Management of Dry Eye Syndrome

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DESCRIPTION

Dry eye disease (DED) is a multifactorial disease of the ocular surface with loss of homeostasis of the tear film and ocular symptoms. Tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles. DED is also known as keratoconjunctivitis sicca, dry eye syndrome (DES), and dysfunctional tear syndrome.

In epidemiological studies performed globally, the prevalence of dry eye syndrome (DES) ranges from 5 to 50 percent. Based on data from the National Health and Wellness Survey, 6.8 percent of the United States adult population (approximately 16.4 million people) have been diagnosed with DES. The prevalence increased with age (2.7 percent in those 18 to 34 years old versus 18.6 percent in those ≥75 years old) and was higher in women than men (8.8 versus 4.5 percent).

Risk Factors
Risk factors for DES include:

- Advanced age
- Contact lens wear
- Decreased corneal sensation
- Environments which increase tear evaporation (e.g., windy, smoky, dry, or low humidity)
- Genotypical XY individuals
- Hormonal changes primarily due to decreased androgens
- Nutritional deficiencies (e.g., vitamin A deficiency)
- Ocular medications especially those containing preservatives
- Ophthalmic surgery (especially corneal refractive surgery)
- Systemic diseases (e.g., diabetes mellitus, Parkinson disease, Sjorgren's syndrome)
- Systemic medications including amiodarone, antihistamines, anticholinergics, estrogen, isotretinoin, selective serotonin receptor antagonists, and nicotinic acid

Dry eye syndrome (DES), particularly when severe, can have a significant impact on visual acuity, daily activities, social and physical functioning, and workplace productivity.

DES has a complex and multifactorial etiology. The tear film of the eye consists of aqueous, mucous, and lipid components. A healthy tear film relies on a synergistic interaction of the lacrimal glands, eyelids, and ocular surface, which together comprise the lacrimal functional unit. Dysfunction of any component in the lacrimal functional unit can lead to DES.

DES has been classified into two general groups: decreased tear production (resulting in aqueous deficient DES) and abnormal meibomian gland physiology (resulting in evaporative DES). However, it is now believed that both mechanisms are present in most patients, although one may be predominant. For all patients, tear film hyperosmolarity and subsequent ocular surface inflammation lead to the variety of symptoms and signs associated with DES.

Symptoms in DES result from activation of sensory nerves of the ocular surface, either due to tear hyperosmolarity, the presence of inflammatory mediators, or hypersensitivity of the sensory nerves.

Causes

- Decreased tear production: Impaired lacrimal tear production can be caused by any form of lacrimal gland destruction or dysfunction. The reduced volume of aqueous fluid leads to hyperosmolarity of the tear film and subsequently the ocular surface, which incites inflammation of the ocular surface cells.
- Deficiency of aqueous tear production can be subclassified into two subtypes:
    - Sjogren's syndrome**:** Sjogren's syndrome is a chronic autoimmune inflammatory disorder characterized by diminished lacrimal and salivary

gland function with resultant dryness of the eyes and mouth. The onset of Sjögren's syndrome is rare after age 65 years.
    - Dry eye syndrome not due to Sjogren's syndrome – This syndrome refers to patients with aqueous tear-deficient DES involving lacrimal dysfunction without associated systemic findings. The most common form is age-related DES in which it is believed that there is lacrimal ductal obstruction over time, leading to decreased lacrimal gland function. Lacrimal gland obstruction can also be due to conjunctival scarring conditions such as trachoma, pemphigoid, vitamin deficiency, post-viral syndromes, and ocular burns. This syndrome can also be caused by lacrimal gland infiltration due to sarcoidosis, lymphoma, graft versus host disease, and episcleritis. Other causes include contact lens use, which is associated with reduced corneal sensitivity and subsequent reduced reflex sensory tear secretion, and diabetes mellitus
- Increased evaporative loss: Excessive water loss from the ocular surface leads to tear film instability and a cycle of tear hyperosmolarity and lacrimal functional unit inflammation. Increased tear evaporation is most commonly caused by meibomian gland dysfunction, also known as posterior blepharitis, in which the accessory lacrimal glands responsible for the lipid component of the tear film are dysfunctional. In a normally functioning eye, the nature of the mucin allows even spreading of the tear film to form a membrane, and the lipid layer provides a barrier to minimize evaporation of tears. Abnormalities of the lipid layer are associated with a higher rate of tear film evaporation. Structural abnormalities of eyelid position or decreased blink function also increase evaporation of the tear film by increasing the area or the time of tear film exposure. Lastly, topical medicated or preserved eye drop use, chronic contact lens wear, and ocular allergy syndromes can cause ocular surface irritation and increased tear film evaporation

Symptoms

Most patients will present with symptoms of chronic eye irritation associated with mild to moderate discomfort. However, there is considerable variability in patient-reported symptoms and clinically measurable signs over time, as well as a recognized lack of correlation between these signs and symptoms. Common eye complaints include:

- Blurred vision
- Burning sensation
- Dryness
- General irritation
- Gritty sensation
- Light sensitivity
- Paradoxical excessive testing
- Red eyes

Questionnaires
Due to the variability of findings on clinical evaluation of dry eye syndrome (DES), some clinicians base their assessment of DES on the results of validated questionnaires. These can also be used for monitoring DES and can be useful for standardizing the identification and classification of DES.

Available questionnaires used specifically for the evaluation of DES symptoms include:

- Dry Eye Questionnaire (DEQ-5) – Five-item questionnaire reduced from the Dry Eye Questionnaire and validated to determine DES symptom severity.
- Impact of Dry Eye on Everyday Life (IDEEL) – Fifty-seven questions in three modules validated in patients with DES.
- Ocular Surface Disease Index (OSDI) – Twelve-item questionnaire validated in patients with DES. The OSDI can be useful clinically, particularly in patients with more severe symptoms, to monitor the response to therapy and variability in symptoms over time.
- Salisbury Eye Evaluation Questionnaire (SEE) – Six-item questionnaire used in self-reported, population-based prevalence surveys to determine visual impairment among older adult subjects.

Diagnosis
The diagnosis of dry eye syndrome (DES) is based on characteristic patient symptoms and supporting findings on the physical examination, both of which can vary considerably in intensity over time and under different environmental conditions.

There is no single diagnostic test or set of tests to confirm or rule out DES. Examples of methods often used to evaluate ocular surface include, but are not limited to:

- Meibography: Is the imaging and study of the morphology (structure and function) of meibomian glands. Near-infrared dual imaging uses reflective and transilluminated light purportedly to improve meibography techniques (i.e., reduce time and discomfort) and enhance results. The LipiScan is one example of biography device. The LipiView II is an example of a meibography device capable of ocular surface interferometry involving a three- mode ophthalmic camera for imaging the lipid layer of the tear film, meibomian glands, ocular surface, and eyelids. In the ocular imaging mode, the device captures high resolution images or video of the ocular surface or eyelids. The lipid imaging-mode uses white light interferometry to provider a video color assessment of the tear film distribution over the cornea during blinking. The gland imaging mode relies on near-infrared illumination reflected by the meibomian glands to obtain an image. The evidence is insufficient is insufficient to determine that the technology results in an improvement in the net health outcome.

Treatment
Current treatment for DES is aimed at improving symptoms by increasing or supplementing tear production, slowing tear evaporation, reducing tear resorption, or

reducing ocular surface inflammation. In addition to symptomatic relief, treatment with artificial tears may improve visual acuity and prevent against ocular damage.

First line treatments may include the following:

- Amelioration of eyelid abnormalities including blepharitis
- Application of warm compresses to soften secretions in obstructed meibomian gland excretory ducts
- Discontinuation of systemic or ocular medications that can contribute to dryness, if possible
- Environmental coping strategies
- Tear supplementation

Other treatments are available for DES and are discussed below.

Clinical Context and Therapy Purpose
The purpose of therapy in patients who have dry eye syndrome (DES) is to provide a treatment option that is an alternative to or an improvement on existing therapies.

Population
The relevant population of interest is individuals with dry eye syndrome (DES). DES is often classified into the aqueous-deficient subtype or the evaporative subtype, although classification is not mutually exclusive. Dry eye syndrome is a multifactorial disease of the ocular surface that may require a combination approach to treatment. Meibomian gland dysfunction (MGD), characterized by changes in gland secretion with or without concomitant gland obstruction, is recognized as the most common cause of evaporative dry eye and may also play a role in aqueous-deficient dry eye.

Interventions
The testing/therapy being considered is Imaging studies using near-infrared dual imaging (i.e., simultaneous reflective and transilluminated light) or interferometry of meibomian glands, Tear film imaging (e.g., LipiView Ocular Surface Interferometer), LipiFlow Thermal Pulsation System, iLux Thermal Pulsation System, Systane iLux2 Thermal Pulsation System, intranasal neurostimulation (TrueTear, iTEAR100), autologous eye drops (autologous serum tears), intraductal probing (Maskin Device), intense pulsed light (IPL), and electrothermal heat (TearCare System).

Comparators
The following practices are currently being used to treat dry eye syndrome (DES): standard treatment with warm compresses and eyelid massage. Current treatment options for meibomian gland dysfunction (MGD) include physical expression to relieve the obstruction, administration of heat (warm compresses) to the eyelids to liquefy solidified meibomian gland contents, eyelid scrubs to relieve external meibomian gland orifice blockage, and medications (e.g., antibiotics, topical corticosteroids) to mitigate infection and inflammation of the eyelids.

Outcomes
The general outcomes of interest are symptoms, morbid events, and functional outcomes.

Autologous Eye Drops (e.g., Autologous Serum Tears)
Autologous eye drops (autologous serum tears) have been proposed for dry eye syndrome (DES) and are made by mixing the individual's serum with other substances. There is not strong evidence for long-term or significant benefit over artificial tears and access to these eye drops, and the cost are additional barriers to its use. Additional large, high-quality RTCs are needed 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 autologous eye drops (autologous serum tear) therapy for (DES). The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes.

(2019) A Report by the American Academy of Ophthalmology Ophthalmic Technology Assessment Committee Cornea and Anterior Segment Disorders Panel on Autologous Serum-Based Eye Drops for Treatment of Ocular Surface Disease OTA to describe the safety and effectiveness of using autologous serum-based eye drops for the treatment of severe dry eye and persistent corneal epithelial defect. A literature search was completed which included the PubMed and Cochrane Library databases were conducted most recently in March 2019. The searches identified 281 citations, which were reviewed in abstract form. Of these, 48 were selected for a full-text review, and 13 met the inclusion criteria and were assigned a quality-of-evidence rating by the panel methodologist. Eight of these studies were rated level II and 5 were rated level III; there were no level I studies. This analysis included 10 studies of the use of autologous serum-based eye drops for severe dry eye disease and 4 studies of persistent epithelial defect. Several studies showed good effectiveness, with some improvement in symptoms, signs, or both. Eight of the studies reported improved symptoms for severe dry eye disease, and all noted improvement in at least 1 clinical sign. For persistent epithelial defects, all of the studies showed improvement, with 3 of the 4 demonstrating an improvement rate of more than 90%. Adverse events were rare. The authors concluded although autologous serum-based tears may be effective in the treatment of severe dry eye and persistent epithelial defect, conclusions are limited owing to the absence of controlled trials.

Electothermal Heat (e.g., TearCare System)
The TearCare® system is intended as an alternative to warm compresses to reduce dry eye syndrome (DES) symptoms caused by meibomian gland blockages. The system comprises four components: a smart hub to control thermal energy emission, a charger for the hub, two pairs of single-use thermal emitters (SmartLid™ devices), and a single use, blunt-tipped, tweezer-like device (Clearance Assistant™).

An optometrist or ophthalmologist delivers the TearCare treatment during an office visit. The clinician applies the SmartLid devices to the individual's upper and lower eyelids over the meibomian glands and activates the hub. The connected emitters heat the eyelids to 41°C to 45°C for 12 minutes. During treatment, individuals keep their eyes open and

blink normally; blinking is intended to help clear meibomian gland obstructions and re-lubricate eyes. After removing emitters, the clinician applies a drop of 0.5% tetracaine to each eye and expresses any remaining meibomian gland blockages from the individuals's eyelids using the Clearance Assistant.

(2019) Badawi reported on a study which was a 6-month extension of an initial 6-month, prospective, single-center, randomized pilot clinical trial whose results were previously reported. This extension study was conducted in full accordance with the tenets of the Declaration of Helsinki and US Food and Drug Administration regulations for the protection of human subjects in medical research. Only a subset of patients, those who had received the investigational TearCare® treatment in the initial study, were enrolled in this extension study and were retreated with the TearCare® treatment and followed for another 6 months. There are some limitations to this extension study. For example, this was a single-treatment, single-investigator study. As a result, it was not possible to mask subjects or the investigator. Also, the sample size was 12 subjects who had previously undergone a TearCare treatment. A larger, multi-center randomized, and masked, prospective trial is currently being planned. A larger study will enhance the evidence base for the use of TearCare® in the treatment of DED. While previous trials, such as the LipiFlow trial, followed treated patients up to 1 month, this trial followed patients up to 13 months. Patients received a treatment at entry and then at 7 months. Objective and subjective end points improved in a repeatable fashion. In other words, the signs and symptoms of DED improved in patients up to 13 months. Further studies comparing TearCare® to other treatments are currently being prepared. Based on the statistically significant improvement in the signs and symptoms of DED following a second treatment with the TearCare® system observed in this extension study, repeated application appears to provide additional benefit to patients with DED. Larger, multicenter, randomized, prospective trials are planned to further evaluate this treatment for DED.

The system is currently undergoing clinical trials. The evidence is insufficient to determine the technology results in an improvement in the net health outcomes.

Intense Pulsed Light (IPL)
Intense Pulsed Light (IPL) therapy 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 (DES).

(2021) Leng et al. completed a systematic review and meta-analysis, examined the safety and efficacy of IPL for the treatment of MGD. PubMed, Embase, Web of Science, Cochrane Library, Google Scholar, China National Knowledge Infrastructure (CNKI), Wanfang, VIP, and SinoMed databases were searched through February 24, 2020. Randomized clinical trials and cohort studies comparing IPL+ meibomian gland expression (MGX) or IPL alone with control groups were included. The weighted MD (WMD) was calculated to analyze the OSDI score and SPEED score, and the SMD was calculated to analyze the TBUT. Heterogeneity was quantified by the I2 statistic ranging from 0 to 100 %, and a random effects model was used in this meta-analysis. All

analyses were performed by RevMan 5.3. All p values were calculated by the t-test, and p values were regarded as statistically significant at $p < 0.05$. The Cochrane Collaboration's tool for assessing risk of bias was used to identify and evaluate bias in the literature. A total of 9 studies with a total of 539 patients were included; 8 studies examined TBUT, 6 examined OSDI scores, and 4 examined SPEED scores. IPL combined with MGX showed superiority regarding the TBUT (SMD 2.33, 95 % CI: 1.04 to 3.61), and OSDI scores (WMD 11.93, 95 % CI: - 17.10 to - 6.77), with high heterogeneity. The SPEED scores were not significantly different. The authors concluded that IPL combined with MGX may be a safe and effective treatment for MGD, however, it could not improve all symptoms; IPL alone was not superior to MGX. The efficacy was also affected by the number and average frequency of treatments. The efficacy of IPL may decrease within 6 months after the last treatment, so it should be considered a long-term adjuvant therapy combined with MGX. When patients received 3 or 4 treatments (once every 3 to 4 weeks), a return visit at 6 months after the last treatment was needed.

(2020) Cote et al. reported MGD is the major cause of evaporative DED, which is the more prevalent form of dry eye disease; IPL therapy, involving treatment of the skin near the eyelids, has emerged as a potential treatment for MGD. In a Cochrane review, these researchers examined the safety and effectiveness of IPL for the management dry eye disease resulting from MGD. They searched CENTRAL, Medline (Ovid), Embase Ovid and 3 trial registers for eligible clinical trials on August 1, 2019. There were no restrictions on publication status, date or language. These investigators included RCTs studying the safety or effectiveness of IPL for treating MGD. Outcome measures included the change from baseline in subjective dry eye symptoms, adverse events (AEs), changes to lipid layer thickness, TBUT, tear osmolarity, eyelid irregularity, eyelid telangiectasia, meibomian gland orifice plugging, meibomian gland drop-out, corneal sodium fluorescein staining and conjunctival lissamine green staining. Two review authors independently screened abstracts and full-text articles extracted data from eligible RCTs and judged the risk of bias using the Cochrane tool. They reached consensus on any disagreements by discussion; and summarized the overall certainty of the evidence using the GRADE Working Group approach. These investigators included 3 RCTs, 1 from New Zealand, 1 from Japan and 1 from China, published between 2015 and 2019. Together, these trials enrolled 114 adults (228 eyes). Two studies used a paired-eye (inter-eye comparison) design to evaluate the effects of a sham (control) IPL treatment relative to an actual IPL treatment. One study randomized individuals to either an IPL intervention combined with meibomian gland expression (MGX), or MGX alone (standard therapy). The study follow-up periods ranged from 45 days to 9 months; none of the trials were at low risk of bias in all 7 domains. The first authors of 2 included studies were in receipt of funding from patents or the manufacturers of IPL devices. The funding sources and declaration of interests were not given in the report of the 3rd included trial. All 3 trials evaluated the effect of IPL on dry eye symptoms, quantified using the SPEED questionnaire. Pooling data from 2 trials that used a paired-eye design, the summary estimate for these studies indicated little to no reduction in dry eye symptoms with IPL relative to a sham intervention (mean difference [MD] -0.33 units, 95 % CI: -2.56 to 1.89; $I^2 = 0$ %; 2 studies, 144 eyes). The other study was not pooled as it

had a unit-of-analysis error but reported a reduction in symptoms in favor of IPL (MD -4.60, 95 % CI: -6.72 to -2.48; 84 eyes). The body of evidence for this outcome was of very low certainty, thus, these researchers were uncertain regarding the effect of IPL on dry eye symptoms. There were no relevant combinable data for any of the other secondary outcomes, thus the effect of IPL on clinical parameters relevant to dry eye disease were currently unclear. For sodium fluorescein TBUT, 2 studies indicated that there may be an improvement in favor of IPL (MD 2.02 seconds, 95 % CI: 0.87 to 3.17; MD 2.40 seconds, 95 % CI: 2.27 to 2.53; 172 eyes total; low-certainty evidence). These investigators were uncertain of the effect of IPL on non-invasive TBUT (MD 5.51 seconds, 95 % CI: 0.79 to 10.23; MD 3.20, 95 % CI: 3.09 to 3.31 seconds; 2 studies; 140 eyes total; very low-certainty evidence). For tear osmolarity, 1 study indicated that there may be an improvement in favor of IPL (MD -7.00 mOsmol/L, 95 % CI: -12.97 to -1.03; 56 eyes; low-certainty evidence). The researchers were uncertain of the effect of IPL on meibomian gland orifice plugging (MD -1.20 clinical units, 95 % CI: -1.24 to -1.16; 84 eyes; very low-certainty evidence). These investigators were uncertain of the effect of IPL on corneal sodium fluorescein staining. One study reported no evidence of a difference between the IPL and sham intervention arms at 3 months of follow-up ($p = 0.409$), and a second study reported data favoring IPL (MD -1.00 units, 95 % CI: -1.07 to -0.93 units; 172 eyes in total; very low-certainty evidence). They considered the incidence of AEs at the study endpoint, as a measure of safety. As most trials did not specifically report AEs, the safety of IPL as a treatment for MGD could also not be determined with any certainty. Very low-certainty results from individual studies suggested some adverse effects that may be experienced by participants, include mild pain and burning, and the potential for partially losing eyelashes (due to clinician error). The authors concluded that this systematic review found a scarcity of RCT evidence relating to the safety and effectiveness of IPL as a treatment for MGD. Whether IPL is of value for modifying the symptoms or signs of evaporative dry eye disease is currently uncertain. Due to a lack of comprehensive reporting of AEs, the safety profile of IPL in this patient population is also unclear. The current limitations in the evidence base should be considered by clinicians using this intervention to treat MGD and outlined to individuals potentially undergoing this procedure with the intent of treating dry eye disease. The results of the 14 RCTs currently in progress will be of major importance for establishing a more definitive answer regarding the safety and effectiveness of IPL for treating MGD. They intend to update this review when results from the trials become available.

(2020) Arita and Fukuoka examined currently available non-pharmaceutical treatment modalities for MGD. A detailed search of the PubMed and Medline databases was carried out to identify original articles in English that have examined such non-pharmaceutical therapies in patients with this condition. Conventional therapies such as application of a warming compress, the practice of lid hygiene, and manual expression of meibomian glands as well as more technologically advanced approaches such as intra-ductal probing, thermal pulsation, and IPL therapy were included in the review. The authors noted that neither subjects nor investigators were masked to treatment allocation in the studies of intra-ductal probing performed to-date indicating that caution should be

exercised in drawing conclusions from their findings. The follow-up periods of the studies were also relatively short, with the result that data on the long-term safety and efficacy of this invasive technique are lacking. The authors concluded additional large-scale RCTs are also needed to provide more information such as the specific indications best suited to each treatment modality, the efficacy of such approaches in combination with pharmaceutical-based therapy, and the mechanisms of action of some of the more technologically advanced systems.

(2020) Liu and colleagues noted that MGD is frequently encountered by eye care practitioners. It is characterized by obstruction of the Meibomian glands and/or alterations in the consistency of glandular secretions. At present, no definitive treatment exists for this condition. In a systematic review and meta-analysis, these researchers examined the efficacy of intense pulsed light (IPL) therapy in the management of MGD. Databases including Embase, PubMed, Cochrane Central, Medline and Google Scholar were systematically searched to identify clinical trials that evaluated the efficacy of IPL in the treatment of MGD. Outcome measures were described as the standardized mean difference (SMD). The fixed- or random-effects model was selected for analysis based on the Cochrane I2 values representing heterogeneity. Publication bias was visually inspected using Begg's funnel plot. Data were synthesized from 4 RCTs comprising 122 subjects in the IPL group and 120 subjects in the control group. Pooled analysis indicated no statistically significant difference in the SPEED scores between the 2 groups [SMD -0.16 (95 % CI: -0.41 to 0.10)]; but a significant increase in Non-Invasive Tear Break-Up Time (NIBUT) scores in the IPL group (SMD, 0.90; 95 % CI: 0.40 to 1.40). The authors concluded that the findings of study did not provide any conclusive evidence for the efficacy of IPL therapy in the management of MGD. The analysis indicated that IPL therapy may result in an improvement of objective NIBUT scores but had no effect on subjective SPEED scores. They stated given the limited number of studies performed to-date, there is a need for more prospective, well-designed RCTs with a larger sample size to provide further evidence on the efficacy of IPL therapy.

Summary of Evidence: Intense Pulsed Light (IPL)
While study results of intense pulsed light therapy treatment for dry eye syndrome (DES) caused by meibomian gland dysfunction (MGD) may be promising, further multi-center randomized clinical trials (RCTs) with a larger sample, treatment comparison groups to assess long-term effectiveness and safety are needed. The evidence is insufficient to determine the technology results in an improvement in the net health outcomes.

Intraductal Probing (e.g., Maskin Device)
Intra-ductal probing is performed using local or topical anesthetic and introduces a thin stainless-steel wire probe into the meibomian gland orifices to forcefully expel any obstructing material and restore patency.

Review of Evidence: Intraductal Probing (e.g., Maskin Device)
UpToDate reviews on “Blepharitis” by Shtien in 2021, “Dry eyes” by Shtien in 2021, and “Treatment of dry eye in Sjogren's syndrome: General principles and initial therapy” by

Baer and Akpek in 2019 and "Treatment of moderate to severe dry eye in Sjogren's syndrome" by Baer and Akpek in 2019 do not mention meibomian gland probing as a therapeutic option.

(2021) Arita et al. noted that treatment options for MGD have increased greatly—in particular, with the recent advent of nonpharmaceutical treatments—since the International Workshop on Meibomian Gland Dysfunction in 2011. Selection of a treatment for MGD is currently based on the stage classification proposed at the 2011 workshop. Such stage classification is itself based on a comprehensive evaluation of subjective symptoms, lid margin abnormalities (plugging, vascularity), meibum grade, and degree of ocular surface staining. However, it is often difficult to select a treatment method according to this complicated classification in the clinic. Moreover, it is unclear at what stage nonpharmaceutical treatment options, such as intraductal probing, thermal pulsation therapy, and intense pulsed light, should be performed.

(2021) Fallah and Loer examined the effect of VTPT (vectored thermal pulsation treatment) for the treatment of MGD on objective measures of LLT and tear osmolarity. A total of 100 patients with MGD were recruited to participate. At their initial visit, baseline study parameters were recorded, and VTPT was administered. At the 2- to 3-month follow-up visit, the study parameters were reevaluated. Subjective symptoms were evaluated using the OSDI questionnaire; LLT was measured using an ocular surface interferometer. Tear osmolarity was calculated using impedance measurement of tear fluid collected from the eyelid margin. A total of 96 patients (192 eyes) completed the follow-up. Mean improvement in OSDI was 5.6 points (9 5% CI: -9.0 to -2.1, p = 0.002). There was no significant change in tear osmolarity (mean change -1.6 mOsm/L, 9 5% C: -4.7 to +1.3 mOsm/L, p = 0.3). There was no significant change in LLT (mean change -4.3 nm, 95 % CI: -9.1 to +0.5 nm, p = 0.08). The authors concluded that the hypothesis that VTPT would decrease tear osmolarity and increase LLT was not substantiated. Although they detected significant improvement in subjective symptoms, the improvement was smaller than the improvements reported in previous studies. They stated these findings suggested the current understanding of the effects of VTPT is incomplete.

(2020) Arita and Fukuoka examined currently available non-pharmaceutical treatment modalities for MGD. A detailed search of the PubMed and Medline databases was carried out to identify original articles in English that have examined such non-pharmaceutical therapies in patients with this condition. Conventional therapies such as application of a warming compress, the practice of lid hygiene, and manual expression of meibomian glands as well as more technologically advanced approaches such as intra-ductal probing, thermal pulsation, and IPL therapy were included in the review. The authors noted that neither subjects nor investigators were masked to treatment allocation in the studies of intra-ductal probing performed to-date indicating that caution should be exercised in drawing conclusions from their findings. The follow-up periods of the studies were also relatively short, with the result that data on the long-term safety and efficacy of this invasive technique are lacking. Furthermore, in most studies, probing was

not compared with standard treatments in the clinical setting such as eyelid warming, lid hygiene, or meibomian gland expression; thus, further studies without potential bias are needed to confirm the safety and efficacy of this procedure. The author's concluded that additional large-scale RCTs are also needed to provide more information such as the specific indications best suited to each treatment modality, the efficacy of such approaches in combination with pharmaceutical-based therapy, and the mechanisms of action of some of the more technologically advanced systems.

(2020) Kheirkhah et al. noted obstructive MGD can be refractory to medical therapy. Intra-ductal meibomian gland (MG) probing may offer a potential therapeutic approach for these patients, but no randomized trials have been conducted to-date. In a randomized, double-masked, single-center, sham-controlled clinical trial, the researchers examined clinical changes after intraductal MG probing for patients with refractory obstructive MGD. A total of 42 patients with refractory obstructive MGD associated with lid tenderness were included in this trial. Enrolled patients received one of the following treatments: MG probing plus post-procedural topical sulfacetamide/ prednisolone ointment (Blephamide); MG probing plus post-procedural lubricating ointment (GenTeal); or sham probing plus GenTeal ointment. The probing was performed on the upper lids of both eyes. Primary outcome measures were symptoms as measured by OSDI and Symptom Assessment iN Dry Eye (SANDE), as well as TBUT; and secondary outcome measures were other clinical signs. Safety of the procedure was also assessed by examining the treatment-related AEs. At baseline and 4 weeks after the procedure a masked observer examined the following outcome measures: symptom questionnaires, including OSDI and SANDE, upper lid tenderness, lid margin telangiectasia, corneal fluorescein staining, conjunctival lissamine green staining, TBUT, Schirmer's test, and meibomian glands yielding liquid secretion (MGYLS). Compared to baseline, the MG probing/Blephamide group showed significant improvements in both OSDI and SANDE scores and the MG probing/GenTeal group demonstrated a significant improvement only in SANDE score. In contrast, the Sham/GenTeal group did not show any statistically significant changes in symptoms. There were no statistically significant changes in clinical signs in any group at the 4-week visit, except for improvement of lid tenderness in the sham probing group. The authors concluded that MG probing/Blephamide ® resulted in a significant improvement in symptoms in patients with refractory obstructive MGD without any significant effect on clinical signs. Moreover, these researchers stated that larger studies are needed to determine the effectiveness of MG probing.

(2018) Maskin and Testa noted in a retrospective study, examined the impact of meibomian gland probing (MGP) on meibomian gland (MG) area from the upper lids of patients with O-MGD. This trial compared pre-MGP/post-MGP non-contact infrared meibography results in patients with O-MGD, viewing signs of MG growth within total measurement field. Post-MGP meibography of 34 lids (19 patients, greater than or equal to 4.5 to less than or equal to 12 months' follow-up) showed 41.2 % with MG growth; 10 lids had meibographies suitable for analysis, showing significant collective (116 glands) increase in mean individual glandular area (MIGA) of 4.87 % ($p = 0.0145$); 4 of 10 lids

independently showed significant increase in MIGA, ranging from 10.70 % to 21.13 % ($p < 0.0001$, $p = 0.0277$, $p = 0.0292$, $p = 0.0345$), while 6 did not. At greater than 12 and less than 25 months' follow-up, 16 lids (9 additional patients) had follow-up showing 25 % with signs of MG growth. Analysis of 3 lids showed a significant collective (33 glands) increase in MIGA of 11.19 % ($p = 0.0004$); 2 of 3 lids independently showed significant increase in MIGA of 13.73 % and 20.00 % ($p = 0.0097$, $p = 0.0001$). Collectively, for all 13 analyzed lids (149 glands), there was a significant increase of 6.38 % in total glandular area ($p = 0.0447$) and a significant increase of 6.23 % in MIGA ($p = 0.0003$). The authors reported MGP was associated with increased MG tissue area and growth of atrophied MGs as viewed on meibography; MGP provided unequivocal physical proof of a patent meibum outflow tract through the natural orifice and may promote glandular growth in part by direct mechanical establishment of a patent duct/orifice system. Moreover, the authors noted future research is needed to study these post-MGP meibography changes in a randomized controlled clinical trial (RCT).

Summary of Evidence: Intraductal Probing (e.g., Maskin Device)
While study results of Intraductal Probing (e.g., Maskin Device) for dry eye syndrome (DES) caused by meibomian gland dysfunction (MGD) may be promising, further multi-center randomized clinical trials (RCTs) with a larger sample and treatment comparison groups are needed to assess long-term effectiveness and safety. The evidence is insufficient to determine the technology results in an improvement in the net health outcomes.

Intranasal Neurostimulation (e.g., TrueTear and iTEAR100)
TrueTear is a handheld stimulator with a prolonged hydrogel-containing disposable tip with a reusable cover. The tip provides the contact for conducting the stimulation current, produced by the base unit, to the target site inside the nasal passages. The device is inserted into the nostrils where a tingling sensation is felt. The stimulation intensity is adjustable, and the device automatically turns off after one minute. The process purports to stimulate a nerve that innervates the lacrimal glands, causing tear production. The device has a usage limit of 30 minutes in a 24- hour period and the disposable tip should be discarded after 24 hours.

(2020) Ji et al. completed a multicenter, open-label, single-arm clinical trial that included adult patients with DED with a Schirmer score of ≤10 mm in at least one eye. Enrolled subjects were instructed to apply the study device at least twice per day for 30 seconds bilaterally to the external nasal nerve. After the initial baseline visit, patients were followed up at days 3, 14, 30, 90, and 180. The primary efficacy endpoint was the Schirmer index (change from unstimulated to stimulated tear production as measured by the Schirmer test) at day 30. The major secondary endpoint was the change in symptoms of DED at day 30 evaluated using the Ocular Surface Disease Index (OSDI). A total of 101 subjects evaluated at day 30 had a mean Schirmer index of 9.4 mm (95% confidence interval [CI], 7.4–11.3), and the baseline OSDI improved by an average of 14.4 (95% CI, 11.1–17.7). Both endpoints were highly statistically and clinically significant at all time points. There were two mild unanticipated adverse events definitely related to the device.

The safety and efficacy of the iTEAR device observed in this study support its indication for treating DED. Further data are needed to assess long-term effectiveness and safety. One limitation of this study is the absence of a control or sham group; however, the primary endpoint of immediate tear production onto a Schirmer strip is not likely to be affected by placebo or Hawthorne effect. Indeed, a separate single-day study (unpublished) showed that a sham device that made noise but did not impart energy to the skin did not result in any tear production above the basal tearing on the Schirmer strip. The OSDI and other symptom scores are susceptible to Hawthorne and placebo types of effects. The OSDI, in particular, has been validated over many years and a decrease of >8 and certainly >13 is widely accepted as evidence of clinical benefit. The meibomian gland expression score and the increase in basal tears were not expected benefits at the outset of the study based on available data for the ITN. These endpoints are newer to studies of DED; therefore, future studies will utilize a control to further understand the clinical effect size.

(2019) Pang and colleagues conducted a systematic review and meta-analysis of randomized controlled trials that compared the efficacy of VTPT and WCT in treating DED. The primary outcome was the gland function. The secondary outcomes were the tear breakup time, Schirmer test, tear osmolarity, lipid layer thickness, Standard Patient Evaluation for Eye Dryness, and the improvement of subjective symptoms as assessed by using the Ocular Surface Disease Index. PubMed, Embase, Cochrane Library, and ClinicalTrials.gov registries were searched for studies published before July 2018. They stated that MGD is the main cause of DED and is traditionally managed using warm compress treatment (WCT). Vectored TPT (VTPT) is a novel method for treating DED.. This study consisted of 4 trials with 385 patients. Significantly greater improvement was observed in meibomian gland function (MD: 2.19; 95 % CI: 0.95 to 3.43), TBUT [MD: 1.08; 95 % CI: 0.06 to 2.10)], and SPEED [MD: -2.76; 95 % CI: -4.22 to -1.30)] at 2 to 4 weeks in the VTPT group than in the WCT group. A significantly greater decrease in OSDI was observed at 2 to 4 weeks [MD: -8.61; 95 % CI: -13.62 to -3.61) and 3 months [MD: -6.92; 95 % CI: -11.95 to -1.89) in the VTPT group than in the WCT group. The authors concluded that a single 12-min VTPT was more effective than traditional WCT in treating DED either in objective or subjective measurements and recommended choosing an appropriate treatment after shared decision-making.

(2018) Senchyna et al. completed a prospective, multicenter, randomized-sequence, subject-masked, cross-over study. Subjects with dry eye disease were exposed to the CAE and when the ocular discomfort score (ODS) threshold measured with the Ora Calibra® Ocular Discomfort Scale was reached, subjects performed either the intranasal or extranasal application, administered in a randomized sequence, for ~3 minutes. The eye dryness score (EDS, assessed with a visual analog scale) and ODS were measured every five minutes during CAE exposure including prior to and following TrueTear application. The primary effectiveness measure was the change in EDS from the measure immediately prior to TrueTear application to the measure immediately following application. The primary safety measure was device-related adverse events (AEs). 185 subjects (mean age 59 y, 74.6% female) were enrolled; 143 (77.3%) performed both

applications and completed the study. Mean change in EDS (standard error [SE]) from pre- to post-application was significantly greater with intranasal (−16.5 [1.7]) than extranasal application (−3.1 [1.7]) (LS mean difference [SE], 13.4 [2.0]; p<.0001; ANOVA). Mean decrease in ODS score in the analysis eye from pre-to post-application was also significantly greater with intranasal application (−0.93 [0.08]) than extranasal application (−0.34 [0.08]) (LS mean difference [SE], 0.60 [0.10]; p<.0001; ANOVA). Only one AE was reported: transient mild epistaxis. In conclusion, intranasal application of TrueTear during CAE exposure resulted in statistically significant improvements in eye dryness and ocular discomfort compared with the control application of the device. TrueTear demonstrated a good safety profile; there were no serious adverse events, and no subject discontinued the study because of an adverse event. By increasing tear production and reducing DED symptoms, TrueTear represents a promising new management strategy for DED.

Summary of Evidence: Intranasal Neurostimulation (e.g., TrueTear and iTEAR100)
For individuals who suffer from dry eye syndrome Intranasal Neurostimulation (e.g., TrueTear and iTEAR100) is a promising intervention, however, further randomized clinical trials (RCTs) are needed to include a presence of a control or sham groups to assess long-term effectiveness and safety. The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes.

Thermal Pulsation System
The LipiFlow Thermal Pulsation System (TearScience) is a new device developed to address the limitations of current treatment options to relieve MGD. This device is designed to heat the palpebral surfaces of both the upper and lower eyelids, while applying graded pulsatile pressure to the outer eyelid surfaces. The LipiFlow® System is composed of a disposable ocular component and a handheld control system. Following application of a topical anesthetic, the heated inner portion of the LipiFlow eyecup is applied to the conjunctival surface of the upper and lower eyelids. The outer portion of the device covers the skin surface of the upper and lower eyelids. The device massages the eyelids with cyclical pressure from the base of the Meibomian glands in the direction of the gland orifices, thereby expressing the glands during heating. It is proposed that a single 12-minute session is at least as effective as twice daily lid warming and massage over 3 months.

In 2017 and 2020, two eyelid thermal pulsation systems (iLux® System and Systane iLux2®) were also cleared by the FDA. These devices were identified by FDA as a "battery-operated, handheld device that the physician uses in an in-office procedure to control the application of warmth and massage to the eyelids. The handheld device connects to a single-use disposable unit made of biocompatible polycarbonate and silicone that is inserted around the patient's eyelids. The device provides controlled warmth to the inner eyelid surface, close to the location of the meibomian glands, and intermittent massage to the outer eyelid surface to facilitate release of lipid from the cystic meibomian glands." The devices are indicated for "the application of localized heat and pressure therapy in adult patients with meibomian gland dysfunction (MGD), which

is associated with evaporative dry eye." The Systane iLux2® system is also indicated "to capture/store digital images and video of the meibomian glands."

Review of Evidence: Thermal Pulsation System
(2021) Park et al. investigated the use of preoperative VTP on meibomian gland dysfunction in subjects prior to cataract surgery. Outcomes were measured by TBUT, Oxford corneal staining score, and LLT. OSDI and Dry Eye Questionnaires (DEQ) were also assessed. The authors also reported on meibomian gland atrophy, degree of gland expressibility, and quality of gland secretions. Participants were followed for 3 months. Analysis included 60 participants in the VTP treatment group and 48 participants in the control group (those who did not receive VTP prior to cataract surgery). In the control group, the authors report a decrease in meibomian gland expressibility, worsened quality of meibomian gland secretions, decreased LLT, and worsened corneal staining. The VTP treatment group showed improved patency of meibomian glands, improved meibum quality, increased TBUT, and reduced corneal staining. OSDI and DEQ questionnaires reported an improvement in subjective outcomes. While these studies report improvements after using VTP prior to cataract surgery, there remains a lack of comparison of VTP to conventional treatment to assess improved health outcomes using an automated process.

(2021) Zhao et al. reported the efficacy of preoperative VTP therapy for individuals prior to cataract surgery. Participants were followed for 3 months after treatment. The primary outcome measure was an improvement in MGYLS. Efficacy was measured using symptoms of dry eye, LLT, tear break up time (TBUT), corneal staining, SIT, MGYLS, and meibomian gland dropout. There were 32 participants previously diagnosed with meibomian gland dysfunction enrolled. Each participant received VTP on one eye. Of the 32 participants, 16 had cataract surgery following VTP and 16 received only VTP and did not have surgery. Scores from a questionnaire of ocular symptoms decreased in both those who had cataract surgery and those who did not have surgery. There were no significant changes in SIT and corneal staining between VTP surgery group and the VTP non-surgery group. LLT values were stable for the 3-month follow-up time. The authors reported a significant difference in TBUT in the surgical group when comparing the eye that received VTP to the eye that didn't receive VTP at week 1 and 1-month exams (4.47 ± 2.77 vs 3.44 ± 2.23 and 4.72 ± 2.78 vs 3.44 ± 2.24 respectively). There was an increase seen in MGYLS from baseline to the 1-week visit in the VTP surgery group. There continued to be in increase in meibomian gland function at 3 months, but no difference was seen in the VTP non-surgery group. The authors report improvement in MGYLS after using VTP in both the surgery group and non-surgery group but acknowledge limitations to the study including no relief of subjective symptoms by the participants who underwent cataract surgery and improvement of symptoms in those who did not have surgery. The authors also note the SPEED questionnaire was not good at differentiating symptomatic and asymptomatic participants and recommend larger multicenter studies to confirm the results. There is also lack of comparison of automated VTP treatment to a manual process.

(2020) Hura et al. completed a retrospective, single-blinded cohort study noting visible meibomian gland structure was evaluated at baseline and at 1-year in treatment (30 patients, 48 eyes) and control (13 patients, 22 eyes) groups. Meibography images were captured using dynamic meibomian imaging. Images were assessed using a novel morphometric analysis technique and analyzed for change in area of VGS (pixels). Additional outcomes measured include tear break up time, corneal staining, tear osmolarity, matrix metalloproteinase-9 (MMP-9), meibography grading, and meibomian gland evaluation. As high as 69% of eyes in the treatment group showed an improvement in VGS versus 27% of eyes in the control group. As high as 31% of eyes in the treatment group showed a decline in VGS versus 73% of eyes in the control group. TBUT ($p = 0.0001$), corneal staining ($p = 0.0063$), and meibomian gland evaluation scores ($p = 0.0038$) all significantly improved after VTP treatment. However, SPEED scores, MMP-9, tear osmolarity, and meiboscale scores were not significantly improved 1-year post treatment. The author's concluded morphometric analysis protocol of meibography provides clinically meaningful information that is undetectable with the standard semiquantitative method of grading meibomian gland structure. This is the first report indicating that gland structure may increase post-VTP relative to untreated controls, thus presenting significant implications regarding benefits and timing of VTP therapy. The described protocol is currently more appropriate for research than for clinical practice.

(2020) Li et al. completed an interventional study by reported on the use of LipiFlow to treat OMGD (n=25 participants) and HMGD (n=25 participants), evaluating the efficacy over a 12-week period. Efficacy was assessed using SPEED scores, OSDI scores, Schirmer I test (SIT), noninvasive keratographic breakup time (NIKBUT), tear meniscus height (TMH), lipid layer thickness (LLT), and partial blink rate (PBR). Compared to baseline, the SPEED and OSDI scores decreased in both OMGD and HMGD groups after 12 weeks. In both groups, mean NIKBUT and TMH increased at the 4-week point, and gradually decreased until the 12-week point. SIT improved in both groups at 4 weeks then gradually decreased until the 12-week point. LLT peaked at 4 weeks and gradually decreased in both groups. The PBR also decreased in both groups. There was overall improvement in both groups following treatment, however there was greater improvement noted in the OMGD group compared to the HMGD group. While this study shows improvement in participants with both OMGD and HMGD, lack of a control group makes it difficult to determine efficacy of an automated process compared to a manual process for treatment of meibomian gland dysfunction.

(2020) Tauber reported a single-center RCT comparing the LipiFlow System to twice-daily administration of lifitegrast ophthalmic solution 5% in patients with inflammatory MGD (N=50; 25 patients per group). The co-primary outcomes were change in eye discomfort and tear lipid layer thickness from baseline to day 42. Results demonstrated that changes in the eye discomfort scores were significantly greater in the group that received lifitegrast, while changes in lipid layer thickness did not reach statistical significance between groups. Trial limitations included lack of masking, attrition in the lifitegrast group (3 patients discontinued therapy), and selection of patients that had both

MGD and inflammation (results may have differed in populations with MGD without inflammation).

(2018) Hagen et al. completed a prospective, randomized, parallel-group study looked at 28 participants with moderate-to-severe meibomian gland dysfunction. The participants were randomized to receive either doxycycline treatment (n=14) or VTP (using the LipiFlow System). The oral doxycycline was given daily for 3 months and the VTP was given once in a single bilateral 12-minute procedure. Any adjunctive treatment (for example, artificial tears, fish oil supplements, lid scrubs, and warm compresses) was continued as long as it had been used for at least 3 months prior to the doxycycline or VTP. Primary endpoint was evaluation of dry eye symptoms using a standard dry eye questionnaire (the Standard Patient Evaluation for Eye Dryness [SPEED]) and meibomian gland function assessed by counting the number of glands yielding liquid secretion (meibomian glands yielding liquid secretion [MGYLS]), tear breakup time, and corneal and conjunctival staining. In the doxycycline group, 2 participants discontinued their treatment due to intolerance to study medication. In the VTP group, 1 participant was lost to follow-up. These participants were not included in the final analysis. In the VTP group, the SPEED scores, MGYLS and tear breakup time were improved from their baseline levels. There was also improvement in the corneal and conjunctival staining. In the doxycycline group, SPEED scores, MGYLS and conjunctival stain improved significantly from the pretreatment levels, but improvement in tear breakup time and corneal stain did not reach statistical significance. While the results show improvement using the VTP compared to the oral doxycycline, there was no comparison of the VTP to a conventional method of lid warming and massage. Additional larger studies are necessary with comparison of the automated process to a manual process to determine efficacy of the automated process.

(2016) Blackie et al. completed a 2-stage multicenter RCT, evaluated treatment effects of the LipiFlow System for patients with MGD and dry eye symptoms. The first stage involved the open-label evaluation of treatment effects over the short term. Trialists compared the single, in-office, LipiFlow treatment with conventional treatments consisting of warm compress and eyelid hygiene control therapy, conducted twice daily for 3 months. Significant treatment effects relative to controls were observed for OSDI scores and meibomian gland secretion score (higher scores reflect less dysfunction). The second stage involved an observational crossover study to evaluate the long-term effects (from 3 to 12 months) of a single session using the LipiFlow System or in combination with other conventional treatments when considered necessary. Sustained treatment effects for the single LipiFlow treatment compared with the combination treatment subgroups were observed over the long-term for OSDI scores, but not for meibomian gland secretion scores. Trial limitations included lack of masking and lack of massage combined with warm compression, the usual treatment approach. The clinical significance of the 17- to 22-point improvement in OSDI scores observed across treatment and controls may be relatively small because final OSDI scores indicated that patients in both groups improved from severe disease to mild disease (treatment) or

moderate disease (controls). The lack of blinding might also have led to an overestimation of the treatment effect of LipiFlow.

(2016) Greiner et al. completed a prospective, cohort, observational, single-center study design, signs (meibomian gland secretion [MGS] scores and tear film breakup time [TBUT]) and symptoms (Ocular Surface Disease Index [OSDI] and Standard Patient Evaluation of Eye Dryness [SPEED] questionnaires) were determined in 20 patients (40 eyes) with MGD and dry eye symptoms at baseline (BL), 1 month, and 3 years post-TPS treatment using LipiFlow. Meibomian gland secretion scores increased from BL (4.5±0.8) to 1 month (12.0±1.1, P≤0.001). Improvement persisted at 3 years (18.4±1.4) relative to BL (P≤0.001). Meibomian gland secretion scores in all regions of the lower eyelid were improved over BL at 1 month (nasal [P≤0.001], central [P≤0.001], temporal [P≤0.01]) and 3 years (nasal [P≤0.001], central [P≤0.001], temporal [P≤0.001]). TBUT increased from BL (4.1±0.4) to 1 month (7.9±1.4, P≤0.05) but was not significantly different than BL at 3 years (4.5±0.6, P>0.05). The OSDI scores decreased from BL (26.0±4.6) to 1 month (14.7±4.3, P≤0.001) but returned to BL levels at 3 years (22.5±5.4, P>0.05). The SPEED scores decreased from BL (13.4±1.0) to 1 month (6.5±1.3, P≤0.001), and this improvement persisted at 3 years (9.5±1.6, P≤0.001). The author's concluded thermal pulsation may be a uniquely efficacious treatment option for DED secondary to MGD in that a single 12-min procedure is associated with significant improvement in MGS and SPEED scores for up to 3 years.

Summary of Evidence: The LipiFlow Thermal Pulsation System
For individuals who have dry eye syndrome (DES) who receive LipiFlow eyelid thermal pulsation, the evidence includes randomized controlled trials (RCTs,) nonrandomized comparison study, and longer- term follow-up of patients from RCTs and observational studies. The trials do not provide strong evidence of long-term efficacy. Two RCTs have demonstrated positive findings for most outcome measures over the short term (up to 3 months). Observational studies have shown sustained treatment effects for most outcomes up to 3 years. The nonrandomized study showed similar outcomes for eyelid thermal pulsation and standard treatment. Further randomized clinical trials (RCTs) are needed to include trials with longer follow-up to assess long-term effectiveness and safety. The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes.
Guidelines and Position Statements

American Academy of Ophthalmology (AAO)
(2018) The American Academy of Ophthalmology (AAO) preferred practice patterns guidelines on *dry eye syndrome (DES*) states the following*:*

- "In-office, physical heating and expression of the meibomian glands (including device-assisted therapies, such as LipiFlow, or intense pulse light treatment)" as 1 of several step-up treatments for patients who do not respond to conventional management, including the elimination of environmental factors and offending medications, dietary modifications, ocular lubricants, and lid hygiene and warm compresses. (*Accessed May 2022*)

(2018) The American Academy of Ophthalmology preferred practice patterns guidelines on *blepharitis* has the three clinical subcategories of blepharitis:

- staphylococcal, seborrheic, and meibomian gland dysfunction (posterior blepharitis specifically affects the meibomian glands). The following statements are made relevant to thermal pulsation treatment:
- "There are also several in-office procedural treatments available that may theoretically unclog the inspissated meibomian gland orifices using intense pulsed light (IPL) or mechanical means (e.g., microblepharoexfoliation of the eyelid margin, meibomian gland probing, and/or devices using thermal pulsation). Although there have been industry-sponsored studies, independent, randomized, masked clinical trials have yet to be performed to assess efficacy of these costly, primarily fee-for-service treatments."

(*Accessed May 2022*)

Regulatory Status

Several devices been approved by the U.S. Food and Drug Administration (FDA) for marketing through the 510(k) process which are approved to be used to aid in the diagnosis or treatment of dry eyes. *The tables below are not intended to be all-inclusive.*

Diagnostic Tests			
Device/Test	**Manufacturer**	**Approval Year/Number**	**Information**
LipiView II Ocular Surface Interferometer	TearScience Inc	2015/K152869	It is indicated "for use by a physician in adult patients to capture, archive, manipulate and store digital images of the tear film, meibomian glands, ocular surface and eyelids." LipiView II, like its predicate LipiView, perform the same principal functions of ocular imaging and for specular observations of the tear film using white light interferometry. Neither device provides a diagnosis.

Therapies			
Device/Test	**Manufacturer**	**Approval Year/Number**	**Information**
iLux® System	Tear Film Innovations, Inc.	2017/K172645	It is an eyelid thermal pulsation system which is indicated for "the application of localized heat and pressure therapy in adult patients with Meibomian Gland Dysfunction (MGD), which is associated with evaporative dry eye. It is"Battery-operated, handheld device that the physician uses in an in-office procedure to control the application of warmth and massage to the eyelids. The handheld device connects to a single-use disposable unit made of biocompatible polycarbonate and silicone that is inserted around the patient's eyelids. The device provides controlled warmth to the inner eyelid surface, close to the location of the meibomian glands, and intermittent massage to the outer eyelid surface to facilitate release of lipid from the cystic meibomian glands." The FDA classified these devices as class II (special controls) to provide a "reasonable assurance of safety and effectiveness" of the device
iTEAR100	Olympic Ophthalmics	2022/K213623	This device type is a non-implantable device intended to increase tear production via mechanical stimulation via a battery-operated handheld electromechanical actuator with a vibratory tip, and software controller. The device activates

			tear production through stimulation of the nasolacrimal reflex. Stimulation mechanically activates external nasal nerve and initiates the nasolacrimal reflex, resulting in tear secretion. To produce the intended effect, the vibratory tip of the device should be applied to the lateral aspect of the nose for several seconds.
LipiFlow® Thermal Pulsation System	TearScience	2011/K112704	It is an eyelid thermal pulsation system which is indicated for "the application of localized heat and pressure therapy in adult patients with Meibomian Gland Dysfunction (MGD), which is associated with evaporative dry eye. "Battery-operated, handheld device that the physician uses in an in-office procedure to control the application of warmth and massage to the eyelids. The handheld device connects to a single-use disposable unit made of biocompatible polycarbonate and silicone that is inserted around the patient's eyelids. The device provides controlled warmth to the inner eyelid surface, close to the location of the meibomian glands, and intermittent massage to the outer eyelid surface to facilitate release of lipid from the cystic meibomian glands."
Systane® iLux2®	Tear Film Innovations, Inc.	2020/K200400	It is an eyelid thermal pulsation system which is indicated for "the application of localized heat and pressure therapy in adult patients with Meibomian

			Gland Dysfunction (MGD), which is associated with evaporative dry eye. "Battery-operated, handheld device that the physician uses in an in-office procedure to control the application of warmth and massage to the eyelids. The handheld device connects to a single-use disposable unit made of biocompatible polycarbonate and silicone that is inserted around the patient's eyelids. The device provides controlled warmth to the inner eyelid surface, close to the location of the meibomian glands, and intermittent massage to the outer eyelid surface to facilitate release of lipid from the cystic meibomian glands." It is also indicated "to capture/store digital images and video of the meibomian glands." The FDA classified these devices as class II (special controls) to provide a "reasonable assurance of safety and effectiveness" of the device
TearCare® System	Sight Sciences, Inc.	2021/K213045	FDA-cleared eyelid thermal pulsation system for "the application of localized heat and pressure therapy in adult patients with evaporative dry eye disease due to Meibomian Gland Dysfunction (MGD), when used in conjunction with manual expression of the meibomian glands."

TrueTear Intranasal Tear Neurostimulator	Allergan	2020/K193589	This device type is intended to temporarily increase tear production using neurostimulation to improve dry eye symptoms. The intranasal electrostimulation device for dry eye symptoms is a handheld device with two electroconductive tips that are inserted into the nasal cavity during neurostimulation. The disposable tips are made of rigid biocompatible USP Class VI plastic and the conductive tips are made of silicone hydrogel. Additional hardware components include a reusable base, charging station, and cover. The base has two buttons that allow the user to select the stimulation level (device is locked from use after a predetermined amount of stimulation has been triggered). The device is powered by a rechargeable battery.

PRIOR APPROVAL

Not applicable.

POLICY

Diagnostic Tests
The following diagnostic tests are considered **investigational** for the diagnosis of dry eye syndrome (DES), because the evidence is insufficient to determine that the technology results in an improvement in the net health outcome:

- Imaging studies using near-infrared dual imaging (i.e., simultaneous reflective and transilluminated light) or interferometry of meibomian glands (0507T)
- Tear film imaging (e.g., LipiView Ocular Surface Interferometer) (0330T)

Therapies
Therapies for the treatment of dry eye syndrome (DES) due to decreased tear production and/or increased evaporation loss is considered **investigational** including but not limited

to the following, because the evidence is insufficient to determine that the technology results in an improvement in the net health outcomes:

- Autologous eye drops (e.g., autologous serum tears)
- Intense Pulsed Light (e.g., IPL)
- Intraductal probing (e.g., Maskin Device) (68810 or 68811)
- Intranasal Neurostimulation (e.g., TrueTear, iTEAR100)
- Thermal Pulsation/electrothermal heat systems to include but not limited to:
    - iLux Thermal Pulsation System
    - LipiFlow Thermal Pulsation System (0207T)
    - Systane iLux2 Thermal Pulsation System
    - TearCare System (0563T)

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 0207T Evacuation of meibomian glands, automated, using heat and intermittent pressure, unilateral. (*may be utilized for LipiFlow Thermal Pulsation System*)
- 0330T Tear film imaging, unilateral or bilateral, with interpretation and report. (*may be utilized for LipiView Ocular Surface Interferometer*)
- 0507T Near-infrared dual imaging (i.e., simultaneous reflective and trans-illuminated light) of Meibomian glands, unilateral or bilateral, with interpretation and report
- 0563T Evacuation of meibomian glands, using heat delivered through wearable, open-eye eyelid treatment devices and manual gland expression, bilateral (*may be utilized for TearCare*)
- 17999 Unlisted procedure, skin, mucous membrane and subcutaneous tissue (*may be utilized for Intense Pulsed Light (e.g., IPL)*)
- 67999 Unlisted procedure, eyelids (may be utilized for *iLux Thermal Pulsation System or Systane iLux2 Thermal Pulsation System*)
- 68810 Probing of nasolacrimal duct, with or without irrigation (*may be utilized for Intraductal probing (e.g., Maskin Device)*)
- 68811 Probing of nasolacrimal duct, with or without irrigation; requiring general anesthesia (*may be utilized for Intraductal probing (e.g., Maskin Device)*)
- 68899 Unlisted procedure, lacrimal system (*may be utilized for Autologous eye drops (e.g., autologous serum tears)*)
- 92499 Unlisted ophthalmological service or procedure (*may be utilized for TrueTear, iTEAR100, iLux Thermal Pulsation System or Systane iLux2 Thermal Pulsation System*)

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POLICY HISTORY		
Date	**Reason**	**Action**
June 2022	Annual Review	Policy Revision
June 2021	Annual Review	Policy Revised
June 2020	Annual Review	Policy Revised
September 2019	Annual Review	Policy Revised
September 2018	Annual Review	Policy Revised
September 2017	Annual Review	Policy Revised
September 2016		New Policy

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
Des Moines, IA 50306-9232

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