Prior Authorization Review Panel
MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review. Policies submitted without this form will not be considered for review.

Plan: Aetna Better Health
Submission Date: 10/01/2019

Policy Number: 0457
Effective Date: 09/13/2019

Policy Name: Dry Eyes

Type of Submission – Check all that apply:

☐ New Policy
☒ Revised Policy*
☐ Annual Review – No Revisions
☐ Statewide PDL

*All revisions to the policy must be highlighted using track changes throughout the document.

Please provide any clarifying information for the policy below:

CPB 0457 Dry Eyes

This CPB is revised to remove topical lifitegrast ophthalmic solution (Xiidra) from the experimental interventions for treatment of severe dry eyes.

This CPB has been revised to state that the following are considered experimental and investigational: (i) determination of conjunctival Nod-1 expression for evaluating the severity of dry eye; (ii) botulinum toxin for treatment of dry eyes; and (iii) cross-linked hyaluronic acid gel occlusive devices for the treatment of dry eye disease.

Name of Authorized Individual (Please type or print):
Dr. Bernard Lewin, M.D.

Signature of Authorized Individual:

Revised July 22, 2019
Dry Eyes

Number: 0457

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.*

I. Aetna considers punctal plugs, standard punctoplasty by electrodessication or electrocautery medically necessary for members with severe dry eyes that are not adequately treated by conservative interventions including a 2 or more week trial of artificial tears, ophthalmic cyclosporine (Restasis) where indicated, and adjustment to medications that may contribute to dry eye syndrome. Members must have a diagnosis of severe dry eyes (also known as dry eye syndrome, keratoconjunctivitis sicca, xerophthalmia, xerosis, or sicca syndrome) with documented objective evidence of lacrimal gland deficiency (e.g., Schirmer test or the tear break-up time test) or evidence of corneal decompensation on slit-lamp exam (i.e., an ocular surface dye staining pattern (rose bengal, fluorescein, or lissamine green) characteristic of dry eye syndrome).

Aetna considers punctal occlusion procedures experimental and investigational for treatment of contact lens intolerance and for all other indications because their effectiveness for indications other than the one listed above has not been established.

II. Replacement of punctal plugs:
Aetna considers repeat punctal plug procedures medically necessary for the following indications:

A. A procedure is considered medically necessary to replace temporary dissolvable punctal plugs with long-lasting semi-permanent punctal plugs. Note: Temporary punctal occlusion with a dissolvable collagen plug that lasts 1 week may be medically necessary to assess the member's response to punctal occlusion. The repeat use of temporary (collagen) plugs for ongoing therapy for dry eye syndrome has no proven value;

B. A separate procedure for occlusion of upper puncta may be medically necessary for persons with insufficient relief from occlusion of lower puncta.

C. Replacement of silicone punctal plugs or other long-lasting plugs is generally not medically necessary more frequently than every 6 months; a more frequent replacement procedure may be medically necessary if the plug does not stay in place because the member fails to follow post-operative instructions. If punctal plugs do not stay in place because of anatomical reasons, other forms of punctal occlusion should be considered.

D. Replacement with flow controller punctal plugs is considered medically necessary for persons who experience epiphoria with standard punctal plugs.

E. Use of shorter-acting punctal plugs composed of resorbable materials that last 3 to 6 months (see background) is considered medically necessary for persons whose dry eyes are due to temporary or seasonal conditions.

III. Aetna considers the use of the laser to occlude the tear duct opening experimental and investigational because it has not been proven to be as effective as electrodessication or thermal cautery.

IV. Aetna considers measurement of tear osmolarity medically necessary for determining the severity of dry eyes.
V. Aetna considers measurement of tear lactoferrin experimental and investigational for assessing persons with dry eyes.

VI. Aetna considers tear film imaging (e.g., the Tear Stability Analysis System) for evaluation of dry eyes or any other indications experimental and investigational because its effectiveness has not been established.

VII. Aetna considers immunoassay for elevated levels of the matrix metalloproteinase-9 protein in human tears (Inflammadry) experimental and investigational for the diagnosis of dry eyes because its clinical value has not been established.

VIII. Aetna considers determination of conjunctival Nod-1 expression experimental and investigational for evaluating the severity of dry eye because the effectiveness of this approach has not been established.

IX. Aetna considers autologous serum tears medically necessary for the treatment of severe dry eyes.

X. Aetna considers the following interventions for the treatment of dry eyes experimental and investigational because the effectiveness has not been established (not an all-inclusive list):

A. Acupuncture
B. Botulinum toxin
C. Cross-linked hyaluronic acid gel occlusive devices
D. Etanercept
E. Hydroxychloroquine
F. Intense pulsed light
G. Mesenchymal stem/stromal cells
H. Minor salivary gland auto-transplantation
I. Rituximab
J. Tacrolimus
K. Thermal pulsation treatment
L. Tofacitinib
M. Topical diquafosol
N. Topical lacritin.
Background

Dry eyes, also known as dry eye syndrome, dysfunctional tear syndrome, keratitis sicca, keratoconjunctivitis sicca, xerophthalmia, xerosis or sicca syndrome, refers to chronic dryness, inflammation and irritation of the cornea and conjunctiva. Dry eye syndrome can occur alone or in conjunction with autoimmune disorders such as rheumatoid arthritis, systemic lupus erythematosus or Sjögren’s syndrome (SS).

Dry eye syndrome occurs when the eye cannot maintain a normal layer of tears to coat the cornea and conjunctiva. Tear fluid provides lubrication to cleanse and moisten the surface of the eye and contains enzymes which protect the eye against bacteria. Dry eye syndrome is generally due to decreased tear production and/or excessive evaporative loss which may have underlying causes such as anatomical abnormalities, medication side effects or other ocular conditions.

Dry eye syndrome is generally classified as mild, moderate or severe. Although most individuals with dry eyes will experience discomfort, some may be relatively asymptomatic or notice symptoms intermittently. In severe cases, the cornea may become damaged or infected and lead to vision loss.

Slit lamp evaluation is used to examine and assess the conjunctiva, cornea and eyelids. There are 3 commonly used objective tests for documenting and assessing the severity of dry eyes: (i) the Schirmer test, (ii) the Rose Bengal test, and (iii) tear film break-up time (TFBUT). All are usually performed by ophthalmologists.

Tear production may be measured using the Schirmer test. A small piece of sterile filter paper, supplied in a standard kit, is placed in the lateral third of the lower eyelid. The extent of wetting in a given time is measured. Wetting of less than 5 mm in 5 mins is considered abnormal. Use of topical anesthesia and blotting of the tear reservoir prior to the test may improve accuracy as a measure of basal tear production. The findings are typically similar in both eyes.

End-organ damage to conjunctival and corneal epithelial cells may be assessed by ocular surface staining, which stains areas of devitalized tissue. Rose bengal, lissamine green, or fluorescein dyes may be used to assess the ocular surface. To perform the Rose Bengal test, 10 microliters of 1 % Rose Bengal are instilled into the inferior fornix of the unanesthetized eye. The patient is asked to blink twice to spread the stain over the conjunctiva and cornea. Staining can then be scored by the ophthalmologist using a slit lamp. A pattern of exposure zone (interpalpebral) corneal and bulbar conjunctival staining is typically seen with aqueous tear
deficiency. Lissamine green dye has a staining profile similar to that of rose bengal and may cause less ocular irritation. It is not recommended for evaluating corneal epithelial disease.

Fluorescein dye stains areas of the corneal and conjunctival epithelia where there is sufficient disruption of intercellular junctions to allow the dye to permeate into the tissue. Saline-moistened fluorescein strips or 1% to 2% sodium fluorescein solution is used to stain the tear film. One to 2 mins after instilling the eye, the ocular surface is examined through a biomicroscope using a cobalt blue filter. Staining is more intense when it is observed with a yellow filter. Mild fluorescein staining can be observed in normal eyes and may be more prominent in the morning. Exposure-zone punctate or blotchy fluorescein staining is observed in dry eye, and staining is more easily visualized on the cornea than on the conjunctiva.

The TFBUT (or tear clearance) provides a global assessment of the function of the lacrimal functional unit and tear exchange on the ocular surface. The test is performed by measuring break-up time and tear osmolality after instillation of fluorescein eye stain. Blinking spreads the dye to coat the tear film (protective layer) of the eye. The eye is then examined under a blue light. Break-up times less than 10 seconds are considered abnormal.

A number of other tests have also been used. Phenol red thread test is similar to the Schirmer’s test but uses special red thread instead of paper and no numbing drops are used. The red thread is placed into the lower eyelid, the eyes are gently closed and after approximately five minutes, the thread is removed and evaluated for moisture.

Tear osmolarity is the measurement of the salt concentration in the tear fluid. Tear osmolarity is considered a key point in dry eye disease (DED) and its measurement is the gold standard in the diagnosis of dry eye. In a prospective, multi-site clinical study, Sullivan et al (2010) evaluated the clinical utility of commonly used tests and tear osmolarity for evaluating the severity of DED. A total of 314 consecutive subjects between the ages of 18 and 82 years were recruited from the general patient population, 299 of which qualified with complete datasets. Osmolarity testing, Schirmer test without anesthesia, TFBUT, corneal staining, meibomian dysfunction assessment, and conjunctival staining were performed bilaterally. A symptom questionnaire, the Ocular Surface Disease Index (OSDI), was also administered to each patient. Distributions of clinical signs and symptoms against a
continuous composite severity index were evaluated. Osmolarity was found to have the highest correlation coefficient to disease severity \( r(2) = 0.55 \), followed by conjunctival staining \( r(2) = 0.47 \), corneal staining \( r(2) = 0.43 \), OSDI \( r(2) = 0.41 \), meibomian score \( r(2) = 0.37 \), TFBUT \( r(2) = 0.30 \), and Schirmer result \( r(2) = 0.17 \). A comparison of standard threshold-based classification with the composite severity index revealed significant overlap between the disease severities of prospectively defined normal and dry eye groups. Fully 63 % of the subjects were found to be poorly classified by combinations of clinical thresholds. The authors concluded that tear film osmolarity was found to be the single best marker of disease severity across normal, mild/moderate, and severe categories. Other tests were found to be informative in the more severe forms of disease; thus, clinical judgment remains an important element in the clinical assessment of dry eye severity. The results also indicate that the initiation and progression of dry eye is multi-factorial and supports the rationale for re-defining severity on the basis of a continuum of clinical signs.

Suzuki et al (2010) studied the association between tear osmolarity and dry eye severity grade, based on a modified Dry Eye Workshop (DEWS) scale, and between osmolarity and the signs and symptoms that determine dry eye disease severity. A total of 19 patients with DED were asked to complete an evaluation of dry eye signs and symptoms composed of the OSDI questionnaire, corneal staining with fluorescein, conjunctival staining with lissamine green, TFBUT, Schirmer's test with anesthesia, and tear sample collection. Tear samples were collected in 5-microliter microcapillaries. Tear osmolarity was measured in the right eye with a tear osmometer. Tear osmolarity correlated significantly with dry eye severity grade (modified DEWS). Schirmer's test and tear osmolarity correlated significantly at \( r = -0.52 \), with Schirmer's test result, with adjustment for age, contributing significantly to the independent estimate of tear osmolarity. The authors concluded that tear osmolarity correlates with dry eye severity and therefore could provide a biomarker for disease severity.

Other evidence suggests that assessment of tear osmolarity provides the most objective, measurable test for determining improvement in patients with DED. Benelli et al (2010) assessed the effectiveness of 3 commercially available lubricant eye drops for the treatment of mild, dry, irritated eyes. This randomized investigator-masked study included 60 patients in which 20 subjects used carboxymethylcellulose sodium (CMC), 0.5 % (Cellufresh), Allergan Inc., Irvine, CA (group 1); 20 subjects used a drop containing polyethylene glycol 400, 2.5 % and
sodium hyaluronate (Blink Intensive Tears, Abbott Medical Optics Inc., Santa Ana, CA) (group 2); and 20 subjects used HP Guar 0.18 % (Systane, Alcon Laboratories Inc., Ft. Worth, TX) (group 3). Study visits were at baseline and 1 month. Tests performed at both visits included Schirmer, TFBUT, visual acuity, fluorescein staining, tear osmolarity and wavefront aberrometry. Osmolarity testing was performed prior to instillation of the lubricant eye drops and then a final time 5 mins after instillation of the drop at both day 1 and day 30. Tear osmolarity was performed only in the right eye and only one time before and after instillation of lubricant eye drops. At day 1, the mean reduction in osmolarity 5 mins after instillation of the lubricant eye drop was, -5.0 +/- 1.9 mOsm/L in group 1, -9.0 +/- 4.2 mOsm/L in group 2 and -5.0 +/- 2.2 mOsm/L in group 3. At day 30, the mean reduction in osmolarity 5 mins after instillation of the lubricant eye drop was, -5.6 +/- 2.3 mOsm/L in group 1; -9.9 +/- 2.8 mOsm/L in group 2 and -4.5 +/- 1.8 mOsm/L in group 3. The differences were statistically significant between groups 1 and 2, and 2 and 3. There was a reduction of osmolarity from day 1 to day 30, but the differences were not statistically significant. These researchers felt that after a 30-day treatment with the lubricant eye drops, the lower osmolarity values could indicate that the tear film is progressing towards a more normal osmolarity value. A future study could examine the tear osmolarity value after 60 or 90 days of usage. LogMAR BCVA results showed an improvement in group 2 compared with baseline with no change in BCVA in groups 1 and 3. There was no statistically significant change from day 1 to 1 month in TFBUT, while the Schirmer test showed an improvement in all groups at 1 month. The authors concluded that assessment of tear osmolarity provides the most objective, measurable test for determining improvement in patients with DED.

Tear osmolarity can be measured in the clinical setting. Versura and colleagues (2010) evaluated tear osmolarity in patients with DED versus a control group to assess its diagnostic performance compared to clinical and laboratory tests performed in either clinical or research settings. Tear osmolarity was measured with the TearLab Osmolarity System (OcuSense) in 25 normal subjects and 105 DED patients (severity score 1 to 4, DEWS). The following tests were also performed: OSDI symptoms questionnaire, Schirmer I test, TFBUT, ferning test, lissamine green staining, tear clearance, corneal esthesiometry, and conjunctival cytology by scraping and imprint. Statistical evaluation was performed by un-paired Student's t and Mann-Whitney tests, the Spearman's rho and the Pearson's r correlation coefficients (significance p < 0.05); all variables were also analyzed for sensitivity, specificity, Receiver Operating Characteristics (ROC) curves, likelihood
ratio LR+, and positive predictive value (PPV). Tear osmolarity normal values were 296.5 +/- 9.8 mOsm/L, increasing values were shown stepwise DED severity (mild to moderate to severe dry eye, respectively: 298.1 +/- 10.6 versus 306.7 +/- 9.5 versus 314.4 +/- 10.1, p < 0.05). A progressive worsening occurred in all the parameters with DED severity increase. Tear osmolarity exhibited the larger correlation strength versus tear clearance, TFBUT and clinical score, strength increased with DED severity, mainly to inflammatory score and corneal sensitivity. Tear osmolarity 305 mOsm/L was selected as cut-off value for dry eye, 309 mOsm/L for moderate dry eye, 318 mOsm/L for severe dry eye (Area-under-the-curve was 0.737, 0.759, and 0.711, respectively). The authors concluded that tear osmolarity can now be considered a test suitable to be performed in a clinical setting. It showed a good performance in the diagnosis of DED, higher than the other tests considered, mainly in severe dry eye. Tear osmolarity values should be interpreted as an indicator of DED evolutionary process to severity.

The American Academy of Ophthalmology (AAO) recommends the following conservative interventions for dry-eye syndrome: elimination of exacerbating medications where feasible; ocular environmental interventions; computer work site interventions; aqueous tear enhancement with topical agents or external means; and medications. In addition, any lid abnormalities should be corrected. Punctal occlusion or tarsorraphy are indicated in severe cases of dry eye syndrome that are refractory to conservative management.

Individuals are often educated in self-management and environmental coping strategies to alleviate early symptoms of mild dry eyes. These approaches are generally recommended regardless of the severity of the condition or other treatments in progress. Examples include: avoidance of air currents, fans or vents; frequent blinking when reading or using computer; frequent breaks from visually demanding tasks; increasing ambient humidity with humidifiers; and warm compresses.

Treatment of dry eye syndrome may include over the counter (OTC) eye lubricants, such as artificial tear substitutes, gels and ointments for mild conditions. For moderate cases anti-inflammatory agents such as topical corticosteroids or other prescription medications may be used. Procedures may be necessary when medical treatments have failed.
Cyclosporine ophthalmic emulsion (Restasis) has been approved by the Food and Drug Administration (FDA) to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. In patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca, cyclosporine emulsion is thought to act as a partial immunomodulator.

Tarsorrhaphy is a surgical procedure in which the eyelids are partially sewn together in order to protect the eye, especially when there is incomplete closure of the eyelids. Tarsorrhaphy is indicated in individuals with exposure keratopathy or severe dry eye who have not responded to other therapies.

Punctal plugs are placed in the puncta (openings into the lacrimal canals that drain into the sinuses) to slow the loss of tears from the eye’s surface. The plugs may be temporary (made of dissolvable collagen or absorbable material) or semi-permanent (made of silicone). If the plugs are effective, the openings to the lacrimal drainage system may be surgically closed (occlusive punctoplasty or closure of the lacrimal punctum).

Guidelines from the American Optometric Association (AOA, 2002) state that punctal occlusion may be necessary for persons with severe dry eyes. In its position statement on punctal occlusion for dry eye, the AAO affirmed that punctal occlusion is a surgical procedure, and that it is considered only in patients with moderately severe to severe dry eye when symptoms and signs of dry eye are not adequately controlled by artificial tears and adjustment of medications that may contribute to dry eye symptoms. The AAO position statement explained that patients with mild dry eye frequently do not respond to punctal occlusion, and that failure of response to artificial tears and punctal occlusion suggests other problems, such as blepharitis.

Punctal plugs provide a temporary or semi-permanent means of occluding the punctum (tear duct opening) in patients with severe dry eyes. Temporary occlusion can be performed using collagen plugs, which dissolve within 1 week, to determine if punctal occlusion results in epiphoria. If a trial of temporary punctal occlusion proves successful, patients may then be offered semi-permanent or permanent forms of occlusion. There is little chance that permanent occlusion would be helpful if the plugs did not decrease symptoms of dry eye syndrome.
The opening of the tear ducts (the puncta) can be permanently occluded to retain tears, although it occasionally leads to excess tearing (epiphoria). Semi-permanent (reversible) punctual occlusion can be achieved by non-dissolvable silicone punctual plugs. Less commonly, semi-permanent occlusion may be achieved by suturing the punctum. If the semi-permanent plugs help but do not remain in position, then permanent surgical punctal occlusion can be performed.

The most typical usage of plugs is in the lower two puncta, but some people have plugs in all 4 ducts (2 lower, 2 upper). Punctal plugs are generally made of silicone; silicone punctal plugs last for 6 or more months. More recently, plugs for long-term (6 or more month) punctal occlusion made of thermodynamic acrylic polymer (SmartPlug) and hydrogel (Oasis FormFit plug) have been developed.

Short-term punctal plugs, composed of absorbable synthetic materials, have been developed that last less than 6 months have been developed for persons with seasonal symptoms or whose dry eyes are caused by a temporary condition. Examples of short-term punctal plugs include those composed of PCL (e.g., Duraplug Extended Temporary Canalicual Inserts), which last 3 to 6 months; absorbable copolymer of glycolic and trimethylene carbonate (ProLong long term absorbable plugs), which last 3 or more months; synthetic polydioxanone (Dissolvable VisiPlug Lacrimal Plugs), which last approximately 3 months; and synthetic collagen (Oasis extended duration absorbable, Oddesy Extend absorbable implants), which last up to 3 months.

Flow controller plugs that allow partial punctal plug occlusion may be used for persons with epiphoria from standard punctal plugs. Examples of these plugs include the FCI Perforated Plugs, and Eagle Vision Flow Controller Plugs.

Surgical punctal occlusion (occlusive punctoplasty) may be achieved by cautery, electrodessication, simple excision, or argon laser surgery. In its position statement, the AAO affirmed its earlier conclusion that the preferred surgical methods of permanent punctal occlusion are electrodessication or thermal cautery, and that laser punctal occlusion should be discouraged because it is less effective and more expensive than other methods.

In a randomized, controlled, double-masked, single-center clinical trial, Geldis and Nichols (2008) described the impact of punctal occlusion in symptomatic dry eye contact lens wearers and the relation between subjective and objective outcomes.
A previously described dry-eye questionnaire was used to determine subject eligibility. Tear interferometry was performed to evaluate pre-lens tear film thickness, contact lens center thickness, and post-lens tear film thickness. Each subject was randomly assigned to receive the punctal plugs or a sham procedure. At the outcome examination, the subject completed the dry-eye questionnaire and answered 1 question rating the efficacy of the punctal plug treatment in addition to undergoing tear interferometry using an identical protocol as the first visit. A total of 19 subjects completed both visits of this study. There was a significant improvement in the dry-eye questionnaire scores from baseline to the outcome visit for both the plug (z = -2.52, p = 0.01) and sham groups (z = -2.93, p = 0.003). A significant increase in pre-lens tear film thickness occurred within the sham group from baseline to the outcome visit (z = -1.96, p = 0.05), but not for the punctal plug group. No other layers measured by interferometry were shown to change significantly for either group. The authors concluded that results comparing the sham and plug groups were not significantly different from each other with regards to the questionnaire score and treatment benefit assessment, indicating either the treatment effect was not detected, although present, or punctal occlusion had no treatment effect at all.

In a pilot study, Hadassah et al (2010) evaluated the effectiveness of succinylated collagen punctal plugs (SCPP) in the treatment of patients with dry eye syndrome (DES). Succinylated collagen punctal plugs were prepared from succinylated collagen with the exact dimensions of the punctum (length 1.5 to 2.5 mm, diameter 0.2 to 0.5 mm, water content between 50 and 55%). Subjects were evaluated for best corrected visual acuity (BCVA), tear fluid levels (TFL), protein content (PC), tear fluid osmolarity (TFO), fluorescence staining of the cornea and TFBUT before and after punctal occlusion with SCPP. Tear fluid levels improved among all the patients after punctal occlusion with SCPP; BCVA showed improvement in case 4 (right eye/left eye), case 5 (left eye) and case 6 (right eye), who had developed dry eyes due to environmental conditions. Protein content increased on day 7 in all the patients and gradually decreased. Tear fluid levels decreased on days 3 and 5 in all patients after punctal occlusion with SCPP, and showed the same levels on day 14; TFL, PC, TFO and TFBUT showed significant improvement in all the patients after punctal occlusion with SCPP. The authors concluded that all patients experienced symptomatic relief after punctal occlusion with SCPP. There was no discomfort, foreign body sensation, plug extrusion, corneal aberration, infection, or formation of pyogenic granuloma with SCPP. They stated that SCPP is a promising alternative to other punctal plugs in the treatment of DES.
In a randomized, patient-assessor blinded, sham acupuncture controlled trial, Shin et al (2010) assessed the safety and effectiveness of acupuncture for ocular symptoms, tear film stability and tear secretion in dry eye patients. A total of 42 subjects with defined moderate to severe dry eye underwent acupuncture treatment 3 times a week for 3 weeks. Seventeen standard points (GV23; bilateral BL2, GB14, TE23, Ex1, ST1 and GB20; and unilateral SP3, LU9, LU10 and HT8 on the left for men and right for women) with “de qi” manipulation for the verum acupuncture group and 17 sham points of shallow penetration without other manipulation for the sham group were applied during the acupuncture treatment. Differences were measured using the ocular surface disease index (OSDI), the visual analog scale (VAS) of ocular discomfort, the TFBUT and the Schimer I test with anesthesia. In addition, adverse events were recorded. There were no statistically significant differences between results on the OSDI, VAS, TFBUT or Schimer I tests from baseline between the verum and sham acupuncture groups. However, results from the within-group analysis showed that the OSDI and VAS in both groups and the TFBUT in the verum acupuncture group were significantly improved after 3 weeks of treatment. No adverse events were reported during this trial. The authors concluded that both types of acupuncture improved signs and symptoms in dry-eye patients after a 4-week treatment. However, verum acupuncture did not result in better outcomes than sham acupuncture.

Lee and colleagues (2011) evaluated the effectiveness of acupuncture as a treatment option for treating the condition of dry eye. These investigators searched the literature using 14 databases from their inceptions to December 3, 2009, without language restrictions. They included randomized clinical trials (RCTs) comparing acupuncture with conventional treatment. Their risk of bias was assessed using Cochrane criteria. A total of 6 RCTs met all the inclusion criteria. Three RCTs compared the effects of acupuncture with artificial tears in patients with xerophthalmia or Sjögren syndrome. A meta-analysis of these data showed that acupuncture improved tear break-up times ($p < 0.0001$), Schirmer test scores ($p < 0.00001$), response rates ($p = 0.002$) and the region of cornea fluorescent staining ($p = 0.0001$) significantly more than artificial tears did. The other 3 RCTs compared the effects of acupuncture plus artificial tears with artificial tears alone -- 2 of these studies failed to show significant effects of acupuncture, while 1 reported significant effects. For Schirmer test scores and frequency of artificial tear usage, 2 RCTs reported superior effects of acupuncture plus artificial tears, while 1 RCT failed to do so. The authors concluded that these findings provide limited evidence
for the effectiveness of acupuncture for treating dry eye. However, the total number of RCTs, the total sample size and the methodological quality were too low to draw firm conclusions.

Akpek and colleagues (2011) performed an outcomes-based review of reported treatment options for patients with dry eye secondary to SS. A search strategy was developed to identify prospective, interventional studies of treatments for SS-associated dry eye from electronic databases. Eligible references were restricted to English-language articles published after 1975. These sources were augmented by hand searches of reference lists from accessed articles. Study selection, data extraction, and grading of evidence were completed independently by 4 or more review authors. The searches identified 3,559 references as of August 10, 2010. After duplicate review of the titles and abstracts, 245 full-text papers were assessed, 62 of which were relevant for inclusion in the review. The authors concluded that in the current literature on SS-associated dry eye, there is a paucity of rigorous clinical trials to support therapy recommendations. Nonetheless, the recommended treatments include topical lubricants, topical anti-inflammatory therapy, and tear-conserving strategies. The effectiveness of oral secretagogues seems greater in the treatment of oral dryness than ocular dryness. Although oral hydroxychloroquine is commonly prescribed to patients with SS to alleviate fatigue and arthralgias, the literature lacks strong evidence for the efficacy of this treatment for dry eye. The authors also noted that "[s]everal studies demonstrate subjective symptom improvement after the use of serum tears, but there is a paucity of objective evidence that the treatment is beneficial in patients with SS".

The Tear Stability Analysis System (TSAS) is a computerized tear film imaging device that is designed to observe the tear film integrity and evaluate ocular surface deficiency. The instrument utilizes an advanced laser to capture and analyze the tear quality of the eye. There is insufficient evidence that the TSAS is effective for the evaluation of patients with dry eyes.

In a prospective case-control study, Gumus et al (2011) evaluated tear film stability in patients with tear dysfunction and an asymptomatic control group by using the novel, non-invasive Tear Stability Analysis System (TSAS). A total of 45 patients with dysfunctional tear syndrome (DTS) were stratified into 3 groups (1, 2, and 3/4) based on clinical severity, with higher scores indicating more severe symptoms; 25 asymptomatic control subjects were evaluated. Tear Stability Analysis System measurements were performed with the RT-7000 Auto Refractor-Keratometer
Images of ring mires projected onto the cornea every second for 6 seconds were captured and analyzed. Focal changes in brightness were calculated as numerical ring break-up (RBU) values, and the elapsed time when the cumulative values (RBU sum) exceeded a threshold was defined as the ring break-up time (RBUT). RBUTs in the DTS groups were all significantly lower than those in the control subjects, with the lowest values found in DTS 3/4. RBUT was significantly shorter in DTS 3/4 than in DTS 1 (p < 0.001). The change in RBU sum over a 6-second period in the DTS groups combined or between the individual groups was statistically significant (p < 0.001), as was the difference between the 1- and 6-second values. For distinguishing between asymptomatic controls and DTS, the sensitivity and specificity of a 5.0-second RBUT cutoff were 82.0 % and 60.0 %, respectively. The authors concluded that the TSAS may be a useful, non-invasive instrument for evaluating tear stability and for classifying DTS severity. The findings from this small case-control study need to be validated by well-designed studies.

In a pilot study, Abelson et al (2012) examined (i) the use of an improved ocular tear film analysis protocol (OPI 2.0) in the Controlled Adverse Environment (CAE) model of dry eye disease, and (ii) the utility of new metrics in the identification of subpopulations of dry eye patients. A total of 33 dry eye subjects completed a single-center, single-visit, pilot CAE study. The primary end-point was mean break-up area (MBA) as assessed by the OPI 2.0 system. Secondary end-points included corneal fluorescein staining, tear film break-up time, and OPI 2.0 system measurements. Subjects were also asked to rate their ocular discomfort throughout the CAE. Dry eye end-points were measured at baseline, immediately following a 90-min CAE exposure, and again 30 mins after exposure. The post-CAE measurements of MBA showed a statistically significant decrease from the baseline measurements. The decrease was relatively specific to those patients with moderate-to-severe dry eye, as measured by baseline MBA. Secondary end-points including palpebral fissure size, corneal staining, and redness, also showed significant changes when pre- and post-CAE measurements were compared. A correlation analysis identified specific associations between MBA, blink rate, and palpebral fissure size. Comparison of MBA responses allowed clinicians to identify subpopulations of subjects who exhibited different compensatory mechanisms in response to CAE challenge. Of note, none of the measures of tear film break-up time showed statistically significant changes or correlations in pre-, versus post-CAE measures. The authors concluded that these findings confirmed that the tear film metric MBA can detect changes in the ocular surface induced by a CAE, and
that these changes are correlated with other, established measures of dry eye disease. The observed decrease in MBA following CAE exposure demonstrated that compensatory mechanisms are initiated during the CAE exposure, and that this compensation may provide the means to identify and characterize clinically relevant subpopulations of dry eye patients. The findings from this small pilot study need to be validated by well-designed studies.

McGinnigle et al (2012) stated that dry eye is a common yet complex condition. Intrinsic and extrinsic factors can cause dysfunction of the lids, lacrimal glands, meibomian glands, ocular surface cells, or neural network. These problems would ultimately be expressed at the tear film-ocular surface interface. The manifestations of these problems are experienced as symptoms such as grittiness, discomfort, burning sensation, hyperemia, and secondary epiphora in some cases. Accurate investigation of dry eye is crucial to correct management of the condition. Techniques can be classed according to their investigation of tear production, tear stability, and surface damage (including histological tests). The application, validity, reliability, compatibility, protocols, and indications for these are important. The use of a diagnostic algorithm may lead to more accurate diagnosis and management. The lack of correlation between signs and symptoms seems to favor tear film osmolarity, an objective biomarker, as the best current clue to correct diagnosis.

Furthermore, the American Academy of Ophthalmology’s guideline on “Dry eye syndrome” (AAO, 2011) as well as the AAO’s “Dry eye syndrome summary benchmark” (AAO, 2012) did not mention the use of the Tear Stability Analysis System.

In a review on “Emerging drugs for the treatment of dry eye disease”, Gadaria-Rathod et al (2013) noted that recently discovered pathophysiology of DED has prompted investigators to explore new molecules that target the core mechanisms that drive DED. These include anti-inflammatory/immune-modulatory drugs, lubricant, hormones, secretagogues, and autologous serum.

Autologous eye drops (autologous serum tears) have been proposed for dry eye syndrome and are made by mixing the individual’s serum with other substances. An American Academy of Ophthalmology Dry Eyes Preferred Practice Pattern (AAO, 2013) states that autologous serum drops have been reported to improve ocular irritation symptoms as well as conjunctival and corneal dye staining in patients with severe dry eyes from Sjogren syndrome and graft-versus-host disease (GVHD).
In a Cochrane review, Pan and colleagues (2013) evaluated the safety and effectiveness of autologous serum eye drops (AS) compared to artificial tears for treating dry eye. These investigators searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (The Cochrane Library 2013, Issue 3), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE,(January 1950 to April 2013), EMBASE (January 1980 to April 2013), Latin American and Caribbean Literature on Health Sciences(LILACS) (January 1982 to April 2013), themetaRegister of Controlled Trials (mRCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). They also searched the Science Citation Index Expanded database (September 2013) and reference lists of included studies. They did not use any date or language restrictions in the electronic searches for trials. They last searched the electronic databases on April 15, 2013. These researchers included RCTs in which AS was compared to artificial tears in the treatment of dry eye in adults. Two review authors independently screened all titles and abstracts and assessed full-text articles of potentially eligible trials. Two review authors extracted data and assessed the methodological quality and characteristics of the included trials. They contacted investigators for missing data. For both primary and secondary outcomes, they reported mean differences with corresponding 95% confidence intervals (CIs) for continuous outcomes. These investigators identified 4 eligible RCTs in which AS was compared with artificial tear treatment or saline in individuals (n = 72 participants) with dry eye of various etiologies (Sjogren’s syndrome-related dry eye, non-Sjogren’s syndrome dry eye and post-operative dry eye induced by laser-assisted in situ keratomileusis (LASIK)). The quality of the evidence provided by these trials was variable. A majority of the risk of bias domains were judged to have an unclear risk of bias in 2 trials owing to insufficient reporting of trial characteristics. One trial was considered to have a low risk of bias for most domains while another was considered to have a high risk of bias for most domains. Incomplete outcome reporting and heterogeneity in the participant populations and follow-up periods prevented the inclusion of these trials in a summary meta-analysis. For the primary outcome, improvement in participant-reported symptoms at 1 month, 1 trial (12 participants) showed no difference in participant-reported symptoms between 20% AS and artificial tears. Based on the results of 2 trials in 32 participants, 20% AS may provide some improvement in participant-reported symptoms compared to traditional artificial tears after 2 weeks of treatment. One trial also showed positive results with a mean difference in tear break-up time (TBUT) of 2.00 seconds (95%
CI: 0.99 to 3.01 seconds) between 20 % AS and artificial tears after 2 weeks, which were not similar to findings from the other trials. Based on all other objective clinical assessments included in this review, AS was not associated with improvements in aqueous tear production measured by Schirmer's test (2 trials, 33 participants), ocular surface condition with fluorescein (4 trials, 72 participants) or Rose Bengal staining (3 trials, 60 participants), and epithelial metaplasia by impression cytology compared to artificial tears (1 trial, 12 participants). Data on adverse effects were not reported by 3 of the included studies. In one study, there were no serious adverse events reported with the collection of and treatment with AS. The authors concluded that overall there was inconsistency in the possible benefits of AS in improving participant-reported symptoms and TBUT and lack of effect based on other objective clinical measures. Moreover, they stated that well-planned, large, high-quality RCTs are warranted, in different severities of dry eye and using standardized questionnaires to measure participant-reported outcomes and objective clinical tests as well as objective biomarkers to assess the benefit of AS therapy for dry eye.

Gottenberg and colleagues (2014) stated that primary SS is a systemic autoimmune disease characterized by mouth and eye dryness, pain, and fatigue. Hydroxychloroquine is the most frequently prescribed immunosuppressant for the syndrome. However, evidence regarding its effectiveness is limited. These investigators evaluated the effectiveness of hydroxychloroquine for the main symptoms of primary SS: dryness, pain, and fatigue. From April 2008 to May 2011, a total of 120 patients with primary SS according to American-European Consensus Group Criteria from 15 university hospitals in France were randomized in a double-blind, parallel-group, placebo-controlled trial. Participants were assessed at baseline, week 12, week 24 (primary outcome), and week 48. The last follow-up date for the last patient was May 15, 2012. Patients were randomized (1:1) to receive hydroxychloroquine (400 mg/day) or placebo until week 24. All patients were prescribed hydroxychloroquine between weeks 24 and 48. The primary end-point was the proportion of patients with a 30 % or greater reduction between weeks 0 and 24 in scores on 2 of 3 numeric analog scales (from 0 [best] to 10 [worst]) evaluating dryness, pain, and fatigue. At 24 weeks, the proportion of patients meeting the primary end-point was 17.9 % (10/56) in the hydroxychloroquine group and 17.2 % (11/64) in the placebo group (odds ratio [OR], 1.01; 95 % CI: 0.37 to 2.78; p = 0.98). Between weeks 0 and 24, the mean (SD) numeric analog scale score for dryness changed from 6.38 (2.14) to 5.85 (2.57) in the placebo group and 6.53 (1.97) to 6.22 (1.87) in the hydroxychloroquine
group. The mean (SD) numeric analog scale score for pain changed from 4.92 (2.94) to 5.08 (2.48) in the placebo group and 5.09 (3.06) to 4.59 (2.90) in the hydroxychloroquine group. The mean (SD) numeric analog scale for fatigue changed from 6.26 (2.27) to 5.72 (2.38) in the placebo group and 6.00 (2.52) to 5.94 (2.40) in the hydroxychloroquine group. All but 1 patient in the hydroxychloroquine group had detectable blood levels of the drug. Hydroxychloroquine had no efficacy in patients with anti-SSA autoantibodies, high IgG levels, or systemic involvement. During the first 24 weeks, there were 2 serious adverse events in the hydroxychloroquine group and 3 in the placebo group; in the last 24 weeks, there were 3 serious adverse events in the hydroxychloroquine group and 4 in the placebo group. The authors concluded that among patients with primary SS, the use of hydroxychloroquine compared with placebo did not improve symptoms during 24 weeks of treatment. They stated that further studies are needed to evaluate longer-term outcomes.

Sacchetti et al (2014) noted that topical cyclosporine A (CsA) is a therapeutic option for DED to control ocular surface inflammation and improve tear function. These investigators reviewed data from RCTs evaluating safety and effectiveness of topical CsA treatment for DED. Articles published up to December 2012 were identified from Medline, Embase and the Cochrane Controlled Trials Register. A total of 18 RCTs that evaluated the safety and effectiveness of different topical CsA formulations for the treatment of DED were selected according to the set criteria. The Jadad score was calculated to assess RCT quality. The mean Jadad score of the included RCTs was 2.8 ± 0.6. All CsA formulations proved safe for the treatment of DED. Symptoms improved in 100 % (9/9) RCTs, tear function improved in 72 % (13/18) RCTs and ocular surface damage was ameliorated in 53 % (9/17) RCTs in patients with DED. No improvements with CsA treatment versus control were observed in DED resulting from surgical procedures, contact lens use and thyroid orbitopathy. Statistical comparison of CsA efficacy through a meta-analysis of data was not possible due to a lack of standardized criteria and comparable outcomes among studies. The authors concluded that although topical CsA appears to be a safe treatment for DED, evidence emerging from RCTs is limited, and this affected the strength of recommendations to healthcare providers and policymakers for optimal management. They stated that standardized diagnostic criteria to assess the efficacy of topical CsA are recommended to improve the design of future RCTs in DED.
Colligris et al (2014) noted that the vast majority of new compounds under development for the treatment of dry eye disease are anti-inflammatories, steroids, non-steroids and antibiotics; however, there are also some novel lubricating drops and mucin-tear secretagogues. A future aggressive therapy for dry eye, depending on the severity of the symptoms, would include combinations of soft steroids, anti-inflammatories, such as cyclosporine A, with the addition of the new polyvalent mucin and tear secretagogues.

Zhou and Wei (2014) conducted a systematic review and meta-analysis of RCTs on CsA versus placebo in treating DES to evaluate the treatment safety and effectiveness of CsA. These investigators searched for RCTs published after 1990, in MEDLINE, EMBASE, the Cochrane library, and ClinicalTrials.gov. The RCTs that were included compared topical CsA and placebo for DES treatment by evaluating scores of ocular surface disease index, tear break-up time, or Schirmer test. Cochrane risk of bias tool was used for assessing the risk of bias. These researchers included 12 RCTs involving 3,034 eyes of 1,660 participants. They observed statistically significant improvements on scores of break-up time (standardized mean difference [SMD], 0.80; 95 % CI: 0.13 to 1.46; I = 95 %) and scores of Schirmer test with anesthesia (SMD, 0.78; 95 % CI: 0.09 to 1.46; I = 97 %) after treatment with topical CsA. Scores of ocular surface disease index (SMD, 0.77; 95 % CI: -1.05 to 2.58; I = 98 %) and scores of Schirmer test without anesthesia (SMD, 0.08; 95 % CI: -0.11 to 0.27; I = 0 %) were not improved. Adverse events (odds ratio [OR], 1.61; 95 % CI: 1.28 to 2.02; I = 21 %) were observed. The authors concluded that topical CsA could be an effective treatment for DES, especially for DES associated with conjunctival injury. Moreover, they stated that further RCTs with larger sample sizes for different clinical types of DES are needed to determine the effectiveness and limitation for different clinical types of DES.

Vijmasi et al (2014) stated that lacritin is a tear glycoprotein with pro-secretory, pro-survival, and mitogenic properties. These researchers examined lacritin levels in the tears of SS patients and explored the therapeutic potential of topical lacritin for the treatment of keratoconjunctivitis sicca. Tears from healthy controls (n = 14) and SS patients (n = 15) were assayed for lacritin using a C-terminal antibody. In a paired-eye study, autoimmune regulator (Aire) knockout (KO) mice (n = 7) were treated 3 times daily for 21 days with 10 μL of 4 μM lacritin (left eye) or vehicle (PBS) control (right eye). Tear secretion and ocular surface integrity were assessed at baseline and after treatment. Immunohistochemical staining of CD4+
T cells, cytokeratin-10 (K10), and cytokeratin-12 (K12) expression in the cornea and CD4+ T cell infiltration in the lacrimal glands were assessed. Lacritin monomer (421.8 ± 65.3 ng [SS] versus 655.8 ± 118.9 ng [controls]; p = 0.05) and C-terminal fragment protein (125 ± 34.1 ng [SS] versus 399.5 ± 84.3 ng [controls]; p = 0.008) per 100 μL of tear eluate were significantly lower in SS patients. In Aire KO mice treated with lacritin, tear secretion increased by 46 % (13.0 ± 3.5 mm versus 8.9 ± 2.9 mm; p = 0.01) and lissamine green staining score significantly decreased relative to baseline (-0.417 ± 0.06 versus 0.125 ± 0.07; p = 0.02). Expression of K10 but not K12 in the cornea was significantly decreased in lacritin-treated eyes. Focal CD4+ T cell infiltration of the lacrimal glands was significantly reduced on the lacritin-treated side versus the untreated side. The authors concluded that lacritin is significantly reduced in the tears of SS patients; topically administered lacritin has therapeutic potential for the treatment of aqueous-deficient dry eye disease.

Devauchelle-Pensec et al (2014) noted that primary SS (pSS) is an autoimmune disorder characterized by ocular and oral dryness or systemic manifestations. In a randomized, placebo-controlled, parallel-group trial, these researchers evaluated the effectiveness and harms of rituximab in adults with recent-onset or systemic pSS. Study personnel (except pharmacists), investigators, and patients were blinded to treatment group. A total of 120 patients with scores of 50 mm or greater on at least 2 of 4 visual analogue scales (VASs) (global disease, pain, fatigue, and dryness) and recent-onset (< 10 years) biologically active or systemic pSS were included in this study. Participants were randomized (1:1 ratio) to rituximab (1 g at weeks 0 and 2) or placebo. Primary end-point was improvement of at least 30 mm in 2 of 4 VASs by week 24. No significant difference between groups in the primary end-point was found (difference, 1.0 % [95 % CI: -16.7 % to 18.7 %]). The proportion of patients with at least 30-mm decreases in at least 2 of the 4 VAS scores was higher in the rituximab group at week 6 (22.4 % versus 9.1 %; p = 0.036). An improvement of at least 30 mm in VAS fatigue score was more common with rituximab at weeks 6 (p < 0.001) and 16 (p = 0.012), and improvement in fatigue from baseline to week 24 was greater with rituximab. Adverse events were similar between groups except for a higher rate of infusion reactions with rituximab. The authors conclude that rituximab did not alleviate symptoms or disease activity in patients with pSS at week 24, although it alleviated some symptoms at earlier time points.
Valim et al (2015) noted that DED is a multi-factorial disease of the tears and ocular surface that causes tear film instability with potential damage to the ocular surface. The prevalence of dry eye in the world population ranges from 6 to 34 %. It is more common in those aged over 50, and affects mainly women. Since the introduction of the Schirmer's test in 1903, other tests have been developed to evaluate dry eye, such as biomicroscopy, TBUT, vital dyes (lissamine green and rose bengal), fluorescein, leaf fern test, corneal sensitivity test, conjunctiva impression cytology, optical coherence tomography (OCT), and tear osmolarity measurement. Although there is no gold standard, it is advisable to combine at least 2 tests. Strategies for treating DED have recently been modified and include patient education, tear substitute, corticosteroids, secretagogues, fatty acids, immunomodulators, occlusion of lacrimal puncta surgery and, tarsorrhaphy. Biological therapy and new topical immunomodulators such as tacrolimus, tofacitinib and IL-1 receptor inhibitor are being tested.

Intense pulsed light (IPL) delivers bursts of light at specific wavelengths. The light energy is converted to heat. IPL therapy has been suggested as a treatment for dry eye syndrome. In a retrospective non-comparative interventional case-series study, Toyos et al (2015) examined the clinical benefits of intense-pulsed-light therapy for the treatment of dry-eye disease caused by meibomian gland dysfunction (MGD). A total of 91 patients presenting with severe dry eye syndrome were included in this study. Treatment included intense-pulsed-light therapy and gland expression at a single out-patient clinic over a 30-month study. Pre/post tear breakup time data were available for a subset of 78 patients. For all patients, a specially developed technique for the treatment of dry eye syndrome was applied as a series of monthly treatments until there was adequate improvement in dry eye syndrome symptoms by physician judgment, or until patient discontinuation. Primary outcomes included change in TBUT, self-reported patient satisfaction, and adverse events. Physician-judged improvement in dry eye TBUT was found for 68 of 78 patients (87 %) with 7 treatment visits and 4 maintenance visits on average (medians), and 93 % of patients reported post-treatment satisfaction with degree of dry eye syndrome symptoms. Adverse events, most typically redness or swelling, were found for 13 % of patients. No serious adverse events were found. The authors concluded that although preliminary, study results of intense-pulsed-light therapy treatment for dry eye syndrome caused by meibomian gland dysfunction are promising. They stated that a multi-center clinical trial with a larger sample, treatment comparison groups, and randomized controlled trials is currently underway.
Lee and colleagues (2015) stated that DES is one of the most common ocular diseases affecting nearly 10% of the U.S. population. Most of the currently available treatments are palliative, and few therapeutic agents target biological pathway of DES. Although DES is a multi-factorial disease, it is well-known that inflammation in the ocular surface plays an important role in the pathogenesis of DES. Mesenchymal stem/stromal cells (MSCs) have been shown to repair tissues by modulating excessive immune responses in various diseases. Thus, these investigators examined the therapeutic potential of MSCs in a murine model of an inflammation-mediated dry eye that was induced by an intra-orbital injection of concanavalin A. They found that a peri-orbital administration of MSCs reduced the infiltration of CD4(+) T cells and the levels of inflammatory cytokines in the intra-orbital gland and ocular surface. Also, MSCs significantly increased aqueous tear production and the number of conjunctival goblet cells. Subsequently, corneal epithelial integrity was well-preserved by MSCs. The authors concluded that the results demonstrated that MSCs protect the ocular surface by suppressing inflammation in DES, and suggested that MSCs may offer a therapy for a number of ocular surface diseases where inflammation plays a key role.

An UpToDate review on “Dry eyes” (Shtein, 2015) states that “A 2013 systematic review of 18 randomized trials concluded that topical cyclosporine was a safe treatment for dry eyes. While meta-analysis was not possible because of lack of standardized criteria and outcome measures, 9 of 9 trials that evaluated symptoms and 13 of 18 trials that evaluated tear function found improvement. No improvements were found in patients with dry eyes from surgical procedures, contact lens use, or thyroid orbitopathy … Despite the available evidence, we have not seen such a degree of beneficial results in our practice. There appears to be a subset of patients who do respond favorably to this treatment, but there are no good predictive models available to guide clinical decision-making at this time.

The American Academy of Ophthalmology Preferred Practice Pattern (AAO, 2018) stated that “Topical lifitegrast 5% was approved by the FDA for treatment of dry eye. Published studies show benefit in signs (corneal and conjunctival staining) as well as symptoms (eye dryness score and ocular discomfort) over a period of 3 months of using lifitegrast. Although, the drug seems to be safe over 12 months, long-term effects are unknown.”

InflammaDry
InflammaDry uses a tear sample to detect the inflammatory marker matrix metalloproteinase-9 (MMP-9), which may be elevated in the tears of individuals with dry eye disease.

In a pilot study, Zimmermann and Erb (2013) analyzed the matrix metalloproteinase-9 protein (MMP-9) concentration in tear film in pseudoexfoliation (PEX) syndrome. In addition, an assessment of the feasibility, reliability and readability of the test was done. These researchers randomly selected 10 patients with PEX syndrome and 10 healthy control subjects and measured tear film MMP-9 of 1 eye with the RPS InflammaDry Detector (Rapid Pathogen Screening Inc., Sarasota, FL). These researchers detected increased levels of MMP-9 in tear film in PEX syndrome; 80% of the PEX patients and 20% of the controls showed a positive test result (greater than or equal to 40 ng/ml MMP-9) indicating a test specificity and sensitivity of 80%. This corresponded approximately to the published values for the DE (sensitivity: 87%, specificity: 92%). The performance of the test is simple. The patients tolerated the inclusion of the test strips well. However, it is difficult to estimate whether enough tear film was used and in many cases, the intensity of the "indicator line" was weak. The authors concluded that the rapid MMP-9-immunoassay is a novel, meaningful approach for the detection of inflammatory activity of the ocular surface. They have shown an up-regulation of the non-specific inflammatory marker MMP-9 in tear film in PEX syndrome and suggested an association with a tear film disorder. However, they stated that an improvement in the estimation of the amount of collected tears and readability is desirable.

Sambursky, et al. (2014) conducted a study was to determine the negative and positive agreement of a point-of-care matrix metalloproteinase-9 test in confirming the diagnosis of dry eye and to evaluate the ease of use by untrained ophthalmic technicians. The study was a prospective, sequential, masked, clinical trial with 4 clinical trial sites. The InflammaDry test was compared with the clinical assessment of tear break-up time, Schirmer tear testing, and corneal staining for the confirmation of dry eye, both with and without the inclusion of the Ocular Surface Disease Index (OSDI), as a confirmatory test. The study enrolled 237 patients. If the OSDI is included in the definition for mild dry eye, the InflammaDry test was shown to have a total positive agreement of 81% (127/157) and a negative agreement of 98% (78/80). The removal of the OSDI shifted the categorization of 11 patients previously considered positive for dry eye to become categorized as negative for dry eye. If the OSDI is excluded from the definition of dry eye, the
InflammaDry test demonstrates a positive agreement of 86% (126/146) and a negative agreement of 97% (88/91) against the clinical assessment. The investigators concluded that the InflammaDry test demonstrates a high positive and negative agreement for confirming suspected dry eye disease. In addition, the test was safely and effectively performed by untrained operators. These findings support the intended use of the InflammaDry test as an aid in the diagnosis of dry eye.

Bartlett et al (2015) stated that the accurate diagnosis and classification of DED is challenging owing to wide variations in symptoms and lack of a single reliable clinical assessment. In addition, changes and severity of clinical signs often do not correspond to patient-reported symptoms. To better understand the inconsistencies observed between signs and symptoms, these researchers conducted a systematic literature review to evaluate published studies reporting associations between patient-reported symptoms and clinical signs of DED. PubMed and Embase were searched for English-language articles on the association between clinical signs and symptoms of DED up to February 2014 (no lower limit was set). A total of 34 articles were identified that assessed associations between signs and symptoms, among which 33 unique studies were reported. These included 175 individual sign-symptom association analyses. Statistical significance was reported for associations between sign and symptom measures in 21 of 33 (64%) studies, but for only 42 of 175 (24%) individual analyses. Of 175 individual analyses, 148 reported correlation coefficients, of which the majority (129/148; 87%) were between -0.4 and 0.4, indicating low-to-moderate correlation. Of all individual analyses that demonstrated a statistically significant association, 56% of reported correlation coefficients were in this range. No clear trends were observed in relation to the strength of associations relative to study size, statistical methods, or study region, although results from 3 studies suggested that disease severity may be a factor. The authors concluded that associations between DED signs and symptoms were low and inconsistent, which may have implications for monitoring the response to treatment, both in the clinic and in clinical trials. They stated that further studies to increase understanding of the etiopathogenesis of DED and to identify the most reliable and relevant measures of disease are needed to enhance clinical assessment of DED and the measurement of response to therapeutic interventions.

Foulks and associates (2015) provided a consensus clinical guideline for management of DED associated with Sjogren disease by evaluating published
treatments and recommending management options. Using the 2007 Report of the International Workshop on Dry Eye (DEWS) as a starting point, a panel of eye care providers and consultants evaluated peer-reviewed publications and developed recommendations for evaluation and management of dry eye disease associated with Sjogren disease. Publications were graded according to the AAO Preferred Practice Pattern guidelines for level of evidence. Strength of recommendation was according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines. The panel recommended: (i) 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, (ii) objective parameters of tear film stability, tear osmolarity, degree of lid margin disease, and ocular surface damage should be used to stage severity of DED to assist in selecting appropriate treatment options, and (iii) 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. This consensus clinical guideline did not mention measurement of MMP-9 levels in the tear as a diagnostic test.

Chan and colleagues (2015) evaluated the performance of a point-of-care test for detection of MMP-9 levels in post-laser-assisted in-situ keratomileusis (LASIK) dry eyes. A comparative study between patients with mild-to-moderate post-LASIK dry eyes and age-matched normal subjects was conducted. Ocular surface disease index, TBUT, and tear film MMP-9 and total protein levels were compared between the 2 groups. A point-of-care test device (InflammaDry) was used to confirm elevated MMP-9 levels in tear film. A total of 14 post-LASIK dry eyes and 34 normal eyes were included. There was no significant difference in age and gender between both groups (p > 0.175). The OSDI was significantly higher (25.5 ± 7.7 versus 7.4 ± 2.5; p < 0.001) and TBUT levels were significantly lower (5.4 ± 0.9 versus 13.5 ± 2.3; p < 0.001) in patients with dry eye compared with normal subjects. 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 greater than 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 greater than or equal to 38.03 ng/ml. Agreement between InflammaDry and MMP-9 was excellent with Cohen κ value of 0.857 in post-LASIK dry eyes. The authors concluded that only 50 % of post-LASIK dry eyes were found to have significant inflammation associated with elevated MMP-9. They stated that the OSDI is useful to non-
specifically identify patients with symptomatic dry eye while the InflammaDry
determined which patients with dry eye were associated with significant
inflammation that may guide therapeutic management decisions.

In a cross-sectional study, Lanza et al (2016) compared DE symptoms and signs in
subjects who tested positive versus those who tested negative for ocular surface
MMP-9 using the InflammaDry point of care test. Individuals seen in the Miami
Veterans Affairs eye clinic with DE symptoms, as evidenced by DE questionnaire 5
(DEQ5) greater than or equal to 6, were given standardized questionnaires to
assess DE symptoms and ocular and non-ocular pain complaints. Also, a complete
evaluation was conducted to measure ocular surface signs of DE. InflammaDry
testing was performed once in each eye, per the manufacturer’s instructions. The
main outcome measure was a comparison of DE symptoms and signs in MMP-9
positive versus negative subjects. Of 128 subjects, 50 (39 %) were positive for MMP-
9 for InflammaDry testing in either eye. No statistically significant differences in
mental health indices, DE symptoms, or ocular surface signs were seen in subjects
based on MMP-9 status. The authors concluded that in their population, there was no
difference in the DE profile by both symptoms and signs between those testing
positive versus negative for MMP-9 on the ocular surface, suggesting that clinical
examination alone cannot predict patients with clinically significant inflammation.

Schargus and colleagues (2015) noted that given that early-stage dry eye is difficult
to diagnose, these researchers examined the performance of MMP-9 and TFO in a
cohort of elderly patients with potential DED. A group of 20 patients, aged 60 years
and above, previously undiagnosed with DED were selected. The following DED
tests were performed: tear osmolarity, MMP-9 (InflammaDry), Schirmer test, tear
film break-up time, Ocular Surface Disease Index (OSDI) questionnaire, corneal
fluorescein staining, and conjunctival lissamine green staining. MMP-9
concentrations in tears collected through Schirmer strips were analyzed by an MMP-
9 enzyme-linked immunosorbent assay [ELISA]. Subjects were classified by
symptoms (classification A: OSDI greater than or equal to 10, n = 9), based on
suspected mild dry eye (classification B: n = 14), TFO difference greater than 8
mOsm/L between both eyes (classification C: n = 13), and TFO cut-off at 308
mOsm/L (classification D: greater than 308 mOsm/L, n = 11). A total of 11 % (1/9)
of the symptomatic and 14 % (2/14) of the suspected mild dry eye were positive for
MMP-9. InflammaDry MMP-9 tests were confirmed to be accurate through an
ELISA; 67 % (6/9) of the symptomatic and 64 % (9/14) of the suspected mild dry
eye were positive for tear osmolarity. None of the evaluated tear film parameters showed a significant correlation, although tear osmolarity and symptoms trended toward significance ($r = 0.433, p = 0.06$), whereas MMP-9 and corneal staining showed a positive association ($r = 0.376, p = 0.10$). The authors concluded that similar to corneal staining, the MMP-9 is likely a late-stage sign that is rarely overexpressed in mild subjects, whereas tear osmolarity tends to be a more frequent early indicator of ocular surface disequilibrium within mild subjects.

Kanellopoulos and Asimellis (2016) stated that DED is a multi-factorial, progressive, and chronic disease of the tears and ocular surface. The disease is multi-factorial and has intermittent symptoms. Discomfort, visual disturbance, tear film instability with potential damage to the ocular surface, and increased tear film osmolarity are known associates. Dry eye is a common clinical problem for eye-care providers worldwide and there is a large number of clinical investigative techniques for the evaluation of DED. Despite this, however, there is no globally accepted guideline for the diagnosis of DED and none of the available tests may hold the title of the "gold standard". The majority of the techniques involved in the diagnosis of DED, particularly for its early stages, has a large degree of subjectivity. These investigators reviewed existing investigative techniques for DED and presented a new objective screening technique for DED based on OCT.

Sambursky (2016) stated that the presence of clinically significant inflammation has been confirmed in the tears of 40 to 65% of patients with symptoms of DED. These researchers performed a retrospective, single-center, medical chart review of 100 patients. All participants were tested with the InflammaDry test to examine if patients exhibited elevated levels of MMP-9. InflammaDry-positive patients were started on a combination of cyclosporine 0.05% twice-daily, 2,000 to 4,000 mg oral omega-3 fatty acids, as well as frequent artificial tear replacement. InflammaDry-negative patients were started on 2,000 to 4,000 mg of oral omega-3 fatty acids and frequent artificial tear replacement. Each patient was re-tested at approximately 90 days. A symptom questionnaire was performed at the initial visit and at 90 days. A total of 60% of the patients with DED symptoms tested positive for elevated MMP-9 at the initial visit; 78% of all patients returned for follow-up at approximately 90 days including 80% (48/60) of the previously InflammaDry-positive patients and 75% (30/40) of the previously InflammaDry-negative patients. A follow-up symptom questionnaire reported at least 75% symptomatic improvement in 65% (31/48) of the originally InflammaDry-positive patients and in 70% (21/30) of the initially InflammaDry-negative patients. Symptomatic
improvement of at least 50% was reported in 85% (41/48) of previously InflammaDry-positive patients and 86% (26/30) of previously InflammaDry-negative patients. Following treatment, 54% (26/48) of previously InflammaDry-positive patients converted to a negative InflammaDry result. The authors concluded that identifying which symptomatic DED patients have underlying inflammation may predict patient responses to treatment and influence clinical management strategies.

This study had several drawbacks: (i) this trial was not a prospective RCT; and retrospective studies have inherent weakness. A future trial should compare the effectiveness of cyclosporine in both the InflammaDry-negative and -positive patients, (ii) rigid periodic therapeutic monitoring throughout the study was not performed. In addition, 22% of patients did not return for the 90-day follow-up period, which could influence the reported clinical success rates, and (iii) the omega-3 therapy was not standardized and its effectiveness was influenced by bioavailability and absorption. These researchers stated that clinically significant inflammation was present only in approximately 50% of the patients with symptomatic DED. This was evidenced by less than 57% of all corne’s studies revealing conjunctival or corneal staining, and the demonstration of only 39 to 57% symptomatic improvement found in clinical trials evaluating the effectiveness of cyclosporine and loteprednol, respectively. Coupled with the results from this study, it suggested that identifying symptomatic DED patients with underlying inflammation may help predict patient responses to treatment and influence clinical patient management strategies. These findings need to be validated by well-designed studies.

Dohlman and associates (2016) noted that DED is a complex, multi-factorial condition that is challenging to diagnose and monitor clinically. To-date, diagnosis has consisted largely of self-reported symptom questionnaires and a collection of clinical tests including vital dye staining, estimation of TBUT and Schirmer’s testing, as no gold standard exists. As the field of DED has made progress in understanding disease pathogenesis, new methods for assessment of this condition have been developed. Dry eye disease is now known to be characterized by tear hyper-osmolarity and ocular surface inflammation, and there are now commercially available devices that accurately and reliably measure tear osmolarity and MMP-9, a marker of inflammation and tissue breakdown. In addition, there are a variety of imaging modalities that have shown promise in their ability to identify patients with DED by assessing tear film dimensions and tear film instability. The
authors concluded that there is a significant need for the development of tear film assessments for accurate diagnosis and monitoring of dry eye; there are a number of new devices and techniques that have shown promise in their ability help clinicians manage patients with DED.

The American Academy of Ophthalmology Preferred Practice Pattern on dry eye syndrome (AAO, 2018) stated: "A commercially available point-of-care matrix metalloproteinase-9 (MMP-9) test can also be used as an aid in the diagnosis of dry eye. The qualitative nature of this test can be used to assess change in the disease state. Although the test does not differentiate dry eye from other inflammatory ocular surface diseases, it may aid in the management."

Etanercept

Shih and colleagues (2017) stated that primary Sjogren's syndrome is an autoimmune disease characterized by dry eye and dry mouth. These researchers systematically reviewed all the RCTs published in the last 15 years that included ocular outcomes. They found 22 trials involving 9 topical, 10 oral, 2 intravenous and 1 subcutaneous modalities of treatment. Fluoromethalone eye drops over 8 weeks were more effective than topical cyclosporine in the treatment of dry eye symptoms and signs; similarly, indomethacin eye drops over 1 month were more efficacious than diclofenac eye drops. Oral pilocarpine 5-mg twice-daily over 3 months was superior to use of lubricants or punctal plugs for treating dry eye, but 5% of participants had gastro-intestinal (GI) adverse effects from pilocarpine, though none discontinued treatment. In contrast, etanercept administered as subcutaneous injections twice-weekly, did not improve dry eye significantly compared to placebo injections. The authors concluded that topical corticosteroids have been shown to be effective in dry eye associated with Sjogren's syndrome. As some topical non-steroidal anti-inflammatory drugs (NSAIDs) may be more effective than others, these should be further evaluated. Systemic secretagogues like pilocarpine have a role in Sjogren's syndrome but the adverse effects may limit their clinical use. Moreover, they stated that it is disappointing that systemic cytokine therapy did not produce encouraging ocular outcomes but participants should have assessment of cytokine levels in such trials, as those with higher baseline cytokine levels may respond better.

Minor Salivary Gland Auto-Transplantation
Wakamatsu and colleagues (2017) stated that the use of salivary glands as a source of lubrication to treat severe cases of dry eye has been proposed by different authors. The first reports proposed parotid or submandibular gland duct transplantation into the conjunctival fornix. However, complications limited the functional outcomes. Minor salivary gland auto-transplantation together with labial mucosa has been used as a complex graft to the conjunctival fornix in severe dry eye with a good outcome. These investigators demonstrated significant improvements in BCVA, Schirmer I test score, corneal transparency, and neovascularization after using this technique. A symptoms questionnaire applied to these patients revealed improvements in foreign body sensation, photophobia, and pain. Similar to tears, saliva has a complex final composition comprising electrolytes, immunoglobulins, proteins, enzymes, and mucins. The authors demonstrated the viability of minor salivary glands transplanted into the fornix of patients with dry eye by performing immunohistochemistry on graft biopsies with antibodies against lactoferrin, lysozyme, MUC1, and MUC16. They noted that these findings revealed the presence of functional salivary gland units, indicating local production of proteins, enzymes, and mucins.

UpToDate reviews on “Dry eyes” (Shtein, 2018), “Treatment of dry eye in Sjögren’s syndrome: General principles and initial therapy” (Baer and Akpek, 2018a), and “Treatment of moderate to severe dry eye in Sjögren's syndrome” (Baer and Akpek, 2018b) do not mention salivary gland transplantation as a therapeutic option.

Thermal Pulsation Treatment

Kim and co-workers (2017) evaluated the effect of thermal pulsation treatment on tear film parameters, specifically osmolarity and MMP-9, in patients with MGD and dry eye disease (DED). A single-center review of 189 eyes that underwent thermal pulsation treatment was performed. Data were collected on pre- and post-treatment osmolarity, MMP-9, TBUT, and OSDI score. Statistical analyses were performed to detect any significant differences after treatment. Thermal pulsation treatment led to significant improvements in TBUT (mean increase from 4.5 to 8.5 seconds [p < 0.001]), OSDI score (mean decrease from 50.5 to 41.6 [p = 0.024]), and MMP-9 (50 % positive rate pretreatment compared to 26 % positive rate post treatment [p < 0.0001]). In the subset of patients who had a baseline osmolarity greater than 307 mOsm/L (i.e., diagnostic for DED), there was a significant improvement in the mean tear osmolarity from 317.1 to 306.6 mOsms/L after treatment (p = 0.002). The authors concluded that treating MGD is an important
component of caring for the DED patient. Thermal pulsation treatment can improve MMP-9 levels on the ocular surface of patients with MGD and DED, as well as improve osmolarity in those with abnormal initial values. They stated that the findings of the present study suggested that meibomian glands play an important role in tear film dynamics and, as such, effective therapy such as thermal pulsation treatment aimed at improving meibomian gland health, can aid the restoration of normal tear film parameters and decrease patient symptoms of DED and MGD.

The authors stated that his study had several drawbacks. First, all patients included in the study represented those presenting to a tertiary care center. Many had tried and failed prior treatments, which may not be generalizable to all populations. Second, there were differential follow-up times, which could make the data susceptible to mean regression. Despite the range in follow-up times, these data points were included in the statistical analysis because they were still within the potential efficacy time frame of thermal pulsation. Next, there was no opportunity to measure patients serially to determine what exact time-points the treatment led to improved tear film inflammation and osmolarity. Future studies may elucidate more precisely when and by how much MMP-9 levels and osmolarity levels change and at what time point. Lastly, it was not possible to include a placebo group because of the retrospective nature. In the future, a randomized trial with a placebo group, which could include a sham treatment, may allow for more direct comparison to validate the findings of this study.

Schallhorn and colleagues (2017) provided an initial retrospective evaluation of the effectiveness of a thermal pulsation system to treat intractable patient-reported dye eye symptoms following laser vision correction. A total of 109 eyes of 57 patients underwent thermal pulsation therapy (LipiFlow; TearScience, Morrisville, NC) for the treatment of dry eye symptoms following laser vision correction. A standardized dry eye questionnaire, the Standard Patient Evaluation of Eye Dryness (SPEED II), was administered to all patients before and after thermal pulsation therapy. The primary outcome was patient-reported dry eye symptoms as measured by this questionnaire. The mean patient age was 49 years (interquartile range [IQR]: 38 to 60), 70% were women, and the primary refractive procedure was LASIK (n = 91, 83%) or photo-refractive keratectomy (PRK) (n = 18, 17%). Patients underwent thermal pulsation therapy at a mean of 40.5 months (IQR: 27.6 to 55.0) after the primary procedure. The mean pre-therapy SPEED II questionnaire score was 17.5 (IQR: 14 to 21), with a reduced mean post-therapy score of 10.2 (IQR: 6 to 14; 95% CI: 8.8 to 11.5, p < 0.001). Patients with PRK tended to report more
improvement. At the follow-up clinical evaluation, objective improvements were noted in TBUT (+1.9 sec; 95 % CI: 1.3 to 2.5), reduction in grade of MGD (-0.69; 95 % CI: -0.54 to -0.84), and corneal staining (-0.74; 95 % CI: -0.57 to -0.91). The authors concluded that in this initial retrospective evaluation, a significant improvement in patient-reported dry eye symptoms was observed following thermal pulsation therapy. They stated that this treatment modality may have clinical utility in the management of dry eye symptoms following laser vision correction, but further study is needed to define its role.

Topical Diquafosol

In a meta-analysis, Zhao and associates (2017) compare the efficacy of diquafosol sodium ophthalmic solution (DQS) and conventional artificial tears (AT) for the treatment of dry eye following cataract surgery. The PubMed, Embase, and the Cochrane Central Register of Controlled Trials were searched from their earliest entries through June 2017 to obtain the studies, which evaluated the efficacy of DQS for patients with dry eye after cataract surgery. The relevant data were analyzed using StataSE 12.0 software. The PRISMA checklist was used as protocol of the meta-analysis and the guideline was followed. The weighted MD (WMD), relative risk (RR), and their 95 % CI were used to assess the strength of the association. These investigators identified 21 references of which 4 studies evaluating the efficacy of DQS for patients with dry eye after cataract surgery were included. The dataset consisted of 291 patients of dry eye following cataract surgery (371 post-operative eyes). The pooling result of this study suggested that the DQS could significantly better improve the indices like corneal and conjunctival fluorescein staining scores, TBUT, and Schirmer I test than AT (p<0.05). Although the scores of symptom questionnaire could not be pooled, the results of each study also proved that DQS could significantly better relieve the symptoms of post-operative dry eye. The authors concluded that based on the available evidence, topical DQS had a superior efficacy than AT in the management of dry eye after cataract surgery; however, further researches with larger sample sizes and focus on indicators such as higher-order aberrations, symptom questionnaire scores, and cost-effective ratio are needed to reach a firmer conclusion.

The authors stated that this study had several drawbacks. Although all the available data had been pooled together by the most reliable way, the final sample size in this meta-analysis was still relatively small, more researches of high quality were needed to get a more solid conclusion; a descriptive analysis was used for
symptom questionnaire scores; and there were insufficient data to analyze the HOAs. Further researches should focus on these 2 points as they were the most direct indices for evaluating the efficacy of 2 drugs; currently, DQS is only approved in Japan and South Korea, the possible effect of ethnic differences should be further evaluated; as DQS is significantly more expensive than common AT, cost-effective ratio should also be evaluated to get a more solid evidence to conclude whether the application of DQS in our routine regimen of post-operative therapy for cataract surgery is appropriate.

**Determination of Conjunctival Nod-1 Expression for Evaluating the Severity of Dry Eye**

In a cross-sectional study, Kim and colleagues (2019) examined the expression pattern of nucleotide-binding oligomerization domain (Nod)-like receptors that detects "danger" intracellular signaling and its correlation with clinical markers for DED. A total of 50 subjects with 50 eyes were included; 23 with SS-DE, 14 with non-SS-DE, and 13 healthy controls with non-DE; OSDI was self-answered and clinical tests including the TFBUT, Schirmer test, and corneal fluorescein staining score (CFS) were performed. Specimens for expression pattern analysis were obtained by conjunctival impression cytology and biopsy. Nod-1, Inhibitor kappa B kinase-alpha (IκKα), and nuclear factor kappa B (NF-κB) expression was determined by reverse transcription quantitative real-time polymerase chain reaction (RT-PCR) and Western blot. Correlations between Nod-1 and ocular surface parameters were determined. Patients with SS-DE had significantly higher OSDI and CFS scores and lower TFBUT and Schirmer test scores than those with non-SS-DE patients (all p < 0.05). Compared with the control group, both the SS-DE and non-SS-DE groups showed significant up-regulations in mRNA expression levels of Nod-1 (relative 3.48-fold and 1.72-fold up-regulations, respectively, p < 0.01), IκKα (relative 1.83-fold and 1.24-fold up-regulations, respectively, p < 0.01), and NF-κB (relative 1.84-fold and 1.32-fold up-regulations, respectively, p < 0.01). Western blot analysis showed that Nod-1 protein expression increased both in the SS-DE and non-SS-DE groups (relative 2.71-fold and 1.64-fold up-regulations, respectively, p < 0.05) compared with that in the control group. Similar findings were observed for IκKα and NF-κB. In DE subjects, the expression of Nod-1 significantly correlated with the OSDI (R² = 0.61, r = 0.78, p < 0.01), Schirmer test score (R² = 0.44, r = -0.66, p < 0.01), and CFS (R² = 0.46, r = 0.68, p < 0.01), but did not significantly correlate with TFBUT (R² < 0.01, r = 0.08, p = 0.66). The authors concluded that Nod-1 expression was increased in the conjunctiva of DE,
especially SS-DE, and was associated with the disease severity. These researchers stated that expression of Nod-like receptors might play an important role in initiating the inflammatory response in DE. These preliminary findings need to be validated by well-designed studies.

Furthermore, an UpToDate review on “Dry eyes” (Shtein, 2019) does not mention determination of expression pattern of nucleotide-binding oligomerization domain (Nod)-like receptors / Nod-1 as a management tool.

Measurement of Tear Lactoferrin for Evaluating the Severity of Dry Eye

The American Academy of Ophthalmology Preferred Practice Pattern for dry eye syndrome (AAO, 2018) state that lacrimal gland dysfunction is associated with decreased tear lactoferrin concentrations. The guidelines noted that decreased tear secretion and reduced tear concentrations of lactoferrin have been reported in patients with hepatitis C (citing Abe, et al., 1999; Siagris, et al., 2012). However, the guidelines make no recommendation for routine performance of this test in the workup of dry eyes.

Sonobe and colleagues (2019) examined the correlation between lactoferrin concentration in the tear film and signs and symptoms of severe DED using a novel micro-fluidic paper-based analytical device (μPAD) and ELISA; a total of 24 patients were recruited. Using a novel μPAD, lactoferrin concentrations were measured in 4 patients with GVHD-related DED, 3 patients with other types of DED, and 2 controls (Group A). For validation by ELISA, 22 patients (7 patients from Group A) comprising 9 patients with GVHD-related DED, 6 patients with other types of DED, and 7 controls were examined (Group B). The link between lactoferrin concentration and clinical data regarding the severity of aqueous tear deficient DED was also examined by both μPAD and ELISA. The lactoferrin concentration in tear fluid of the DED patients was positively correlated between μPAD and ELISA (p = 0.006, r = 0.886). The tear fluid of the GVHD patients showed low or undetectable lactoferrin concentration. Analysis by ELISA demonstrated that lactoferrin concentrations in the tear film from the GVHD patients were significantly lower than those from the non-GVHD patients (p = 0.010576). ELISA revealed lactoferrin concentration correlated with the value of Schirmer test and TFBUT, whereas it was inversely correlated with OSDI, fluorescein, and Rose Bengal scores. The authors concluded that the novel μPAD may pave the way for measuring lactoferrin concentration in tear fluid from DED patients. These
researchers stated that the findings of this study suggested that lactoferrin concentration in tear fluid reflect the severity of DED. They stated that further investigations revising their methods for more quantitative measurements of lactoferrin concentrations in tear fluid as well as further detailed analyses to evaluate the correlation their data with the underlying disease mechanisms are needed. These investigators noted that this device may be useful for dry eye diagnoses, monitoring the severity of dry eye and treatment strategies.

The authors stated that this study had several drawbacks. First, the methods of collecting human tear samples must be improved. Second, for severe chronic GVHD (cGVHD)-related dry eye patients, lactoferrin is not detectable by μPAD because the lactoferrin concentration in severe DED related to cGVHD is extremely low according to the ELISA results for the same samples. The low limitation of measurement by μPAD was between 0.21 pg/μL and 0.26 pg/μL according to their data. These researchers need to determine the lowest limitation of measurement and improve detection in low-concentration samples. Third, according to their data, lacroferrin concentration was not affected by gender. Because there was small number of patients in this study, the gender differences may not be conclusive. Further investigation is needed to confirm it.

Furthermore, an UpToDate review on “Dry eyes” (Shtein, 2019) does not mention measurement of tear lactoferrin as a management tool.

**Botulinum Toxin for the Treatment of Dry Eye Disease**

In a prospective study, Choi and colleagues (2019) examined the effects of botulinum toxin type A (BTX-A) injection on dry eye signs, symptoms, and tear cytokine levels in patients with intractable DED. Participants were randomized to a BTX-A (group A) or control group (group B). Patients were injected with BTX-A or normal saline in the medial part of the upper and lower eyelids. Before and at 2 weeks, 1 month, 2 months, and 4 months after injection, dry eye signs; TFBUT, Schirmer I test, CFS, and symptoms; OSDI; and frequency of lubricants were assessed. The tear levels of MMP-9 and serotonin were measured before and at 1 month after injection. A total of 52 eyes from 26 patients (mean age of 57.7 years) were included. The TFBUT was higher at 2 weeks and at 1 month in group A. The Schirmer I test and OSDI scores were also better in group A for up to 2 months. The CFS grades in group A were significantly lower until 4 months. Repeated measures analysis of variance (RMANOVA) demonstrated significant differences
between the 2 groups over time for the Schirmer I test (p = 0.002), CFS (p = 0.025), OSDI (p = 0.020), and frequency of lubricants (p = 0.029). The MMP-9 conversion rate of group A (76.92 %) was significantly higher than that of group B (38.46 %, p = 0.005). The tear serotonin level in group A was reduced from 2.76 ± 0.34 to 1.73 ± 0.14 ng/ml (p < 0.001). No complications were observed during the study. The authors concluded that BTX-A injection into the medial part of eyelid improves dry eye signs and symptoms and reduced tear cytokine levels. These researchers stated that BTX-A is thus a potential therapeutic option for patients with intractable DED. This was a small study (n = 26 patients) with short-term follow-up (up to 2 months). These preliminary findings need to be validated by well-designed studies.

Furthermore, UpToDate reviews on “Dry eyes” (Shtein, 2019) and “Treatment of dry eye in Sjogren's syndrome: General principles and initial therapy” (Baer and Akpek, 2019) do not mention botulinum toxin as a therapeutic option.

Cross-linked Hyaluronic Acid Gel Occlusive Devices for the Treatment of Dry Eye Disease

In an institutional review board (IRB)-approved, prospective open-label, single-site, study, Fezza (2018) examined the safety and efficacy of a new cross-linked hyaluronic acid (xlHA) gel occlusive device in the treatment of DED. This gel/device was placed in the lower canaliculus. A total of 74 subjects aged 25 to 95 years with DED, who failed treatment with artificial tears, were included. Patients were assessed with corneal slit lamp examination with fluorescein staining and with Schirmer's test, TFBUT, and tear meniscus height (TMH) at baseline, 1 month, and 3 months. Patients were followed at 6 months with a telephone questionnaire. The procedure entailed inserting approximately 0.2 ml of xlHA gel into each lower lid canaliculus with a syringe and lacrimal irrigator; and patients were followed for adverse events (AEs). A total of 63 subjects completed the study (48 women, 15 men), with an average age of 67 years. Slit lamp demonstrated improved corneal fluorescein staining. Schirmer's tests demonstrated an average increase over baseline of 3.67 mm after 3 months. TFBUT improved 87 % and TMH increased by 57 % at 3 months over baseline. All objective measures were statically significant. There was 1 case of conjunctivitis that resolved and was felt to be an incidental viral infection. The authors concluded that the xlHA occlusive device offered a new, safe, and effective method to treat DED. It appeared to have efficacy for at least 3 months on clinical examination. The xlHA gel demonstrated a good tolerance and safety profile. They stated that these findings were encouraging and showed both
subjective and objective improvements in most patients at 3 months. The xlHA gel has many potential benefits over traditional plugs, including biocompatibility, no sizing, no firm edges, the potential for removal, and a promising safety profile. The main drawbacks of this study included that it was performed at a single site, was single-arm, open-label, and without a control group.

Furthermore, UpToDate reviews on “Dry eyes” (Shtein, 2019) and “Treatment of dry eye in Sjogren’s syndrome: General principles and initial therapy” (Baer and Akpek, 2019) do not mention cross-linked hyaluronic acid gel as a therapeutic option.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
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<tbody>
<tr>
<td></td>
<td>CPT codes covered if selection criteria are met:</td>
</tr>
<tr>
<td></td>
<td>Autologous serum tears - no specific code:</td>
</tr>
<tr>
<td>68760</td>
<td>Closure of the lacrimal punctum; by thermocauterization, ligation, or laser surgery</td>
</tr>
<tr>
<td>68761</td>
<td>by plug, each</td>
</tr>
<tr>
<td>68801</td>
<td>Dilation of lacrimal punctum, with or without irrigation</td>
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<tr>
<td>83861</td>
<td>Microfluidic analysis utilizing an integrated collection and analysis device, tear osmolarity</td>
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<tr>
<td></td>
<td>CPT codes not covered for indications listed in the CPB:</td>
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<tr>
<td>20939</td>
<td>Bone marrow aspiration for bone grafting, spine surgery only, through separate skin or fascial incision (List separately in addition to code for primary procedure)</td>
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<tr>
<td>38232</td>
<td>Bone marrow harvesting for transplantation; autologous</td>
</tr>
<tr>
<td>38240</td>
<td>Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor</td>
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<tr>
<td>38241</td>
<td>Hematopoietic progenitor cell (HPC); autologous transplantation</td>
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<tr>
<td>97810 - 97814</td>
<td>Acupuncture</td>
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HCPCS codes covered if selection criteria are met:

http://www.aetna.com/cpb/medical/data/400_499/0457.html 09/20/2019
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<th>Code</th>
<th>Code Description</th>
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<tr>
<td>A4262</td>
<td>Temporary, absorbable lacrimal duct implant, each</td>
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<tr>
<td>A4263</td>
<td>Permanent, long-term, nondissolvable lacrimal duct implant, each</td>
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HCPCS codes not covered for indications listed in the CPB:

Cross-linked hyaluronic acid gel occlusive devices - no specific code:

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<td>J0585</td>
<td>Botulinum toxin type A, per unit [Botox]</td>
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<td>J0586</td>
<td>Injection, Abobotulinumtoxina, 5 units [Dysport]</td>
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<td>J0587</td>
<td>Botulinum toxin type B, per 100 units</td>
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<td>J0588</td>
<td>Injection, incobotulinumtoxinA, 1 unit [Xeomin]</td>
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<tr>
<td>J1438</td>
<td>Injection, etanercept, 25 mg</td>
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<td>J7507</td>
<td>Tacrolimus, immediate release, oral, 1mg</td>
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<td>J7508</td>
<td>Tacrolimus, extended release, (Astagraf XL), oral, 0.1 mg</td>
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<tr>
<td>J7525</td>
<td>Tacrolimus, parenteral, 5 mg</td>
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<tr>
<td>J9312</td>
<td>Injection, rituximab, 10 mg</td>
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ICD-10 codes covered if selection criteria are met:

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<td>H04.121</td>
<td>Dry eye syndrome</td>
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<td>H04.129</td>
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<td>H04.561</td>
<td>Stenosis of lacrimal punctum</td>
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<td>H04.569</td>
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<tr>
<td>H11.141</td>
<td>Conjunctival xerosis, unspecified</td>
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<td>H11.149</td>
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<tr>
<td>H16.221</td>
<td>Keratoconjunctivitis sicca, not specified as Sjögren's</td>
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<td>H16.229</td>
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<tr>
<td>M35.0 - M35.09</td>
<td>Sicca syndrome [Sjögren]</td>
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Tear Film Imaging:

CPT codes not covered for indications listed in the CPB:

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<th>Description</th>
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<td>0330T</td>
<td>Monitoring of intraocular pressure, imaging, screening of visual acuity, sacroiliac joint stabilization</td>
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InflammaDry:

CPT codes not covered for indications listed in the CPB:

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<th>Code</th>
<th>Description</th>
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<tr>
<td>83516</td>
<td>Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; qualitative or semiquantitative, multiple step method</td>
</tr>
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</table>

ICD-10 codes not covered for indications listed in the CPB:

http://www.aetna.com/cpb/medical/data/400_499/0457.html

09/20/2019
The above policy is based on the following references:

25. Kostick DA. Treating dry eyes. Adding or conserving tears. Medical Edge. Buffalo, NY: Medical Edge from Mayo Clinic; April 24, 2006. Available at:

26. National Health Service (NHS), National Library for Health (NLH). In a patient with rosacea and dry eyes is there a specific therapy which is of greater benefit than simple lubricant drops (eg viscotears)? NLH Primary Care Question Answering Service. London, UK: NHS; May 3, 2006.


62. Shtein RM. Dry eyes. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed March 2015.


67. Shtein RM. Dry eyes. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed February 2016.


78. Shtein RM. Dry eyes. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed February 2018.


80. Baer AN, Akpek EK. Treatment of moderate to severe dry eye in Sjögren's syndrome. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed February 2018b.


85. Shtein RM. Dry eyes. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed February 2019.


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Amendment to
Aetna Clinical Policy Bulletin Number: 0457 Dry Eyes

There are no amendments for Medicaid.