraged into existing practices, bringing added value to both the devices and their ECP owners.

In recent years, numerous devices have been developed and marketed for the purpose of gathering additional diagnostic data in the detection and management of OSD. Some of the features currently offered in these devices are listed below **(Figure 4)**.

- Validated questionnaires, assessing symptom severity
- Non-invasive tear break-up time, assessing tear stability
- Tear lipid interferometry, assessing both lipid quantity & quality
- Tear meniscus height, assessing tear volume
- Blink dynamics, assessing blink frequency & quality
- Conjunctival redness score, indirectly assessing inflammation
- Infrared meibography, assessing meibomian gland structure & integrity
- Ocular videography and photography, with vital dye capabilities

Figure 4. Important "value added" features for OSD diagnostic devices.

While adding features to an existing diagnostic device may seem like a logical concept for introducing OSD detection and management into new practices, there are still significant challenges posed by this model. Several of these involve the ergonomics of current topographers and the large office footprint that they typically occupy. Additionally, many of these devices are designed for specific, non-invasive ocular surface assessments; consequently, they do not easily permit the required manipulation of the eyelids that is necessary for some diagnostic tests. This is especially true for meibography, which can prove challenging for a single, unassisted

operator to perform since it requires simultaneous manual control of the eyelids with one hand and operation of the device with the other. Also, because of their rigid design, these devices may not be able to accommodate larger patients, patients with mobility issues, or individuals with unusual or atypical physical characteristics.

Attempts to improve the utility of these devices have resulted in smaller, more focused platforms that occupy less office space and are more portable. Yet there are still some remaining issues that make for challenges to busy ECPs. For example, in an attempt to diminish the footprint, some developers have designed devices with removable "cones" that fit over the main camera lens, allowing practitioners to switch from one type of imaging to another. Unfortunately, this creates an extra step in the examination process, while introducing the possibility that these expensive adaptive cones are dropped, damaged, or misplaced.

Perhaps most significant to the discussion of effective OSD diagnosis is the limitation of data manipulation and interpretation. While all of these devices have the capacity to provide some useful information, the subsequent reports that they generate may be of little value in some cases. Invariably, individual ECPs prefer certain tests over others; however, the technology may not exist within these devices to easily customize exam protocols. Additionally, most of these devices are dependent upon the skill and experience of the operator. Less seasoned individuals may unfortunately end up collecting information that is inaccurate or incomplete.

My litmus test for a diagnostic piece of equipment that's beneficial for the practice and easy to integrate is when our technicians embrace it with open arms. When they don't need those extra training sessions to learn how to master it. That's when you realize you are working with a user-friendly device.

—I. Paul Singh, MD

C.DIAG® offers an impressive variety of features that makes it extremely practical and valuable in clinical practice. The capture rate for typical workup is very fast, usually taking less than 5 minutes, and is entirely delegatable to technicians regardless of their experience level. This is important, since OSD management can be very time intensive, and obtaining precise, usable data is critical. I also appreciate the high resolution camera and video capabilities, since these not only facilitate diagnosis and management strategies, but they also help with patient education.

—Rolando Toyos, MD

Along these same lines, the interpretation of the results provided depends entirely on the operator and the report reader; once again, the results obtained by an experienced clinician may be far superior to those gathered by a novice. Ideally, the development of an automated system that routinely gathers crisp, detailed images and provides accurate data points would represent a critical step toward improving the value of such equipment. Additionally, the incorporation of AI algorithms with a database of normal and abnormal values would aid the less experienced practitioner in determining the appropriate diagnosis and required course of action.

C.DIAG®: The Latest in Ocular Surface Imaging

C.DIAG®, the latest diagnostic offering from Lumibird Medical Group, represents the most complete, automatic, premium imaging platform devoted to OSD diagnosis and management **(Figure 5)**. This innovative product incorporates the latest, most disruptive technologies and exclusive design features to facilitate more accurate diagnoses and less cumbersome examinations for all, with objective follow-up in pre- and post-OSD treatment and surgery. It is expressly designed to enable ECPs to more easily and accurately diagnose, treat, and educate patients.

Figure 5. C.DIAG®. Note the diminished footprint and ergonomic design, as well as the large HD tactile screen and joystick. Image courtesy of Lumibird Medical

C.DIAG® provides the best and most widely accepted indicators for OSD, including the following:

- **Symptom assessment questionnaires** - within the resident software of C.DIAG® are the Ocular Surface Disease Index (OSDI), the Dry Eye Questionnaire (DEQ)-5, and the Standard Patient Evaluation of Eye Dryness (SPEED) questionnaires, any or all of which can be easily completed on the virtual platform to help quantify patients' symptomatology at both the initial and subsequent visits.
- **Video blink assessment** - using the incorporated video camera, C.DIAG® can record blink frequency while differentiating partial blinks from complete blinks, and can also calculate the exposed ocular surface area.
- **Tear stability assessment** - using non-invasive techniques to assess tear film stability and integrity, C.DIAG® can calculate the initial tear break-up time (TBUT), average tear stability, and curve evolution, and provide corneal maps detailing break-up patterns.

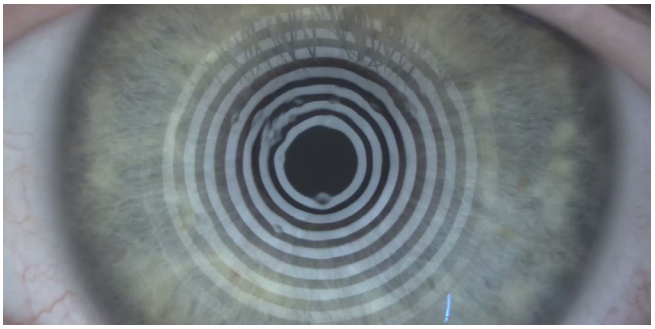

Figure 6. Tear Film Stability obtained with the C.DIAG®
Image courtesy of Lumibird Medical

- **Lipid layer assessment** - with the aid of interferometry, C.DIAG® performs a qualitative analysis of the lipid tear film component, providing classification of severity using the grading scale developed by Jean-Pierre Guillon, BSc (Optom), PhD.

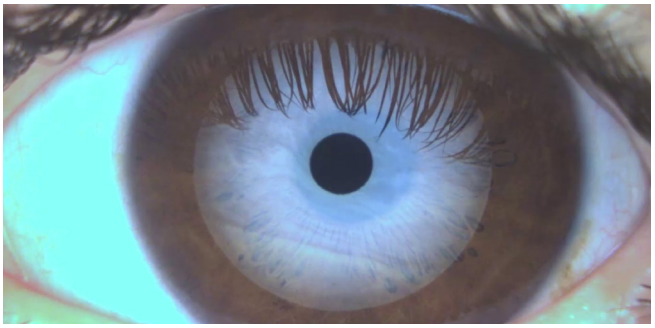

Figure 7. Lipid Layer obtained with the C.DIAG®
Image courtesy of Lumibird Medical

- **Tear meniscus** - this option provides a quantitative analysis of the aqueous tear component by calculating the average of tear meniscus heights. This capability obviates the need for more cumbersome and invasive forms of tear volume assessment, such as the use of Schirmer tear strips or phenol red thread.

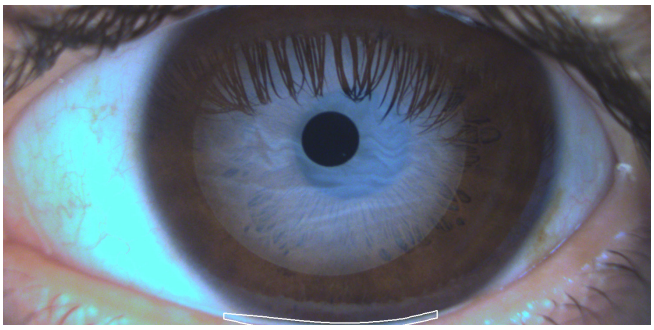

Figure 8. Tear Meniscus obtained with the C.DIAG®
Image courtesy of Lumibird Medical

- **Exclusive meibography** - C.DIAG® incorporates both a standard infrared light source to quantify the meibomian glands as well as transillumination infrared to assess gland functionality. The device's exclusive eyelid everter facilitates this capability, permitting clinicians to gain tremendous insight regarding gland integrity by clearly defining obstruction, meibum accumulation, and telangiectatic blood vessels surrounding the glands **(Figure 9)**. Moreover, by providing clear visualization with greater detail of gland morphology and dysfunction, C.DIAG® offers physicians the ability to select the best treatment for individual patients, whether that involves topical medications, IPL, gland expression, or another modality.

Figure 9. First: C.DIAG's resident transilluminator/lid everter.
Second: Meibography images obtained with the C.DIAG.
Image courtesy of Lumibird Medical

- **Additional exam capabilities** - in addition to the aforementioned features, C.DIAG® incorporates 3 different camera lenses to provide high-resolution images of the cornea, conjunctiva, eyelids, and lashes for greater diagnostic detail. These different imaging sources are accessible by a permanently mounted rotating head, eliminating the need for removable cones. Additionally, the C.DIAG® contains both a yellow filter for patient comfort and a cobalt blue filter to permit examination and image capture using sodium fluorescein dye. It also includes 12 different grading scales (e.g., Efron, Oxford, Pult) with which to help quantify OSD severity.

- **Exam reports** - once all the data has been collected and reviewed, C.DIAG® can produce easy-to-interpret, individualized exam reports for each patient, integrating the evolution curve for an objective follow-up between appointments and interventions **(Figure 6)**.

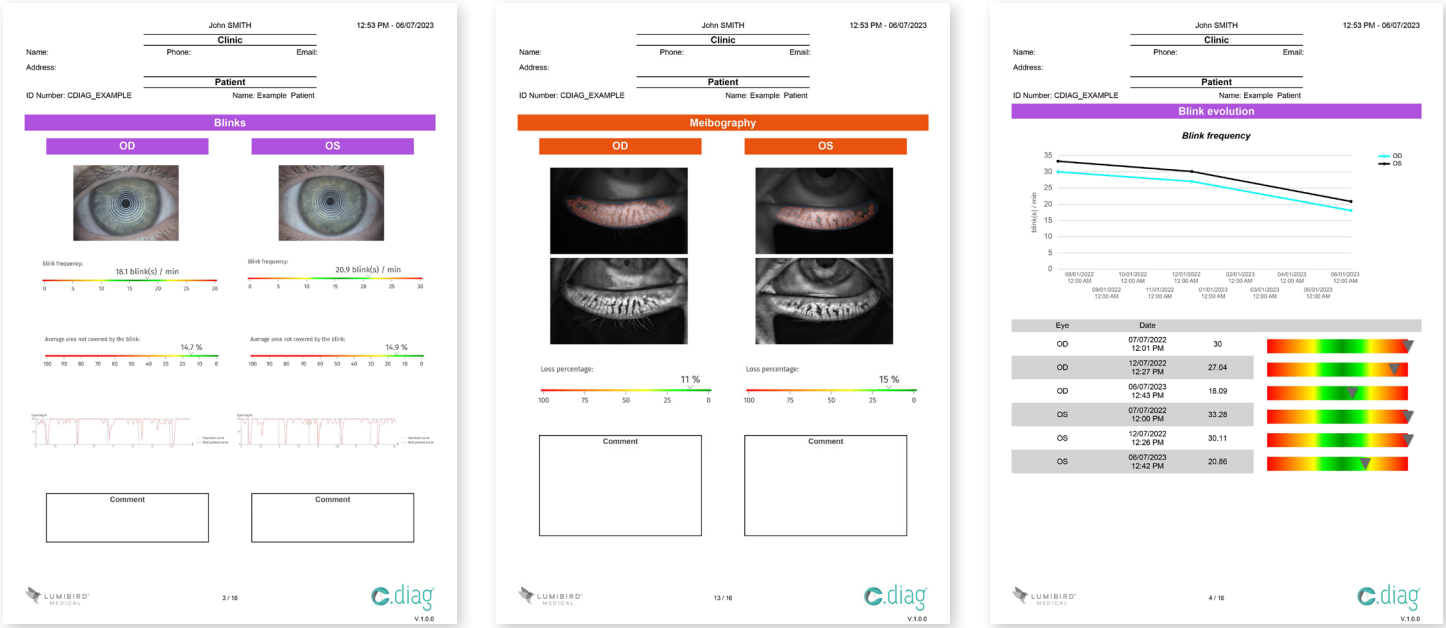

Figure 10. An example of the C.DIAG® OSD evaluation report. | Image courtesy of Lumibird Medical

Regarding additional "bells and whistles", C.DIAG® features a unique, optical liquid lens with autofocus HD camera for accurate and highly reproducible results. The ultrasmart platform essentially removes the technician from the equation, resulting in few if any poor quality images, regardless of operator experience or expertise. Moreover, because of the ergonomic design and versatile capabilities, C.DIAG® offers the fastest imaging possible, increasing office efficiency and productivity. It incorporates a rotating chin rest to accommodate all head sizes and face shapes, as well as a chin rest adaptor to facilitate pediatric evaluations if needed. Its optimized, rotating examination cones limit light reflection and shadows, and the comfortable light intensity makes for quicker and more comfortable screenings for all patients. Finally, the large HD tactile screen and joystick operation help to simplify exam administration for the operator **(Figure 5)**.

It is targeted medicine. Patient-specific medicine. It helps you understand the next step for this patient. Sometimes it isn't MGD, sometimes it's more aqueous deficiency and you can see the tear lake. It gives you an understanding of what the tear lake is for this patient. If it is decreased, I might use an immunomodulator to help improve their tear breakup time or aqueous production or do Lacrifill or a plug to help increase the amount of tears in the eye. It has helped me guide my decisions.

—I. Paul Singh, MD

Equally impressive is the ability of C.DIAG® to provide customizable examination protocols, depending on the physician's preferences and patient needs. Internally, the resident artificial intelligence (AI) software is based on algorithms derived from over 1 million clinically validated images; this allows rapid analysis of examination results against a robust database, resulting in a one-click, diagnostic report that not only qualifies but also quantifies the current disease state. In this way, C.DIAG® helps to remove the subjective approach to diagnosis while generating objective feedback for both the doctor and the patient.

This device is really the first of its kind to offer AI technology where the benefits are readily evident. It utilizes over a million scans from 300 unique patients. Images captured are compared against this broad database of established norms for various elements, helping to assess the severity of multiple important attributes and grade the disease state as mild, moderate, or severe. This in turn helps guide the choice of intervention, and assess the patient's progress over time.

—Rolando Toyos, MD

Conclusion

Managing ocular surface disease is challenging due to its varied presentation and complex pathophysiology. C.DIAG® addresses the most common indicators of OSD, changing how it is treated and managed. Additionally, the ability to generate objective feedback using the resident AI can help assist clinical decision-making and patient education to ensure patient compliance. Since C.DIAG® is customizable to the physician's preferences and patient's needs, it can enhance clinical efficacy and efficiency.

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