Evaluation of Dry Eyes

Policy Number: AHS – G2138 – Evaluation of Dry Eyes	Prior Policy Name and Number, as applicable:
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I. Policy Description

Dry eye disease (dysfunctional tear syndrome, DED) is defined by the Dry Eye Workshop II as "a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles" (Craig, Nichols, et al., 2017). 5-15% of the United States population suffers from dry eye disease, leaving a substantial burden on functional vision, general health status, and workplace productivity (Dana, Meunier, Markowitz, Joseph, & Siffel, 2020).

II. Related Policies

Policy Number	Policy Title
AHS-M2083	Genetic Testing for Ophthalmologic Conditions

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Medical Policy Statements do not ensure an authorization or payment of services. Please refer to the plan contract (often referred to as the Evidence of Coverage) for the service(s) referenced in the Medical Policy Statement. If there is a conflict between the Medical Policy Statement and the plan contract (i.e., Evidence of Coverage), then the plan contract (i.e., Evidence of Coverage) will be the controlling document used to make the determination.

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. If there is a conflict between this Policy and any relevant, applicable government policy [e.g. National Coverage Determinations (NCDs) for Medicare] for a particular member, then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

1. Testing of tear osmolarity in patients suspected of having dry eye **MEETS COVERAGE CRITERIA** to aid in determining the severity of dry eye disease as well as monitor effectiveness of therapy.
2. Testing for MMP-9 protein in human tears **DOES NOT MEET COVERAGE CRITERIA** to aid in the diagnosis of patients suspected of having dry eye disease based on comprehensive eye examination.
3. Testing for lactoferrin and/or IgE to aid in the diagnosis of patients suspected of having dry eye disease **DOES NOT MEET COVERAGE CRITERIA**.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of a patient's illness.

4. All other testing used in the diagnosis of patients suspected of having dry eye disease **DOES NOT MEET COVERAGE CRITERIA**.

IV. Scientific Background

Tears are necessary for maintaining the health of the inner and outer surfaces of the eyelid and for providing clear vision. The tear film of the eye consists of aqueous, mucous, and lipid components. A healthy tear film is necessary for protecting and moisturizing the cornea, as well as for providing a refracting surface for light entering the eye (Willcox et al., 2017). Dysfunction of any component of the tear film can lead to dry eye disease (dysfunctional tear syndrome, DED). Dry eye is a common and often chronic problem, particularly in older adults as age affects the entire lacrimal functional unit (Ezuddin, Alawa, & Galor, 2015). The exact prevalence of dry eye is unknown due to difficulty in defining the disease and the lack of a single diagnostic test to confirm its presence, but the 2013 National Health and Wellness Survey estimated the rate of dry eye in the United States to be 6.8%, or about 16.4 million people; prevalence tended to increase with age, with the 18-34 age group only comprising 2.7% of the total and the 75+ age group comprising 18.6% (Farrand, Fridman, Stillman, & Schaumberg, 2017; Shtein, 2020). Risk factors for dry eye include increasing age, systemic comorbidities such as diabetes and autoimmune disease, and therapeutic treatments for anxiety, depression, and sleep disorders (Periman, 2020).

Further, the 2017 Tear Film & Ocular Surface (TFOS) Society International Dry Eye Workshop (DEW) II reported that "the core mechanism of dry eye disease is tear hyperosmolarity, which is the hallmark of the disease" (Craig, Nichols, et al., 2017).

Dry eye is classified into two general groups: decreased tear production and increased evaporative loss. Decreased tear production may lead to hyperosmolarity of the tear film and inflamed ocular surface cells. An age-related ductal obstruction is the most common cause of decreased tear production. Increased evaporative loss is typically caused by problems in the Meibomian gland when the glands that produce the lipid portion of the tear film fail. This lipid portion normally allows the tear film to spread evenly, minimizing evaporation. In both groups, tear film hyperosmolarity and subsequent ocular surface inflammation lead to the variety of symptoms and signs associated with dry eye (Shtein, 2020).

Most patients will present with symptoms of chronic eye irritation, such as red eyes, light sensitivity, blurred vision, or unusual sensations (gritty, burning, foreign, etc.). However, significant variability in the patient-reported symptoms and signs, as well as a lack of correlation between these symptoms

and signs, make it difficult to diagnose dry eye, and no single definitive test to diagnose dry eye exists. Dry eye is typically diagnosed with a combination of patient symptoms and physical findings, such as reduced blink rate or eyelid malposition (Shtein, 2020). Incomplete blinking may also be considered for mild-to-moderate dry eye assessment (Jie, Sella, Feng, Gomez, & Afshari, 2019). Further, visual acuity was found to be particularly poor in those with vision-related symptoms due to dry eyes (Szczotka-Flynn et al., 2019).

The primary way to treat dry eye is artificial tears, although corticosteroids, topical cyclosporine A, or anti-inflammatories such as Lifitegrast ophthalmic solution 5% may be used to supplement treatment. Avoiding environmental factors, such as heavy smoke or dry heating air, is also recommended (Messmer, 2015). It was recently reported by Holland, Darvish, Nichols, Jones, and Karpecki (2019), who reviewed two decades worth of data on the safety and efficacy of controlled topical ophthalmic drug administration for DED treatment, that poor standardization of endpoints across studies causes challenges in the improvement of this field. However, recent advances in drug delivery and a greater understanding of DED will assist in the improvement of ophthalmic drugs.

Accurate diagnosis of dry eye disease requires a variety of tests including patient-reported symptom questionnaires, tear film break-up time (TFBUT), Schirmer test, ocular surface staining, and meibomian gland functionality. However, many of these tests lack consistency and reliability in diagnosis. New tools have been developed which allow for the quantification of tear film characteristics including measurement of tear osmolarity and measurement of inflammatory mediators such as matrix metallopeptidase enzymes, and biomarkers such as lactoferrin (Shtein, 2020).

Tear Osmolarity

Osmolarity is a measurement of the concentration of dissolved solutes in a solution. Hyperosmolarity of the tear film is a recognized and validated marker of dry eye. The following tear osmolarity thresholds have been suggested for establishing the severity of dry eyes: 270-308 mOsm/L for normal eyes, 308-316 mOsm/L for mild dry eye, and >316 mOsm/L for moderate to severe dry eye (Milner et al., 2017). Tomlinson, Khanal, Ramaesh, Diaper, and McFadyen (2006) suggested a cut-off of 316 mOsm/L, but the sensitivity was found to be 0.59 when applied to the independent sample described in the study. Furthermore, decreasing the cut-off to increase the sensitivity decreased the specificity and overall accuracy significantly. Overall, the overlap between normal and dry eyes contributes heavily to the difficulty in establishing a cut-off (Tomlinson et al., 2006). Some studies suggest that osmolarity shows the strongest correlation with severity of dry eye based on the metrics used, but at the same time lack correlation to other objective signs of dry eye. In general, tear osmolarity results vary between clinical signs and symptoms, which can make them difficult to interpret (Akpek et al., 2018).

The test “TearLab” is based on assessment of the osmolarity of tears. TearLab collects a 50 µL tear sample, analyzes its electrical impedance, and provides an assessment of the osmolarity of the sample and thereby the tear (Willcox et al., 2017). Baenninger et al. (2018) completed an extensive systematic review investigating 1362 healthy eyes of participants from 33 different studies; this review found a weighted mean osmolarity of 298 mOsm/L via the TearLab test. Final comments from the researchers highlighted the great variability of osmolarity measurements that were found with the TearLab system, suggesting caution when interpreting TearLab osmolarity results (Baenninger et al., 2018).

Brissette, Drinkwater, Bohm, and Starr (2019) measured the utility of the TearLab test in 100 patients with DED-like symptoms who had normal tear osmolarity results. This study aimed to use the test to

identify diagnoses other than DED. All patients included in the study had a normal tear osmolarity test (<308 mOsm/L in each eye, and an inter-eye difference <8 mOsm/L). The researchers report that "A possible alternate diagnosis was established in 89% of patients with normal tear osmolarity testing. The most frequent diagnoses included anterior blepharitis (26%) and allergic conjunctivitis (21%)" (Brissette et al., 2019). This highlights the utility of the TearLab test to differentiate between DED and other eye disorders with overlapping symptoms.

In a retrospective study by Tashbayev et al., 757 patients diagnosed with symptomatic dry eye disease (DED) were recruited to investigate the clinical utility of tear osmolarity measurement. The TearLab osmometer was used to measure osmolarity in both eyes and the results were compared to Ocular Surface Disease Index (OSDI), tear film break-up time (TFBUT), ocular surface staining (OSS), Schrimer test, and meibomian gland functionality tests. According to their data, TearLab results were not significantly different between the healthy controls and the DED patients. Many studies confirm that tear osmolarity greater than 308 MOsm/mL indicates a loss of homeostasis in the tear, therefore, is used as a cut-off value. Many of the healthy controls had tear osmolarity levels above the recommended cut-off value of 308 mOsm/L, and a substantial proportion of the diagnosed DED patients had tear osmolarity levels below the cut-off value. In the DED patient group, osmolarity levels in the right and left eye were 275–398 mOsm/L and 272–346 mOsm/L, respectively. In the control group, osmolarity levels in the right and left eyes were 281–369 mOsm/L and 275–398 mOsm/L, respectively. Therefore, the authors suggest that "tear osmolarity measured with TearLab osmometer cannot be used as a key indicator of DED (Tashbayev et al., 2020)."

As shown in the above studies, there have been issues in the past regarding the use of tear osmolarity as a diagnostic tool. First, no criteria for the measurement of osmolarity have been established. Studies reviewing osmolarity as a diagnostic tool do not use uniform numbers in their calculations (e.g. no uniform cut-off values, no standardized severity measures, etc). To compound this issue, high variance in osmolarity due to outside factors, such as sleep deprivation, altitude, or even whether the right or left eye was used to produce the tears, can occur. This difficulty in establishing osmolarity ranges has caused an overlap between the ranges of healthy and dry eye osmolarity. Although measuring fluctuations between osmolarity readings has been suggested as a diagnostic (caused by increased instability), the line between healthy eyes and dry eyes is blurred (Willcox et al., 2017). However, a recent report by the TFOS DEWS II states that tear osmolarity "is a global, early stage marker of the disease and has been shown to be able to effectively track therapeutic response and inform the clinician as to whether there has been a loss of tear film homeostasis" (Craig, Nichols, et al., 2017).

Matrix Metallopeptidase (MMP) Enzymes

Inflammation is a common factor across the subtypes of DED. Levels of inflammatory mediators, such as cytokines, may be assessed in the tear film. For example, the matrix metallopeptidase (MMP) enzymes play an important role in wound healing and inflammation by degrading collagen. Elevated levels of MMP-9, a member of the MMP family produced by corneal epithelial cells (Chotikavanich et al., 2009; Honda et al., 2010), have been observed in the tears of patients with dry eye (Sambursky et al., 2013). A study with 101 patients with DED and controls (54 controls, 47 with DED) was performed to assess correlation of the protein MMP-9 with dry eye. All 101 underwent MMP-9 testing of the tear film and were evaluated for symptoms and signs of DED. The tear film was then analyzed for MMP-9 by *InflammaDry*, which detects MMP-9 levels of more than 40 ng/mL. The MMP-9 results were

positive in 19 of the 47 dry eye patients (40.4%) and 3 of the 54 controls (5.6%). The authors concluded that "MMP-9 correlated well with other dry eye tests and identified the presence of ocular surface inflammation in 40% of confirmed dry eye patients," and suggested it may be helpful to identify patients with autoimmune disease and ocular surface inflammation (Messmer, von Lindenfels, Garbe, & Kampik, 2016). The American Academy of Ophthalmology (AAO) has noted MMP-9 does not differentiate dry eye from any other inflammatory ocular surface disease and does not include this test in its appendix on diagnostic tests (Akpek et al., 2018).

Chan, Ye, Chan, Chu, and Jhanji (2016) aimed to assess the utility of MMP-9 measurement in patients with post-laser-assisted in situ keratomileusis (LASIK) dry eyes compared to aged-matched controls. The *InflammaDry* was used to measure MMP-9 levels in tear film. Results showed that "The tear film MMP-9 levels were 52.7±32.5 ng/mL in dry eyes and 4.1±2.1 ng/mL in normal eyes ($p<0.001$). MMP-9 levels were >40 ng/mL in 7/14 (50.0%) post-LASIK dry eyes. The InflammaDry was positive in 8/14 (57.1%) post-LASIK eyes. All positive cases had tear film MMP-9 levels ≥38.03 ng/mL. Agreement between InflammaDry and MMP-9 was excellent with Cohen κ value of 0.857 in post-LASIK dry eyes" (Chan et al., 2016). However, only half of the post-LASIK patients with dry eyes exhibited significant inflammation with heightened levels of MMP-9 (Chan et al., 2016).

A cross-sectional study by Jun JH (2020) investigated if the tear volume in dry eye disease (DED) patients affects the results of the MMP-9 immunoassay (*Inflammadry*). 188 DED patients were enrolled in the study. Positive MMP-9 tests were confirmed in 120 patients, and negative results were noted in 68 patients. However, the authors observed that with a small sample volume, the reliability of the test result was impaired. The manufacturer also pointed out that less than 6 µl of sample volume could produce false-negative results. In this study, patients with higher tear volumes showed higher band densities, but subjects with lower tear volumes showed lower band densities on the immunoassay. In conditions such as Sjögren syndrome that present with markedly decreased tear secretion, *Inflammadry* could display negative results despite the elevated tear MMP-9 concentration. In addition, "among the participants of the present study, a strong positive band was identified even in patients with mild or nearly no fluorescein staining of the cornea and conjunctiva, who are expected to have very mild inflammatory eye surface inflammation (Jun JH, 2020)." In conclusion, this study determined the volume dependency of the MMP-9 immunoassay, which could induce false-negative results clinically (Jun JH, 2020).

Lactoferrin

Another biomarker associated with inflammation is lactoferrin. Lactoferrin is thought to promote the healing process resulting from inflamed dry eyes and is used to assess the lacrimal glands (Willcox et al., 2017). The test "TearScan" from Advanced Tear Diagnostics (ATD) uses this biomarker to assess dry eye, listing a sensitivity of 83%, a specificity of 98%, and a coefficient of variation of <9% (ATD, 2016b). However, lactoferrin's sensitivity for dry eye discrimination was assessed to be 44.2% by a third party review (Versura, Bavelloni, Grillini, Fresina, & Campos, 2013). TearScan uses a quantitative immunoassay to assess lactoferrin and requires a 0.5 µL tear sample. TearScan also offers a similar test assessing the amount of immunoglobulin E (IgE) in tears, purporting that the test can identify any "allergic component of dry eye etiologies"; the sample report lists a sensitivity of 93%, a specificity of 96%, and a coefficient of variation of <9%, but no other studies corroborated these numbers (ATD, 2016a).

A meta-analysis was performed to highlight the potential role of tear lactoferrin as a diagnostic biomarker for dry eye disease (DED). All original studies reporting an estimate of the average lactoferrin concentration in healthy subjects and those affected by DED were searched. A pooled mean difference of 0.62 (95% CI, 0.35–0.89) in lactoferrin concentration was observed in DED patients, showing a significant decrease in lactoferrin concentrations in the tears of subjects affected by DED. A study reported that administration of lactoferrin protein in mice led to a decrease in oxidative damage and an enhancement of tear function (Kawashima et al., 2012). Lastly, the author notes that "to compare data across studies and to validate lactoferrin as a diagnostic biomarker, there is still a need for further development of standardized protocols of tear collection, processing and storage (Ponzini, Scotti, Grandori, Tavazzi, & Zambon, 2020)."

Additional Tests

Other tests noted by the American Academy of Optometry (AAO) are the tear break-up time test, the ocular surface dry staining test, the Schirmer test, and the fluorescein dye disappearance test. The tear break-up time test evaluates the precorneal tear film's stability with a fluorescein dye, which is inserted in the lower eyelid. If the tear film layer develops a dark discontinuity (usually blue) in under 10 seconds, the result is considered abnormal. The ocular surface dry staining test stains areas of discontinuity of the corneal epithelial surface, which may contribute to dryness. A fluorescein dye is typically used, although a rose bengal dye or a lissamine green dye may be used as well. The Schirmer test quantifies the amount of tears produced by each eye. This is done by placing small strips filter paper in the lower eyelid and checking the length (in mm) of wet strips in a certain amount of time. This test is noted as an extremely variable test, so it should not be used as the only diagnostic test. Finally, the fluorescein dye disappearance test places a certain amount of fluorescein dye on the ocular surface, and then evaluates how much of that dye was cleared from the surface (Akpek et al., 2018; Shtein, 2020).

Evaluation of dry eyes is difficult for numerous reasons. Currently, no "gold standard" or globally accepted guideline for diagnosis of dry eye exists, and no threshold between healthy and affected eyes has been established. Many other features of testing (repeatability, high variability, including highly variable sensitivity and specificity of tests and dependence on clinical conditions) and the disease itself—its multifactorial status, examiner subjectivity, reliance on patient-based questionnaires, for example—make diagnosis of dry eye especially challenging (Kanellopoulos & Asimellis, 2016). Despite promising sensitivities, specificities, or other strong statistical findings, these numbers should still be considered in the context of clinical findings (Akpek et al., 2018).

V. Guidelines and Recommendations

Dysfunctional Tear Syndrome (DTS) Panel (Milner et al., 2017)

A study assessed the new diagnostic techniques and treatment options for DED and associated tear film disorders. Experts from the Cornea, External Disease, and Refractive Society (DTS Panel) convened by the study found examining tear osmolarity useful in diagnosis "in combination with other

clinical assessments and procedures." The same panel also stated that the use of MMP-9 may only be valid for more severe cases of dry eye since the diagnostic test is only positive past 40 ng/mL. The panel recommended that osmolarity be evaluated before any ocular surface assessment, then an evaluation of ocular inflammation can be done, and finally a Schirmer strip test should be done (Milner et al., 2017).

American Academy of Ophthalmology (AAO) (Akpek et al., 2018)

The AAO states "no single test is adequate for establishing the diagnosis of dry eye" and recommends that the combination of findings from diagnostic tests can be useful to understanding a patient's condition. In particular, the AAO states, "tests results should be considered within the context of symptoms and other clinical findings. Rather than relying solely on a single measure of tear osmolarity, correlation with clinical findings or differences in osmolarity over time or under different conditions is more informative for confirming the diagnosis of dry eye. Indeed, most recent studies confirm that normal subjects have exceptionally stable tear film osmolarity, whereas tear osmolarity values in dry eye subjects become unstable quickly and lose homeostasis with environmental changes. These data reinforce the long-held belief that tear film instability due to increased evaporation of tears resulting in hyperosmolarity (i.e., evaporative dry eye) is a core mechanism of the disease" (Akpek et al., 2018). The guideline covers the currently used diagnostic tests, which are as follows: assessment of tear osmolarity, MMP-9, tear production, fluorescein dye or tear function index, tear break up time, ocular surface dye staining, and lacrimal gland function (Akpek et al., 2018).

The following table is provided by Akpek et al. (2018):

Table 2 Characteristic Findings for Dry Eye Disease Diagnostic Tests

Test	Characteristic Findings
Tear osmolarity	Elevated; test-to-test variability; inter-eye differences considered abnormal
Matrix metalloproteinase-9	Indicates presence of inflammation which dictates treatment
Aqueous tear production (Schirmer test)	10 mm or less considered abnormal
Fluorescein dye disappearance test/tear function test	Test result is compared with a standard color scale
Tear break-up time	Less than 10 seconds considered abnormal
Ocular surface dye staining	Staining of inferior cornea and bulbar conjunctiva typical
Lacrimal gland function	Decreased tear lactoferrin concentrations

Tear Film & Ocular Surface (TFOS) Society (Craig, Nelson, et al., 2017; Craig, Nichols, et al., 2017)

The TFOS society held the International Dry Eye Workshop II in 2017. From this workshop, the society published recommendations on the management and treatment of DED. The authors state that when diagnosing DED, it is important to distinguish between the type (aqueous deficient dry eye or

evaporative dry eye) and to determine the underlying etiology as this is crucial for proper management (Craig, Nelson, et al., 2017). These guidelines also stated that "neurotrophic keratopathy accompanied by neuropathic pain and symptoms should definitely be considered in differential diagnosis of patients with intense symptoms despite mild signs (Craig, Nelson, et al., 2017)."

Regarding diagnostic testing, the TFOS states that any patient who obtains a positive score on the Dry Eye Questionnaire-5 or Ocular Surface Disease Index should be subject to a clinical examination. "The presence of any one of three specified signs; reduced non-invasive break-up time; elevated or a large interocular disparity in osmolarity; or ocular surface staining (of the cornea, conjunctiva or lid margin) in either eye, is considered representative of disrupted homeostasis, confirming the diagnosis of DED. If a patient has DED symptoms and their practitioner does not have access to all these tests, a diagnosis is still possible, based on a positive result for any one of the markers, but may require referral for confirmation if the available homeostasis markers are negative (Craig, Nelson, et al., 2017)." After confirmation with any of the aforementioned tests (i.e. reduced non-invasive break-up time <10 seconds, an elevated or large interocular disparity in osmolarity ≥308 m0sm/L in either eye or an interocular difference > 8 m0sm/L, or ocular surface staining including > 5 corneal spots, > 9 conjunctival sports, or a lid margin ≥ 2mm in length and ≥ 25% in width), further evaluation should be conducted including meibography, lipid interferometry, and tear volume measurement to assess severity and help determine the best treatment plan (Craig, Nelson, et al., 2017).

Further, the consensus recommendation from the society on tear osmolarity testing states, "The low variation of normal subjects contributes to the high specificity of the marker and makes it a good candidate for parallelization and therapeutic monitoring. Accordingly, normal subjects don't display elevated osmolarity, so a value over 308 mOsm/L in either eye or a difference between eyes >8 mOsm/L are good indicators of a departure from tear film homeostasis and represent a diseased ocular surface" (Craig, Nichols, et al., 2017).

Regarding MMP-9 testing, the guidelines state that "With the availability of newer immunosuppressive medications and trials concerning these drugs it is logical that inflammation should be assessed. The exact modality used may need to be varied depending on the pathway or target cell upon which the immunosuppressive drug acts, and such diagnostic tools should be used for refining patient selection as well as monitoring after commencement of treatment. Costs of these diagnostic tests should be considered, but these should be calculated from a holistic standpoint. For example, if the tests can assist the channeling of patients to appropriate healthcare services there may be cost savings for reduced referrals" (Craig, Nichols, et al., 2017).

American Optometric Association (AOA, 2010)

The AOA published consensus-based clinical practice guidelines for care of a patient with ocular surface disorders. These guidelines note that there is a "lack of a defined diagnostic test or protocol and a lack of congruity between patient symptoms and clinical tests." The AOA also notes that the condition itself is ill defined and that dry eye is often a symptom of another condition such as blepharitis or another glandular dysfunction (AOA, 2010). There have not been any updates on this topic from the AOA since this 2010 statement.

Consensus Guidelines for Management of Dry Eye Associated with Sjögren Disease (Foulks et al., 2015)

In 2015, clinical guidelines for management of dry eye associated with Sjögren disease were published by a consensus panel which evaluated reported treatments for DED. The recommendations state,

"Evaluation should include symptoms of both discomfort and visual disturbance as well as determination of the relative contribution of aqueous production deficiency and evaporative loss of tear volume. Objective parameters of tear film stability, tear osmolarity, degree of lid margin disease, and ocular surface damage should be used to stage severity of dry eye disease to assist in selecting appropriate treatment options. Patient education with regard to the nature of the problem, aggravating factors, and goals of treatment is critical to successful management. Tear supplementation and stabilization, control of inflammation of the lacrimal glands and ocular surface, and possible stimulation of tear production are treatment options that are used according to the character and severity of dry eye disease" (Foulks et al., 2015). Further, tear osmolarity was identified as the testing method with the highest level of evidence for all DED related tests.

American Society of Cataract and Refractive Surgery (ASCRS) Cornea Clinical Committee (Starr et al., 2019)

American Society of Cataract and Refractive Surgery (ASCRS) released guidelines to aid surgeons in diagnosing visually significant ocular surface disorders (OSD) before refractive surgery. The ASCRS Cornea Clinical Committee recommends initial screening procedures including ASCRS Standard Patient Evaluation of Eye Dryness (SPEED) II questionnaire, tear osmolarity, and matrix metalloproteinase (MMP-9) testing. If any of the three initial screening tests are abnormal, the patient is at risk for ocular surface disease, and additional diagnostic tests can be performed to determine dry eye sub-type. Non-invasive tests are recommended to minimize disruption to the ocular surface, cornea, and tear film. These tests include tear lipid layer thickness, noninvasive tear breakup time (NIKBUT), tear meniscus height, meibography, topography, tear lactoferrin levels, and measures of optical scatter. However, these tests are not essential to the fundamental algorithm.

The ASCRS also notes a point of care test that assesses lactoferrin levels (TearScan). The guideline notes its three proprietary biomarkers which are as follows: "salivary protein-1 (SP-1, immunoglobulin A [IgA], immunoglobulin G [IgG], immunoglobulin M [IgM]); (2) carbonic anhydrase-6 (CA-6, IgA, IgG, IgM); and (3) parotid secretory protein (PSP, IgA, IgG, IgM)". The authors comment that this test can be used to detect Sjögren syndrome early. However, the authors also note that "no member of the ASCRS Cornea Clinical Committee has used it [TearScan] in clinical practice" (Starr et al., 2019).

VI. State and Federal Regulations, as applicable

On December 3, 1993, the FDA approved the lactoferrin microassay system by Touch Scientific, Inc (FDA, 1993). Lactoferrin diagnostic kits are commercially available options for tear film biomarkers (Willcox et al., 2017).

On May 14, 2009, the FDA approved *TearLab* created by Ocusense Inc. From the FDA site: this device is used "to measure the osmolality of human tears to aid in the diagnosis of patients with signs or symptoms of DED, in conjunction with other methods of clinical evaluation" (TearLab, 2009).

On November 20, 2013, the FDA approved *InflammaDry* created by Rapid Pathogen Screening Inc. From the FDA site: "*InflammaDry* is a rapid, immunoassay test for the visual, qualitative in vitro detection of elevated levels of the MMP-9 protein in human tears from patients suspected of having

dry eye to aid in the diagnosis of dry eye in conjunction with other methods of clinical evaluation. This test is intended for prescription use at point-of-care sites" (FDA, 2013).

A search of "dry eye" on the FDA devices webpage on 01/14/2021 yielded 2 results relevant to DED diagnostic testing. Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

VII. Applicable CPT/HCPCS Procedure Codes

Code Number	Code Description
82785	Gammaglobulin (immunoglobulin); IgE
83516	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; qualitative or semiquantitative, multiple step method
83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified
83861	Microfluidic analysis utilizing an integrated collection and analysis device, tear osmolarity

Procedure codes appearing in policy documents are included only as a general reference tool for each policy. They may not be all-inclusive

VIII. Evidence-based Scientific References

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IX. Revision History

Revision Date	Summary of Changes
06-01-2021	Initial presentation