

TearLab osmolarity system for diagnosing dry eye disease

Medtech innovation briefing

Published: 15 December 2015

www.nice.org.uk/guidance/mib47

Summary

The TearLab osmolarity system is a point-of-care device that measures the osmolarity of tears and is used to diagnose and monitor dry eye disease. The published evidence summarised in this briefing comes from 6 non-randomised studies in adults on the value of osmolarity as a biomarker for dry eye disease. Four studies of limited quality showed that tear osmolarity either predicted dry eye disease or correlated with other dry eye tests. Two studies found no or limited correlation. The average cost for TearLab testing per person, including capital equipment and single-use components, is £16.58 excluding VAT.

Product summary and likely place in therapy

- The TearLab osmolarity system is a point-of-care quantitative diagnostic device that measures the osmolarity of tears for diagnosing or measuring response to treatment in dry eye disease (DED).
- If adopted, TearLab would be used by optometrists or ophthalmologists in addition to existing tests for DED in a primary or secondary care setting.

Effectiveness and safety

- The published evidence summarised in this briefing comes from 6 non-randomised studies done in people with known or suspected DED and healthy volunteers.
- Two of the 6 studies (n=36; n=288) evaluated the diagnostic accuracy of TearLab in adults with DED and healthy people as controls. They reported sensitivity ranging from 73% to 87%, and specificity ranging from 81% to 90%.
- One of the 6 studies (n=36) compared osmolarity results from TearLab with those from the Clifton osmometer and found no statistically significant difference.
- Four of the 6 studies showed a statistically significant relationship between osmolarity changes and severity of DED, and noted the value of TearLab as a valid diagnostic tool.
- The results of 2 studies did not confirm the relationship between tear film osmolarity and the severity of DED.
- No reports of adverse events were identified.

Technical and patient factors

- The TearLab osmolarity system consists of 3 components: a pen, a test card and system reader. The pen holds the test card, which collects and analyses the tear fluid. The system reader displays the osmolarity measurement.
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Cost and resource use

- The TearLab reader and pen cost £4370 (excluding VAT).
- Consumables (TearLab test cards) cost £323 (excluding VAT) for 40 cards. One test card is used per eye.
- The cost per procedure is £16.58, including capital and consumable costs (excluding VAT).

Introduction

Tear film is a thin film of fluid that covers the exposed areas of the eyes and extends under the eyelids. It has 3 layers: an outer lipid layer, a middle aqueous layer and an inner mucin layer (Bron et al. 2004).

The tear film is essential for maintaining the transparency and health of the cornea and conjunctiva, providing a smooth, moist surface for light to pass through. It also supplies nutrients and flushes away waste products, protects against shear forces produced by blinking and eye movements, and helps to protect the eye against environmental challenges. Dry eye disease (DED; also known as dry eye syndrome or keratoconjunctivitis sicca) was described in the Report of the International Dry Eye Workshop (DEWS 2007) as 'a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface'. DED often affects both eyes. The [NICE clinical knowledge summary on dry eye syndrome](#) states that symptoms of DED are most commonly caused by:

- Decreased tear production, usually because of dermatosis of the eyelids, an adverse effect of some medicines, or allergic conjunctivitis. (This is referred to as aqueous DED [DEWS 2007].)
- Increased evaporation of tears, usually because of low humidity, low blink rate (for example, from prolonged use of a computer or microscope), high wind velocity, an adverse effect of some medicines (such as antihistamines), or allergic conjunctivitis. (This is referred to as evaporative DED [DEWS 2007].)

Symptoms of DED may include dry, gritty, sore or red eyes, temporary blurred vision, and eyelids sticking together during sleep. DED symptoms vary in severity and are commonly classified using the 4-grade DEWS severity grading scheme (DEWS 2007). Grade 1 refers to very mild or episodic DED, which tends to have limited visual symptoms, whereas grade 4 refers to severe and constant DED with potentially disabling symptoms. Severe symptoms can impair vision, limiting vision-related daily activities such as reading and driving. The complications of DED include conjunctivitis, keratitis (infection of the cornea) and corneal scarring.

The condition is estimated to affect 15–33% of people aged over 65 years, and is about 50% more common in women than men ([NICE clinical knowledge summary on dry eye syndrome](#); Lemp et al. 2012). DED is also more common in people who wear contact

lenses, about 50–75% of whom report symptoms of ocular irritation (DEWS 2007).

Technology overview

This briefing describes the regulated use of the technology for the indication specified, in the setting described, and with any other specific equipment referred to. It is the responsibility of healthcare professionals to check the regulatory status of any intended use of the technology in other indications and settings.

About the technology

CE marking

The TearLab osmolarity system is CE marked as an In Vitro Diagnostic Device (Class IIa). The CE mark was obtained in October 2008 and is held by the manufacturer, TearLab Corporation (USA).

Description

The TearLab osmolarity system is a diagnostic device, which is used at the point of care to measure the osmolarity of human tears and help diagnose DED. The manufacturer also states that TearLab may be used to aid monitoring of treatment.

The TearLab osmolarity system consists of 3 components:

- TearLab osmolarity system reader unit
- TearLab osmolarity system pen
- TearLab osmolarity test card with microchip, which is clipped into the top of the pen.

The system reader is a countertop unit that calculates and displays the osmolarity test result. It is powered by mains (230 V) supply and contains a liquid crystal display (LCD) screen, a simple key pad for operating the system, and docking ports to store system pens. System pens are powered by a rechargeable battery.

The single-use polycarbonate microchip in the test card has a micro-fluid channel that

collects the tear fluid by passive capillary action. Gold electrodes, which allow measurement of tear osmolarity by electrical impedance, are embedded in the microchip within the pen. The composition and concentration of ions in tear fluid affects its electrical conductivity, so this can give a measurement of tear film osmolarity.

To do the test, a small sample of tear fluid (50 nanolitres) is collected by the test card on the top of the pen. The clinician places the tip of the test card next to the inferior lateral meniscus of the tear film, above the lower eyelid, to absorb the correct amount of fluid. It is recommended that tears should be collected at the outermost area of the eyelid to minimise the risk of injury to the cornea. Osmolarity may differ between the left and right eye, so the manufacturer recommends that both eyes are tested and the higher osmolarity reading should be considered as the relevant value. Separate test cards are needed for each eye. The pen confirms when the test card is correctly attached and when the tear fluid sample has been properly collected. Once the pen is docked, the system reader then calculates and displays the osmolarity measurement in mOsm/litre on the LCD screen.

The 2 reusable electronic check cards that come with the TearLab osmolarity system are used to ensure that the system and pen are functioning according to the original factory calibration. The manufacturer recommends that each pen should be tested with a check card before each day of patient testing, or if the pen has been dropped or mishandled, to verify that the system is working within manufactured calibration specifications. The system is calibrated at the factory, and is designed to stay calibrated during the life of the system (about 5 years). Normal and high osmolarity control solutions are used to verify the quantitative functioning of the osmolarity test cards. The manufacturer recommends testing each new batch of test cards with both levels of control solution, and to check test cards in storage monthly. Osmolarity control solutions are not included with the TearLab osmolarity system and must be bought separately. The manufacturer states that if either the control solution test or electronic check card results do not match the expected value range, the user should not test patients. The manufacturer suggests that osmolarity values above 308 mOsm/litre are generally indicative of DED. The DEWS (2007) report recommended a diagnostic cut-off value of 316 mOsm/litre and higher for diagnosing DED.

Setting and intended use

The TearLab osmolarity system is intended to measure the osmolarity of tears to help diagnose DED, in conjunction with other tests and with clinical evaluation. TearLab Corporation recommends that the osmolarity test is done before any other tests, such as the fluorescein dye test, because they could stimulate the production of reflex tears

(which differ from basal tears) and affect the value of the reading. Contact lenses do not have to be removed before the test.

In the NHS, TearLab is most likely to be used by optometrists or ophthalmologists and could be used in a primary or secondary care setting.

Current NHS options

No nationally accredited clinical guidelines or care pathways for the treatment of DED have been identified. Two separate guidelines developed by the Canadian Association of Optometrists (Prokopich et al. 2014) and the Sjogren Syndrome Foundation (Foulks et al. 2015) recommend that tear film osmolarity measurement is the most accurate single test for DED diagnosis. The [NICE clinical knowledge summary on dry eye syndrome](#) gives an overview of the evidence on diagnosing and managing DED. This is mainly based on the recommendations of the 2007 Report of the International Dry Eye Workshop (DEWS; sponsored by the Tear Film and Ocular Surface Society), but also from the Dry Eye Syndrome Preferred Practice Pattern (PPP), produced by the American Academy of Ophthalmology (2013). The NICE clinical knowledge summary on dry eye syndrome indicates that diagnosis can usually be made on medical history and presenting symptoms. The summary also states that special investigations such as slit lamp examination, Schirmer's test, and tear breakup time are not routinely done in primary care, and usually need referral, such as to an optometrist. Other tests include assessing corneal and conjunctival staining, tear film quality, meibomian gland function, and symptom questionnaires.

The following 2 tests are typically used by specialists to check for signs of DED ([NHS website page on dry eyes](#)):

- Tear breakup time (TBUT) test (also known as the fluorescein dye test): eye drops containing a yellow-orange dye are used so that the healthcare professional can see the tears more clearly. After the dye has been administered, a light is used to see how long it takes for a dry patch to appear. Patches beginning to appear in less than 10 seconds are typically taken as an indication of DED. In NHS practice, this test is usually conducted by an ophthalmologist or an optometrist.

- Schirmer's test: small strips of blotting paper are hooked over the lower eyelid. After 5 minutes, the strips are removed and studied to determine how wet the paper is. If the tear fluid has travelled less than 10 mm from the eye surface along the absorbent paper in 5 minutes, this may indicate DED. In NHS practice, this test is usually conducted by an ophthalmologist or an optometrist.

NICE is not aware of any other CE-marked devices that have a similar function to the TearLab osmolarity system. The Clifton osmometer can also be used to measure tear osmolarity, but this is only used in laboratory settings.

Costs and use of the technology

Information on the cost of using the technology has been sourced from the manufacturer.

The manufacturer states that the anticipated lifespan of the system (both the reader unit and the pen) is 20,000 tests. The manufacturer assumes an average of 4,000 tests per year in an NHS clinic and so each device has a lifespan of about 5 years. The cost of a TearLab system is £4370 (excluding VAT). The cost of the TearLab test cards (40 test cards) is £323 (excluding VAT). The manufacturer states that the average rate of use is 2 test cards per patient examination (1 test card per eye), which gives a cost per procedure of £16.58, including capital and consumable costs, excluding VAT. If the TearLab test is done in an ophthalmology outpatient setting, a consultation costs £124 and a follow-up appointment costs £93 (Enhanced Tariff Option 2015/2016, NHS England March 2015). There are no service or maintenance costs, but it is recommended that each pen is tested daily before use to ensure that the system is properly calibrated and working within the manufacturer specifications.

Alternatively, DED can be diagnosed by a GP in a primary care setting. A 30 minute GP consultation costs £117 (Curtis 2014). The GP may also refer people to an optometrist or an ophthalmologist. An optometrist test costs £22 (based on the 2006 costings from Hernandez et al. [2008] inflated to 2014 prices, using the Hospital and Community Health Services index [Curtis 2014]). The national tariff for an ophthalmology outpatient consultation is £104 (NHS England 2013).

The assumed average length of time for each test is 1 minute.

No practical difficulties have been identified in using or adopting the technology.

Likely place in therapy

Because the current care pathway for DED is not clearly defined, the likely place for the TearLab osmolarity system is also uncertain. GPs may be able to diagnose DED based on symptoms and medical history, but may also refer people for further investigation. The manufacturer suggests that the TearLab osmolarity system may be used with other tests to diagnose DED and also for objective monitoring of treatment outcome in ophthalmology clinics by nurse practitioners or consultant ophthalmologists. The manufacturer also states that the TearLab osmolarity system may be used by community optometrists, working within a shared care pathway with local NHS hospitals.

Specialist commentator comments

Two specialist commentators noted that the DEWS (2007) definition of DED is now widely accepted because it refers to both aqueous and evaporative DED, and also acknowledges that inflammation is a significant factor in ocular surface damage.

One commentator highlighted that DED can significantly affect quality of life with symptoms leading to difficulty reading, using computers, watching TV, and driving. They noted that people with DED may report feelings of depression and anxiety, particularly before diagnosis.

One commentator explained that tear osmolarity has been used in DED research for many years, and stated that there is a significant amount of literature that recognises osmolarity as a reliable biomarker for DED. But the commentator noted that the main issue with using osmolarity as a marker for DED is whether it is the 'gold standard' single measurement. The same commentator stated that further large-scale studies are needed to confirm the correlation with other clinical tests for DED and examine the longitudinal pattern of changes in tear osmolarity, which are thought to fluctuate more in people with than without DED.

One commentator explained that although there was no clear care pathway specifically for DED, there were several pathways by which people with general eye conditions may self-refer or be referred by a GP to an optometrist. The same commentator considered that, in theory, only severe DED would be referred to a hospital eye service because mild to moderate DED can be managed by a community optometrist, but care pathways are not available for this in many areas. One specialist commentator noted that, according to their experience, GPs frequently use trial of treatment to aid diagnosis and rarely refer people to

ophthalmology or optometry practices for diagnosis of DED. In contrast, another commentator suggested that GPs only tend to manage very mild DED and refer most other cases to specialist clinics because of a lack of training and access to relevant equipment. So even with training, the commentator indicated that it was unlikely a GP would rely on the TearLab osmolarity system as a diagnostic tool because of the risk of overlooking another eye condition and the cost of consumables needed to use the device. The same commentator noted that the TearLab osmolarity system is best placed in community- or hospital-based eye clinics, to be used by ophthalmologists or ophthalmic nurse practitioners who can interpret findings in the context of history and other clinical findings. Two commentators concurred that measuring tear osmolarity was likely to be more popular in specialised eye clinics or research centres than in primary care settings unless equipment cost is low, because it would not significantly add to what can already be done in primary care. One of them noted that TearLab may be of more interest to GPs who have a special interest in ophthalmology. One commentator noted that although the TearLab system is reasonably priced compared with many ophthalmic instruments, the cost of consumables (2 test cards per person tested) could be significant unless discounts were available for bulk purchasing. The commentator highlighted that this would need to be taken into consideration when purchasing within the NHS to ensure the costs do not exceed NHS tariffs.

One specialist commentator noted that at present there is no single standard test that can clearly differentiate DED from other causes of ocular surface discomfort. Another commentator suggested that the most common tools for DED used by community optometrists were history, symptoms, TBUT and ocular surface integrity using fluorescein. They added that some practices had specific DED clinics that offered DED questionnaires, non-invasive break-up time tests, Schirmer's test, lissamine green, photography and meibomian gland dysfunction evaluations. According to the commentator, NHS ophthalmology clinics often use symptoms, TBUT ocular surface examination or integrity, and Schirmer's test to diagnose DED. The commentator suggested that Schirmer's test is not useful for diagnosing mild or predominantly evaporative DED, and noted that DED questionnaires are important research tools but are less commonly used in clinics because of time pressures. One commentator noted that if a series of tests for DED are being done, non-invasive tests such as symptom questionnaires and slit lamp examinations should be carried out before the more invasive tests, such as the TearLab osmolarity test, TBUT or Schirmer's test.

One commentator stated that the TearLab osmolarity system is the only commercially available, reasonably priced method of measuring tear osmolarity in a clinical or research

setting. According to the commentator's personal experience it is relatively easy to use after training and is minimally invasive, causing little discomfort to people being tested for DED. But the commentator noted that, although there are no published incidents of harm or side effects, it is theoretically possible to scratch the eye surface when collecting the tear sample; for example, if the user was untrained and the person being tested was unable to stay still. Another commentator highlighted that training, using the TearLab system often enough to maintain competence, and inter-rater reliability (the degree of agreement among values obtained by different users) should be considered. One commentator expressed uncertainty about whether using the TearLab osmolarity system to collect tear samples in people with severe DED might lead to reflex tear secretion, and whether the TearLab system could be useful to distinguish between dry eye types such as evaporative and aqueous deficient DED.

Equality considerations

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. In producing guidance and advice, NICE aims to comply fully with all legal obligations to:

- promote race and disability equality and equality of opportunity between men and women
- eliminate unlawful discrimination on grounds of race, disability, age, sex, gender reassignment, marriage and civil partnership, pregnancy and maternity (including women post-delivery), sexual orientation, and religion or belief (these are protected characteristics under the Equality Act 2010).

DED is a common condition, the prevalence of which increases with age, so the TearLab osmolarity system may be particularly beneficial in older adult populations. DED is 50% more common in women than in men, so women in particular may benefit from use of the TearLab osmolarity system. Age and sex are protected characteristics under the Equality Act 2010.

Evidence review

Clinical and technical evidence

Regulatory bodies

A search of the Medicines and Healthcare Products Regulatory Agency website revealed no manufacturer Field Safety Notices or Medical Device Alerts for this device. No reports of adverse events were identified from a search of the US Food and Drug Administration (FDA) database: Manufacturer and User Device Facility Experience (MAUDE).

Clinical evidence

A literature search revealed 38 relevant journal articles. Studies have been included in this briefing if they compared the effectiveness of TearLab against other tests or self-reported symptoms in either diagnosing DED or measuring response to treatment. To avoid confounding results, studies have only been included if the study populations had symptoms of DED, but no other presenting factors (such as allergies, eye deformities or infections). Retrospective studies and studies with fewer than 30 patients were excluded. As a result, 6 studies have been included in this briefing.

The aim of the study reported by Caffery et al. (2014) was to assess the correlation between tear osmolarity readings (measured using TearLab) and symptoms of DED, and to determine how well these correlate with the self-assessment of DED. People (n=249) were recruited from attendees at the American Academy of Optometry conference and did not have clinically diagnosed DED. People who had worn contact lenses in the past 2 weeks were excluded from the study. Patients completed the Dry Eye Questionnaire 5 (DEQ-5) and a Gestalt self-assessment. The DEQ-5 is a validated 5-item self-assessment questionnaire, used to help diagnose DED and quantify its severity. The DEQ-5 questions are related to eye discomfort, eye dryness and watery eyes. The Gestalt self-assessment asks the person whether or not they think they have DED. People then had osmolarity testing using TearLab done by experienced clinicians. There was no statistically significant correlation between the DEQ-5 scores and tear osmolarity. No significant differences were seen between the 'yes' and 'no' (Gestalt self-assessment) self-reported dry eye groups and average osmolarity ($p=0.23$). The authors concluded that there was no statistically significant correlation between tear osmolarity and self-reported ocular symptoms (as

measured by the DEQ-5) or the Gestalt self-assessment.

The aim of the Jacobi et al. (2011) study was to evaluate the diagnostic accuracy of the TearLab osmolarity system to assess the osmolarity of tear samples from people with moderate to severe DED (DEWS Dry Eye severity level 3; n=133) compared with healthy people as controls (n=95). The severity of DED was assessed using Schirmer's test, TBUT and results of the Ocular Surface Disease Index (OSDI) questionnaire. Inclusion criteria were a TBUT of less than 5 seconds, a Schirmer's test result of less than 5 mm per 5 minutes and positive symptoms according to the OSDI. People were placed in the healthy control group if they were asymptomatic and had normal TBUT and Schirmer's test results. Findings from the study revealed a statistically significantly higher osmolarity in people with moderate to severe DED than in healthy people in the control group ($p \leq 0.05$). The sensitivity of the TearLab test was 87%, and the specificity was 81%. The authors concluded that TearLab can be an effective objective diagnostic tool in the diagnosis of DED.

The aim of the Messmer et al. (2010) study was to evaluate the ability of the TearLab osmolarity system to differentiate between people with DED (n=129) and healthy people acting as controls (n=71). A diagnosis of DED was made if more than 3 out of 6 clinical criteria were met. These included results from the OSDI questionnaire, corneal staining, TBUT and slit-lamp examination indicating DED. The results of the comparison showed that there was no correlation between TearLab osmolarity and the 6 DED criteria. The authors concluded that the TearLab test was not sensitive enough to discriminate between people with DED and healthy people.

The aim of the Lemp et al. study (2011) was to assess the diagnostic performance of tear osmolarity compared with that of other tests. People (n=299) were recruited from the general population and had 6 commonly used tests to diagnose DED, including tear osmolarity measurement using the TearLab osmolarity system. Of the 6 tests, tear osmolarity had superior diagnostic performance. The most sensitive threshold between normal and mild or moderate DED was 308 mOsm/litre, whereas the most specific was 315 mOsm/litre. At a cut-off of 312 mOsm/litre, tear osmolarity showed 73% sensitivity and 92% specificity. In contrast, the other tests showed either poor sensitivity (corneal staining 54%; conjunctival staining 60%; meibomian gland grading 61%) or poor specificity (TBUT 45%; Schirmer's test 51%). The authors concluded that tear osmolarity is the best single metric for diagnosing and classifying DED.

The aim of the Sullivan et al. (2012) study was to compare the variability of 6 commonly

used biomarkers for DED diagnosis (tear osmolarity, TBUT, Schirmer's test, staining, meibomian grading and OSDI) over a 3-month period. Two measurements were reported: the range and standard deviation of each test. Patients (n=52) had all been diagnosed with DED within the 2 years before the study. The results showed that tear osmolarity (TearLab) values had a statistically significantly lower range and less variability than corneal staining (range $p=0.029$; variability, $p=0.040$), conjunctival staining (range $p=0.0035$; variability $p=0.002$), and meibomian gland dysfunction score (range $p=0.0001$; variability $p=0.0001$). The average variability of tear osmolarity was also lower than that of TBUT, Schirmer's test and OSDI, but these differences were not statistically significant. At the end of the 3-month observation period, a subset of 10 people with severe DED entered an additional 3-month interventional study to determine the reproducibility of the tests when measuring treatment outcome. Tear osmolarity was the only test to show a statistically significant response to treatment with ciclosporin ($p<0.0001$) with average osmolarity and variability decreasing from 341 ± 18 mOsm/litre to 307 ± 8 mOsm/litre. The authors concluded that tear osmolarity was the only objective test sensitive enough to detect a response to ciclosporin over a 3-month period.

The aim of the Tomlinson et al. (2010) study was to compare osmolarity results from the TearLab osmolarity system with those from the Clifton osmometer (Clifton Technical Physics), and to evaluate the diagnostic accuracy of each instrument. Thirty six people were recruited for this study and were assigned to DED and non-DED groups using inclusion criteria based on the results of several standard DED tests (non-invasive TBUT, Schirmer's test, McMonnies questionnaire). Both the DED (n=15) and non-DED groups (n=21) had osmolarity testing (randomised to instrument). A statistically significant correlation was found between the TearLab and Clifton osmometer measurements ($r=0.904$; $p=0.006$). The values measured by the 2 osmometers showed a high level of agreement with only a minimal number of points falling outside the 95% confidence limits. Cut-off values taken from the distribution of osmolarity values were used to diagnose DED with 73% sensitivity, 90% specificity, and 85% positive predictive value for TearLab and 73% sensitivity, 71% specificity, and 65% positive predictive value for the Clifton osmometer. The authors concluded that TearLab has the potential to provide clinicians with a readily available test that could become the gold standard for DED diagnosis.

Recent and ongoing studies

Two ongoing or in-development trials on the TearLab system for tear film osmolarity measurement were identified in the preparation of this briefing.

TearLab core validation study to establish referent values for dry eye disease (CVS) trial NCT00848198. This is an observational, prospective, case control, multicentre (10 sites in the US, Europe and Japan) study comparing osmolarity measured with TearLab in tear samples from people with DED with age- and gender-matched healthy people as controls. The study began in February 2009 and was expected to complete by July 2010. This study is currently recruiting patients (by invitation only).

Tear osmolarity clinical utility in dry eye disease trial NCT02417116. This is a non-randomised, open label, efficacy study that will investigate the efficacy of 2 non-pharmaceutical eye drops (0.3% hypermellose and hylo-forte 0.2% sodium hyaluronate) combined with an omega 3 nutritional supplement and warm compresses compared with placebo (saline) for people with DED, by measuring tear osmolarity changes over a 3-month period using the TearLab system. This UK-based (Aston University) study began in June 2015 and is expected to complete in December 2015. Estimated enrolment is 120 patients and the study is currently recruiting.

Costs and resource consequences

If the TearLab osmolarity system was adopted in the NHS, it would be used in addition to existing tests and clinical evaluation for diagnosing patients with DED. Dry eye symptoms are common, and in people aged 65 years and older the reported prevalence rates are 15–33%. The NICE clinical knowledge summary on dry eye syndrome notes that the prevalence of DED increases with age and it is more common in women than in men. Because the current care pathway for DED is not clearly defined, the likely NHS usage for the TearLab osmolarity system is difficult to estimate.

There will be no need to change the way in which current services are organised or delivered. No other additional facilities or technologies are needed alongside the technology.

No published evidence on resource consequences of using the TearLab osmolarity system was identified in the systematic review of evidence.

Strengths and limitations of the evidence

The evidence considered in this briefing ranged from small single-centre to multicentre prospective cohort studies. Study patients were adults who were either healthy people

acting as controls or people with DED. No randomised controlled trials were identified. Studies were carried out in various regions, including Europe, the USA and Japan. All studies aimed to examine the relationship between tear film osmolarity and severity of DED and to evaluate the potential of tear osmolarity (measured by the TearLab osmolarity system) as an objective measure in the diagnosis of DED.

A potential source of bias is the composition of the participating population. The cohort used in Caffery et al. (2014) was conference attendees who were self-assessed and had not had a DED diagnosis. It is possible that this population may have had milder forms of DED than those studied in clinical research settings, which could account for the relatively low osmolarity findings. The person's occupation (eye care practitioners, optometry students, optometric staff) may have influenced their answers on the DEQ-5 questionnaire. Finally, by excluding people who wear contact lenses, the study may have missed a significant population with DED.

DED is considered to be a multifactorial condition and there is no gold standard to diagnose it. It is generally recommended (DEWS 2007) that a diagnosis is based on a clinical history, and subjective (DEQ-5, Gestalt questionnaire) and objective tests (including Schirmer's test, TBUT and corneal staining). But the lack of an established combination of tests and cut-off values complicates DED diagnosis, and studies use different combinations to stratify DED severity. Caffery et al. (2014) introduced further uncertainty into their study by using global self-assessment, a single subjective measure, as a surrogate for DED diagnosis.

The results of the Caffery et al. (2014) and Messmer et al. (2010) studies are dependent on the validity of the correlation between subjective symptoms and the objective presence of DED. In a retrospective study on the relationship between signs and symptoms of DED in a clinic-based population, Sullivan et al. (2014) found no consistent relationship between common signs and symptoms of DED and noted that 'each type of measurement provides distinct information about the condition of the ocular surface'. The authors stated that 'symptoms alone are insufficient for the diagnosis and management of DED', and that 'measurements of osmolarity may more closely reflect the central pathogenesis of DED than other commonly used signs and symptoms'. They concluded that a consensus of clinical signs may better reflect all aspects of the disease. Foulks et al. (2015) state that although DED is usually symptomatic, 40% of people with clear objective evidence of dry eye disease are asymptomatic, so correlations between signs and symptoms of DED are questionable as an assessment of the validity of tear osmolarity testing for diagnosing DED.

The Tomlinson et al. (2010) study found a positive correlation between the TearLab system and the Clifton osmometer for measuring tear osmolarity in 15 people with mild to moderate DED and 25 healthy people as controls. The authors noted that the sensitivity, specificity and positive predictive value did not reach the level of diagnostic effectiveness expressed in other reports. The sample size in this study was relatively low compared with other studies presented in this briefing. Smaller sample sizes can lower the power of a study. The study outcomes are not representative of people with severe DED.

Another potential source of bias is the level of training of the clinicians in using TearLab. Caffery et al. (2014) note that the study examiners were clinicians who were experienced in using TearLab in their own clinical settings, and that technical support was available from the manufacturer. In contrast, none of the other studies reported whether the investigators had training with the TearLab osmolarity system, nor did they report the investigators' level of experience.

Messmer et al. (2010) was the only study to report in detail the technical problems that happened while using the TearLab osmolarity system. First, the authors note that the scientific principle of TearLab was not publically available at the time of the study so the investigators did not know whether it measured osmolarity directly or indirectly (for example, by determining salinity). Second, they discuss how TearLab may be inefficient in detecting the small osmolarity changes in tear meniscus between people with and without DED. Third, the authors were uncertain whether, by using the TearLab osmolarity system, they collected the correct type of tear. Pathological changes can only be measured in basal tears (not in reflex tears) making their collection critical for measuring meaningful osmolarities. Although the TearLab pen is designed to collect minimal tear volumes directly from the tear meniscus without inducing reflex tear secretion, the reduced osmolarity values seen are similar to those expected from reflex tears, provoked by contact with conjunctiva and lids. Messmer et al. (2010) measured osmolarity in either the subjectively worse eye or the left eye (if both eyes were equally affected), rather than in both eyes as recommended in the product labelling. The manufacturer recommends using the higher of these 2 measurements for clinical assessment.

Lastly, the studies by Sullivan et al. (2012), Lemp et al. (2011) and Tomlinson et al. (2010) were funded by the manufacturer and this introduces the potential for bias in the reporting of outcomes.

Relevance to NICE guidance programmes

The use of the TearLab osmolarity system is not currently planned into any NICE guidance programme.

The following NICE guidance is relevant to this briefing:

- [NICE's medtech innovation briefing on LipiFlow thermal pulsation treatment for dry eyes caused by blocked meibomian glands](#)
- [NICE's technology appraisal guidance on ciclosporin for treating dry eye disease that has not improve despite treatment with artificial tears](#)
- [NICE's clinical knowledge summary on dry eye syndrome.](#)

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Table 1 Overview of the Caffery et al. (2014) study

Study component	Description
Objectives/ hypotheses	To assess the correlation between tear osmolarity readings (captured with the TearLab osmolarity system) and symptoms of DED, and to determine how well these correlate with the self-assessment of DED.
Study design	Prospective, cross-sectional, single centre study. No follow-up period was reported.
Setting	USA, 3-day study (2012) at optometric conference.
Inclusion/ exclusion criteria	Inclusion criteria: none stated. Exclusion criterion: attendees who had worn contact lenses in the past 2 weeks.
Primary outcomes	The correlation between tear osmolarity and symptoms of DED.

Study component	Description
Statistical methods	<p>Statistical significance was assessed using $\alpha=0.05$ and two-sided hypothesis tests. Pearson correlations were used to assess the relationship between interval-scaled measurements such as age, DEQ-5 score, and osmolarity. Linear regression analyses were used to further characterise these relationships.</p> <p>Intraocular measurements of osmolarity were characterised using the mean difference and 95% limits of agreement. Independent group t tests were used to compare patient characteristics between those with and without self-reported dry eye and also between men and women.</p>
Patients included	Attendees at an optometric meeting: n=249 (140 men [49.8+14.1 years]; 109 women [39.7+12.7 years]).
Results	<p>There was no statistically significant difference between the DEQ-5 scores and average tear osmolarity (correlation coefficient 0.02) and highest osmolarity (correlation coefficient 0.03).</p> <p>The mean DEQ-5 score was significantly higher among people who self-reported dry eye compared with those who did not (11.3 versus 5.4; $p<0.0001$).</p> <p>No significant differences were seen between the 'yes' and 'no' self-reported dry eye groups and average osmolarity ($p=0.23$) and highest osmolarity ($p=0.14$).</p>
Conclusions	No statistically significant correlation was found between tear osmolarity and ocular symptoms as reported on the DEQ-5 or with tear osmolarity and a Gestalt self-assessment of dry eye.

Abbreviations: DED, dry eye disease; DEQ, dry eye questionnaire (DEQ-5 is the short form of the DEQ).

Table 2 Overview of the Jacobi et al. (2011) study

Study component	Description
Objectives/ hypotheses	To assess the differences in the osmolarity in tear samples of people with moderate to severe DED compared with healthy people as controls.
Study design	Prospective, non-randomised, single centre study. No recruitment period was provided. No follow-up period was reported.
Setting	Germany. No further details on the setting were given in the paper.
Inclusion/ exclusion criteria	<p>Inclusion criteria (DED):</p> <ul style="list-style-type: none"> • a TBUT <5 seconds • a Schirmer's test <5 mm • OSDI score >83. <p>Inclusion criteria (controls):</p> <ul style="list-style-type: none"> • asymptomatic • a TBUT >10 seconds • a Schirmer's test >15 mm.
Primary outcomes	The difference in the osmolarity in tear samples of people with moderate to severe DED compared with healthy people as controls.
Statistical methods	Nonparametric tests were used to compare the results between both groups (Mann–Whitney U test).
Patients included	<p>n=133 people with moderate to severe DED (58 years, 51–64 years; 86 women, 47 men).</p> <p>n=95 controls (52 years, 48–61 years; 55 women, 40 men).</p>

Study component	Description
Results	<p>People with moderate to severe DED showed a tear film osmolarity of 320 mOsm/litre (301–324 mOsm/litre).</p> <p>The results of the control group were 301 mOsm/litre (298–304 mOsm/litre).</p> <p>The results revealed a significantly higher tear film osmolarity in people with moderate to severe DED compared with the control group.</p> <p>The sensitivity was 87%, and the specificity was 81%.</p>
Conclusions	TearLab appears to be an effective objective diagnostic tool in the diagnosis of DED.

Abbreviations: DED, dry eye disease; mm, millimetres; mOsm, milliosmole (one-thousandth of an osmole); OSDI, Ocular Surface Disease Index; TBUT, tear film breakup time.

Table 3 Overview of the Messmer et al. (2010) study

Study component	Description
Objectives/ hypotheses	To evaluate the ability of TearLab to differentiate between people with and without dry eye.
Study design	Prospective cohort, single centre. No recruitment period was provided. No follow-up period was reported.
Setting	Germany. No further details on the setting were given in the paper.

Study component	Description
Inclusion/exclusion criteria	<p>When ≥ 3 of 6 dry eye signs were present, the patient was recruited into the DED group.</p> <p>DED signs for inclusion:</p> <ul style="list-style-type: none"> • an OSDI score >15 • any staining of the cornea or conjunctiva in the typical interpalpebral area • a TBUT <7 seconds • a Schirmer's test <7 mm in 5 minutes • blepharitis or meibomitis.
Primary outcomes	Measurement of tear film osmolarity with TearLab.
Statistical methods	Pearson and Spearman correlations, Wilcoxon and Mann–Whitney U tests.
Patients included	<p>129 people (DED): with 3–6 dry eye signs or symptoms (55 years, 19–86 years; 62.8% women).</p> <p>71 people (controls): with up to 2 signs or symptoms of DED (39 years, 16–83 years; 62.0% women).</p>
Results	<p>Tear film osmolarity did not show any correlation with the 6 clinical signs of DED.</p> <p>Osmolarity testing could not discriminate between patients with DED (308.9 ± 14.0 mOsm/litre) and the control group (307.1 ± 11.3 mOsm/litre).</p> <p>Osmolarity did not correlate with artificial tear use.</p> <p>Technical problems with the TearLab, reflex tear secretion, or the difficulty in establishing a DED diagnosis with the recommended tests may account for these results.</p>
Conclusions	Tear film osmolarity could not discriminate between people with DED and healthy people as controls.

Abbreviations: DED, dry eye disease; mOsm, milliosmole (one-thousandth of an osmole); OSDI, Ocular Surface Disease Index; TBUT, tear film breakup time.

Table 4 Overview of the Lemp et al. (2011) study

Study component	Description
Objectives/hypotheses	To assess the diagnostic performance of tear osmolarity (TearLab) compared with other commonly used tests (Schirmer's test, TBUT, staining and meibomian gland grading).
Study design	A prospective, observational, multicentre study. No recruitment period was provided. No follow-up period was reported.
Setting	10 sites in the EU and USA.

Study component	Description
Inclusion/exclusion criteria	<p>Inclusion:</p> <ul style="list-style-type: none"> • 18–82 years of age • general population. <p>Exclusion:</p> <ul style="list-style-type: none"> • active infection of the eye • active ocular allergy • lid deformity or abnormal lid movement disorder • refractive surgery within 1 year of the study visit • pregnancy or lactation • abnormal nasolacrimal drainage • punctal plug placement within 30 days of testing • systemic disease known to affect tear production • starting or changing the dose of chronic systemic medication known to affect tear production within 30 days of testing (such as antihistamines, antidepressants, diuretics, corticosteroids or immunomodulators) • known hypersensitivity to any of the agents used in testing (sodium fluorescein, lissamine green).
Primary outcomes	Sensitivity, specificity, area under the ROC.
Statistical methods	Optimal cut-off values for each test were determined assuming equal risk for false positive and false negative results. Gaussian distributions were generated based on the mean and standard deviation of normal and dry eye disease populations.

Study component	Description
Patients included	Patients from the general population: n=299 (46.3, 18–82 years; 218 women, 81 men).
Results	<p>Tear osmolarity had a 72.8% sensitivity and 92.0% specificity at a cut-off value of 312 mOsm/litre.</p> <p>No other clinical sign showed more than 62% performance in both categories. Corneal staining, conjunctival staining, and meibomian gland grading lacked sensitivity (54.0%, 60.3%, and 61.2% respectively), whereas TBUT and Schirmer's test results lacked specificity (45.3% and 50.7% respectively).</p> <p>Tear osmolarity also had the highest area under the ROC curve (0.89) followed by conjunctival staining (0.83), TBUT (0.81), meibomian gland grading (0.78), corneal staining (0.77), and Schirmer's test (0.71).</p> <p>Inter-eye differences in osmolarity correlated with increasing disease severity ($r^2=0.32$; $p=0.0001$).</p>
Conclusions	Tear osmolarity was the best single objective metric to both diagnose and classify DED. A cut-off threshold of more than 308 mOsm/litre was most sensitive in differentiating normal from mild to moderate DED.

Abbreviations: DED, dry eye disease; OSDI, Ocular Surface Disease Index; ROC, receiver operating characteristic; TBUT, tear breakup time.

Table 5 Overview of the Sullivan et al. (2012) study

Study component	Description
Objectives/hypotheses	To compare the variability of tear osmolarity over a 3-month period with that of other commonly used biomarkers used for diagnosing DED and to determine their reproducibility when measuring response to treatment.
Study design	Prospective, longitudinal, observational case series study with an additional treatment arm. No recruitment period was provided. No follow-up period was reported.
Setting	2 study centres (Spain, Turkey).

Study component	Description
Inclusion/ exclusion criteria	<p>Inclusion:</p> <ul style="list-style-type: none"> • age >17 years • ocular examination showing DED within the 2 years before the study. <p>Exclusion:</p> <ul style="list-style-type: none"> • eyelid deformity or movement disorder, active ocular infection or allergy • laser in situ keratomileusis or photorefractive keratectomy surgery within 1 year of visit 1 or during the study • systemic disease known to affect ocular health • systemic or topical medications that may have affected ocular health • use of artificial tears within 2 hours before their scheduled study visit • known sensitivity to any of the agents used in the testing procedures • if any of the following criteria applied within 30 days of each visit: <ul style="list-style-type: none"> • change in chronic ocular medication • change in systemic medication known to affect ocular health • pregnancy or lactation during the study • punctal plug placement or cauterisation within 30 days of visit 1 or during the study • use of ocular ciclosporin before visit 1, 2, or 3.
Primary outcomes	Variability of tear osmolarity over a 3-month period.

Study component	Description
Statistical methods	The range and standard deviation of each test were reported to compare the variability of the commonly used signs and symptoms of DED. For direct comparison of disease markers, results were expressed as percentages of the total dynamic range of each test. Once normalised, comparisons between the variability of osmolarity and other objective tests were done using the Mann–Whitney nonparametric rank comparison test, and differences were considered significant at $p < 0.05$, with a 95% confidence interval.
Patients included	52 patients completed the study ($n=16$ mild or moderate DED; $n=36$ severe DED; age 47.1 ± 16.1 years).
Results	<p>Tear osmolarity ($8.7 \pm 6.3\%$) had significantly less variability over a 3-month period than corneal staining ($12.2 \pm 8.8\%$; range $p=0.029$; variability $p=0.040$), conjunctival staining ($14.8 \pm 8.9\%$; range $p=0.0035$; variability $p=0.002$), and meibomian grading ($14.3 \pm 8.8\%$; range $p=0.0001$; variability $p < 0.0001$) across the entire patient population. Osmolarity also showed less variation than TBUT ($11.7 \pm 9.0\%$; $p=0.059$), Schirmer's tests ($10.7 \pm 9.2\%$; $p=0.67$), and OSDI ($9.3 \pm 7.8\%$; $p=0.94$), although the differences were not significant.</p> <p>Variation in osmolarity was less for mild dry eye patients ($5.9 \pm 3.1\%$) than severe dry eye patients ($10.0 \pm 6.9\%$; $p=0.038$).</p> <p>After treatment, average osmolarity and variability were lowered from 341 ± 18 mOsm/litre to 307 ± 8 mOsm/litre ($n=10$; $p < 0.0001$).</p> <p>A downward trend in symptoms followed changes in osmolarity, declining from 44 ± 17 mOsm/litre to 38 ± 18 mOsm/litre ($p=0.35$). None of the other signs changed after treatment.</p>
Conclusions	Over a 3-month period, tear film osmolarity had the lowest variability among commonly used signs of dry eye disease. Osmolarity dropped before changes in symptoms during therapy.

Abbreviations: DED, dry eye disease; mOsm, milliosmole (one-thousandth of an osmole); OSDI, Ocular Surface Disease Index; TBUT, tear breakup time.

Table 6 Overview of the Tomlinson et al. (2010) study

Study component	Description
Objectives/ hypotheses	To compare TearLab with the Clifton osmometer (Clifton Technical Physics, USA).
Study design	Prospective, single centre, single visit comparative study. No follow-up period was reported.
Setting	The setting was not described.
Inclusion/ exclusion criteria	<p>Inclusion (DED):</p> <ul style="list-style-type: none"> • noninvasive TBUT <10 seconds using the HirCal grid10 • ≥ 2 positive symptoms using McMonnies questionnaire • Schirmer's test score of ≤ 8 mm in 5 minutes. <p>Inclusion (controls):</p> <ul style="list-style-type: none"> • asymptomatic • Schirmer's test score of ≥ 15 mm in 5 minutes • TBUT of >10 seconds.
Primary outcomes	To compare the OcuSense TearLab osmometer with the Clifton osmometer to determine the comparability of results between the instruments and the diagnostic efficacy of each test for dry eye.
Statistical methods	All data were tested for normality using a Shapiro–Wilk test. A 2-sampled t test was applied to the data. Bland–Altman analysis was used to assess the level of agreement between the results with the OcuSense TearLab osmometer and Clifton osmometers.
Patients included	Mild to moderate DED: n=15 (41.7+16.9 years; 9 women, 6 men). Controls: n=21 (35.0+12.8 years; 12 women, 9 men).

Study component	Description
Results	<p>Osmolarity values measured with TearLab were 308+6 and 321+16 mOsm/litre for controls and dry eye, respectively, and those measured with Clifton were 310+7 and 323+14 mOsm/litre for controls and dry eye, respectively; these values between patients and controls were significantly different.</p> <p>Significant correlation was found between TearLab and Clifton measurements ($r=0.904$; $p=0.006$).</p> <p>Bland–Altman analysis showed agreement between techniques; most points were within the 95% confidence limits, and actual values differed by less than 1%.</p> <p>A cut-off value of <316 mOsm/litre, taken from the distribution of osmolarity values, was used to diagnose DED with an effectiveness of 73% sensitivity, 90% specificity, and 85% positive predictive value for the TearLab test and 73% sensitivity, 71% specificity, and 65% positive predictive value for the Clifton device in the study samples.</p>
Conclusions	TearLab is a suitable alternative test for diagnosing DED and has the potential to become the gold standard.

Abbreviations: DED, dry eye disease; mOsm, milliosmole (one-thousandth of an osmole); TBUT, tear film breakup time.

Search strategy and evidence selection

Search strategy

For the clinical evidence

Embase 1980 to 2015 Week 11, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present; searched 10 March 2015.

1. tearlab.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, an, ui]

2. osmometer.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, an, ui]
3. osmolarity.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, an, ui]
4. Osmolarity testing.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, an, ui]
5. meibomian gland dysfunction.mp. or Dry Eye Syndromes/
6. dry eye disease.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, an, ui]
7. Evaporative dry eye.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, an, ui]
8. dry eye disease severity.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, an, ui]
9. 1 or 2 or 3 or 4
10. 5 or 6 or 7 or 8
11. 9 and 10
12. limit 11 to english language
13. limit 12 to yr="2005 - Current"

For the health economics evidence

Embase 1974 to 2015 July 02, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present; searched on 03 July 2015

1. tearlab.mp.
2. osmometer.mp.
3. osmolarity.mp.
4. Osmolarity testing.mp.

5. 1 or 2 or 3 or 4

6. meibomian gland dysfunction.mp. or Dry Eye Syndromes/

7. Dry Eye Disease.mp.

8. Evaporative Dry Eye.mp.

9. dry eye disease severity.mp.

10. 6 or 7 or 8 or 9

11. cost\$.mp.

12. economic\$.mp.

13. 11 or 12

14. 5 and 10 and 13

15. limit 14 to english language

16. limit 15 to yr="2005 - Current"

Cochrane Database of Systematic Reviews: Issue 7 of 12, July 2015

Cochrane Central Register of Controlled Trials: Issue 6 of 12, June 2015

Database of Abstracts of Reviews of Effect: Issue 2 of 4, April 2015

Health Technology Assessment Database: Issue 2 of 4, April 2015

NHS Economic Evaluation Database: Issue 2 of 4, April 2015

#1 Tearlab

#2 Osmolarity testing

#3 #1 or #2

#4 Meibomian gland dysfunction

#5 Dry Eye Syndromes

#6 Dry Eye Disease

#7 #4 or #5 or #6

#8 cost\$

#9 economic\$

#10 #8 or #9

#11 #3 and #7 and #10

Evidence selection

For the clinical evidence

- Total number of publications reviewed: 38
- Total number of publications considered relevant: 17
- Total number of publications selected for inclusion in this briefing: 6.

For the health economics evidence

- Total abstracts: 6
- Duplicates: 0
- Abstracts reviewed: 6
- Full papers reviewed: 0.

Exclusion criteria: case studies, editorials, letters, reviews, conference proceedings/

abstracts, animal studies, non-English language studies, not using the Tearlab system.

Studies for review: 0

ISBN: 978-1-4731-1584-2