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 et al., 2017).”

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

Evaluation of dry eyes is not covered. BCBSNC will not reimburse for non-covered services or procedures.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Evaluation of Dry Eyes is covered

Not applicable.

When Evaluation of Dry Eyes is not covered

Reimbursement is not allowed for testing for MMP-9 protein in human tears to aid in the diagnosis of patients suspected of having dry eye disease based on comprehensive eye examination.

Reimbursement is not allowed for testing of tear osmolarity in patients suspected of having dry eye to aid in determining the severity of dry eye disease as well as monitor effectiveness of therapy.

Reimbursement is not allowed for testing for lactoferrin and/or IgE to aid in the diagnosis of patients suspected of having dry eye disease.

Policy Guidelines
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).

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 where 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, 2018).

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, 2018). 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 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.

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. 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). The following 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). 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).

There are issues with using tear osmolarity as a diagnostic tool. First, no criteria for the measurement of osmolarity have been established. Studies reviewing osmolarity as a diagnostic 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. A study found the mean tear film osmolarity values range from 270-315 mOsm/L with an overall average of 300 mOsm/L, but the dry eye range was found to be 297-337 mOsm/L with an overall average of 315 mOsm/L. Overall, the current literature on tear osmolarity tests show conflicting results. There have been some studies suggesting the osmolarity shows the strongest correlation with severity of dry eye of the metrics used, but at the same 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). 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).

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 metalloproteinase (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).

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).

Other tests noted by the 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, 2018).

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
Evaluation of Dry Eyes AHS - G2138

other strong statistical findings, these numbers should still be considered in the context of clinical findings (Akpek et al., 2018).

Practice Guidelines and Position Statements

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) (AAO, 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. The guideline covers the currently used diagnostic tests, which are as follows: assessment of tear osmolarity, MMP9, tear production, fluorescein dye or tear function index, tear break up time, ocular surface dye staining, and lacrimal gland function (Akpek et al., 2018).

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

American Optometric Association (AOA) (AOA, 2010)

The AOA notes 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 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.
Evaluation of Dry Eyes AHS - G2138

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).”

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.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

*Applicable service codes: 82785, 83516, 83520, 83861*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources


Evaluation of Dry Eyes AHS - G2138

Centers for Medicare and Medicaid Services (2015). Local Coverage Determination: Diagnostic Evaluation and Medical Management of Moderate-Severe Dry Eye Disease. Retrieved online in July 2017 from https://www.cms.gov/medicare-coverage-database/details/cdcdetails.aspx?LCDId=36232&ver=5&CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=All&KeyWord=dry+eye&KeyWordLookUp=Title&KeyWordSearchType=And&bc=gAAAACAAAAAAAA%3d%3d&


Evaluation of Dry Eyes AHS - G2138


Medical Director review 5/2019


Medical Director review 6/2019

Medical Director review 4/2020

**Policy Implementation/Update Information**

<table>
<thead>
<tr>
<th>Date</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/1/2019</td>
<td>New policy developed. Evaluation of dry eyes is considered <strong>investigational</strong>. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (lpr)</td>
</tr>
<tr>
<td>5/14/19</td>
<td>Reviewed by Avalon 1st Quarter 2019 CAB. Added additional investigational criteria: Testing for lactoferrin and/or IgE to aid in the diagnosis of patients suspected of having dry eye disease is considered investigational and all other testing used in the diagnosis of patients suspected of having dry eye disease is considered investigational. Added the following CPT codes to “Billing/Coding” section: 82785, 83520, 83861. Medical Director review 5/2019. Policy noticed 5/14/19 for effective date 7/16/19. (lpr)</td>
</tr>
<tr>
<td>7/16/19</td>
<td>Specialty Matched Consultant Advisory Panel review 6/19/19. No change to policy statement. Medical Director review 6/2019. (lpr)</td>
</tr>
<tr>
<td>10/29/19</td>
<td>Wording in the policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed. (gm)</td>
</tr>
<tr>
<td>5/12/20</td>
<td>Reviewed by Avalon 1st Quarter 2020 CAB. Medical Director review 4/2020. Updated Description, Policy Guidelines, References. Added “Reimbursement is not allowed for testing for lactoferrin and/or IgE to aid in the diagnosis of patients suspected of having dry eye disease” to When Not-Covered section. Added CPT codes 82785, 83520, 83861 to Billing/Coding section. (lpr)</td>
</tr>
</tbody>
</table>

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational
Evaluation of Dry Eyes AHS - G2138

purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.