dry eye populations.
- Useful for group level comparisons of vision-targeted health related QoL.
- Can be useful for multiple eye conditions.

i. Dry Eye Questionnaire (DEQ) and Contact Lens DEQ
- 21 items: includes contact lens wear, age, sex.
- Categorical scales of prevalence, frequency, diurnal severity and intrusiveness of symptoms in typical day of one week recall period.
- Frequency and intensity of symptoms: comfort, dryness, blurry vision, soreness and irritation, grittiness and scratchiness, burning and stinging, foreign body sensation, light sensitivity, itching.
  Never, infrequent, frequent, constantly
  Time of day worsening
  Effect on activities of daily living
- Medications, allergies, dry mouth, nose or vagina, treatments, patient global assessment, dry eye diagnosis.

j. Melbourne, Australia, Visual Impairment Project Questionnaire

Symptoms of discomfort, dryness, foreign body sensation, itching, tearing and photophobia were graded on a scale from 0 to 3 (0 = no history, 1 = mild, 2 = moderate, 3 = severe). For each symptom, a definition was supplied for mild, moderate and severe.

2. Summary

The Subcommittee agreed on several characteristics of a dry eye questionnaire that contribute to its suitability for use in epidemiologic studies and RCTs. The instrument must be responsive, ie, able to detect and measure a change in symptoms with effective treatment or disease progression. It should be sufficiently sensitive to detect therapeutic response by a drug. It must be reproducible; the changes detected must be real and not due to poor repeatability. The recall period should be specified, as symptoms over time are commonly integrated by patients. For example, "how do your eyes feel now?" vs "on average, over the past week, how have your eyes felt?" Other important points included the ability to set a threshold of severity of disease as an inclusion criterion (ceiling and floor effects). One may elect to use a particular instrument as a screening tool for the study qualification visit and a different questionnaire to perform at baseline and the primary outcome study visit. Specific items within the instrument may be more appropriate for screening, whereas others may be responsive to treatment effects and more relevant for efficacy analysis. Because of the possibility of worsening of dry eye symptoms over the course of the day, dry eye examinations and the questionnaire should be administered at the same time of day in clinical trials.

Vision-targeted health-related quality of life instruments quantify an aspect of dry eye disease that is not measured in other ways. Both generic and disease-specific instruments are available; utility assessment is an alternative strategy. The group recommended inclusion of an item on visual function in the definition of dry eye—for example, fluctuating vision or transient blurred vision—to capture visual effect from dryness and assist in defining a clinically meaningful situation. This is another manifestation of dry eye distinct from "irritative" symptoms.

3. Future Research

Clinically meaningful changes in questionnaire scores need to be defined. If a particular symptom is improved, does the ability to perform common activities of daily living or visual function improve as well?

The concept of the "worst" symptom, which might be defined as the most intense, the most frequent, or the most bothersome symptom, warrants further study.

The relationship between frequency and severity of dry eye symptoms must be better understood to identify a clinically meaningful change in dry eye symptoms. How does a constant but low-intensity irritative symptom compare to a periodic, severe, highly intense but infrequent pain? Although frequency and intensity of symptoms are highly correlated, frequency is relevant to RCTs, because it would be difficult to demonstrate a change in an infrequent but severe symptom.

Psychometric analysis of existing questionnaire data from interventional clinical trials or epidemiologic studies may be useful in identifying specific parameters, questions, or subscales that might be more responsive or more appropriate to demonstrate therapeutic effects from different types of treatment modalities or for dry eye of a particular type or severity. Patient satisfaction with ocular health, therapy, and impression of improvement or worsening with treatment could be explored for use in clinical research

Although important progress has been made since the 1994/1995 Dry Eye Workshop about the available evidence on the epidemiology of dry eye, there is still a need for widely accepted diagnostic criteria of dry eye for epidemiological studies and a need to conduct such studies in different geographical populations and in different races and ethnicities. We still need to clarify the role of individual dry eye questionnaires and vision-targeted and general QoL assessment tools. While certain risk factors, such as age, sex, dietary factors, refractive surgery, and others, have been related to ocular morbidity in dry eyes, the impact of other factors such as cigarette smoking, alcohol, menopause, oral contraceptives, and pregnancy, still remain unclear and will need further prospective research.

III. CONCLUSIONS

There remains a need to build consensus on appropriate dry eye diagnostic criteria for epidemiologic studies. The role of subjective assessment and vision-targeted and general QoL assessments can be clarified. More incidence studies are needed, and epidemiologic studies should be expanded to include additional geographic regions and multiple races and ethnicities. Some modifiable risk factors have been identified for dry eye, and public education resulting this regard should lead to improvement in both

eye and general health, while further, prospective study is needed to elucidate other risk factors.

Detailed templates of questionnaires can be accessed at: www.tearfilm (EDITOR: INSERT COMPLETE INFO)

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Methodologies to Diagnose and Monitor Dry Eye Disease:
Report of the Diagnostic Methodology Subcommittee of the International Dry Eye WorkShop (2007)

ABSTRACT **The role of the Diagnostic Methodology Subcommittee of the Dry Eye Workshop was 1) to identify tests used to screen, diagnose and monitor dry eye disease, 2) to establish criteria for test performance, and, 3) to consider the utility of tests in a variety of clinical settings. The committee created a database of tests used to diagnose and monitor dry eye, each compiled by an expert in the field (rapporteur) and presented within a standard template. Development of the templates involved an iterative process between the Chairman of the subcommittee, the rapporteurs, and an additional group of expert reviewers. This process is ongoing. Each rapporteur was instructed on how to the complete a template, using a proforma template and an example of a completed template. Rapporteurs used the literature and other available sources as the basis for constructing their assigned template. The Chairman of the subcommittee modified the template to produce a standardized version and reviewed it with the rapporteur. The completed database will be searchable by an alphabetical list of test names, as well as by functional groupings, for instance, tests of aqueous dynamics, lipid functions, etc. The templates can be accessed on the website of the Tear Film and Ocular Surface Society (TFOS-http://www.tearfilm.org/ (EDITOR: INSERT WEB ACCESS INFO) This report provides a general overview of the criteria applied in the development of tests for screening and diagnosis.**

KEY WORDS **diagnosis, dry eye, Dry Eye WorkShop, methodology for appraising dry eye tests, questionnaires, tests for dry eye, screening, Sjogren syndrome**

I. INTRODUCTION

The Diagnostic Methodology Subcommittee set out to create a detailed register of diagnostic tests used to diagnose and monitor dry eye. The aim was to perform a thorough review of the literature and other available sources, to summarize findings in a standardized fashion, and to provide the research community with a searchable database of tests, including an assessment of their diagnostic efficacy. The committee considered the feasibility and operational use of tests and questionnaires in a variety of settings, including general eye clinics, dry eye specialty clinics, clinical trials in dry eye, and non-trial clinical research in dry eye. The committee also sought to identify areas in which new tests are needed, and to provide advice on how these might be brought to clinical use.

The attempt to meet these goals has been challenged by the longstanding lack of a uniform set of criteria for the diagnosis of dry eye, for which there has been no generally agreed "gold standard." Studies of test efficacy and/or performance are influenced by the fact that subjects have often been selected based on the same tests that are under scrutiny. Similarly, the performance of any "new" test may be compromised when the test is assessed in a population of dry eye patients who have been diagnosed using unestablished criteria.

An additional challenge relates to the variety of settings in which diagnostic tests are being used. For example, tests may be applied in everyday clinical practice, or to assess eligibility in a clinical trial. Furthermore, tests may be used to follow the natural history of the disorder or to quantify clinical changes over the duration of a clinical trial (ie, in monitoring). Tests that are useful in one setting might differ from those employed in others.

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Proprietary interests of Subcommittee members are disclosed on pages (**EDITOR; INSERT PAGE NUMBERS**)

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  C. Emerging technologies
IX. Summary of recommendations
  A. Diagnosis of dry eye disease
  B. Monitoring dry eye disease
X. Summary and conclusions

II. GOALS OF THE DIAGNOSTIC METHODOLOGY SUBCOMMITTEE

The goals of the Diagnostic Methodology Subcommittee were to identify tests used to screen, diagnose, and monitor dry eye disease, and to establish criteria of test performance (test efficacy) and to consider their practical use in a clinical setting (Table 1).

To achieve these goals, the committee created a database of tests used in the diagnosis and monitoring of dry eye, each compiled by an expert in the field (rapporteur) and presented within a standard template. An alphabetical list of these tests can be found in Appendix 1, and Appendix 2 re-presents them in functional groupings, for instance, tests of aqueous dynamics, tests of lipid functions, etc.

III. DEVELOPMENT OF THE TEMPLATES

Templates were developed by an iterative process between the Chairman of the subcommittee and the rapporteurs. Each rapporteur was sent a set of instructions on how to complete a template, together a proforma template (Appendix 3) and an example of a completed template. Rapporteurs sent their completed templates to the Chairman of the subcommittee, who saved the original version and then modified it to correct any idiosyncrasies and produce a standardized version. A few tests have been covered by more than one rapporteur. The templates were

Table 1. Goals and objectives of the Diagnostic Subcommittee

To create a register of diagnostic tests used in dry eye diagnosis with the following characteristics:
- *A searchable register of referenced tests*
- *Variable sorting, eg,*
  - Alphabetical by test name
  - By organ system tested
    - Aqueous dynamics
    - Tear stability
    - Tear composition
    - Meibomian gland function etc.
  - By utility, eg,
    - Diagnostic classification criteria
    - Clinical trials
      - Recruitment—entry criteria
      - Outcome measures
      - Monitoring specific drug actions, eg, anti-inflammatories; secretagogues
  - Natural history
- *Identification of evidence level*
  - [this will be a second phase of development]
  - —validation/precison and accuracy of tests
  - —system used: eg, BMJ, etc

To consider the operational use of tests in different clinical environments
- *In general clinics*
  - What tests are feasible?
  - What questionnaires can be made available?
- *In dry eye clinics*
  - What tests are feasible?
  - What questionnaires can be made available?
- *In clinical trials*
  - Selection of tests
  - Order of tests
- *In non-trial Clinical Research*

Manuals of operation for individual tests
- Consider for selected, key tests
- Interface with industry

Future prospects
- What new tests are needed?
- How can they be brought to the general clinic?

To consider publication aspects: presentation on the DEWS web site
- Introductory narrative about epidemiological methods pertaining to the validation of tests
- Legal aspects and disclaimers
- Gated access?
- Facilitate for video display (eg, to demonstrate standard conduct of the test)
- Updating policy and procedure
- Maintenance of the web site—long-term goals and feasibility

Possible independent publication

then reformatted to remove redundant material or to add new sections, which are incorporated into the listing provided in Appendix 1. To facilitate searches, template files are titled by the test they describe. The table of functional groupings will enable investigators to identify a battery of tests that explores the influence of dry eye on a number of physiological indices (Appendix 2).

The full complement of templates can be accessed on the website of the Tear Film and Ocular Surface Society **(EDITOR: INSERT COMPLETE ACCESS INFORMATION)**. It is expected that modifications will be made to these templates from time to time as new information becomes available.

Template headings (some of which are not currrently supplied with data) include the following:

1) The name of the original rapporteur;
2) The names of additional reviewers, where available, who have reviewed the templates;
3) The name of the test;
4) The purpose of the test;
5) The version of the test;
6) A short description of the test;
7) Details of studies conducted using the test, if relevant;
8) Details of the conduct of the test;
9) A statement of study results, if relevant;
10) A statement as to whether a web video is available, if relevant;
11) A list of the materials required for the performance of the test;
12) Variations of technique, if applicable;
13) Standardization—an indication of factors that could influence the test result, which, if standardized, could improve the efficacy of the test (eg, time of day, humidity, temperature, air flow, level of illumination, aspects of patient instruction, etc.).

The next sections relate to the performance of the test:

14) "Diagnostic value of the test" in practice, used, for instance, in conjunction with other tests;
15) Repeatability of the test;
16) Sensitivity of the test using a given cut-off value;
17) Specificity of the test using the same cut-off value (100—the false positive rate);
18) Other statistical information, if available.

Next, follows:

19) A box headed "Level of Evidence" for future use. Currently, this box is unused on all templates, since, at the time of writing, evidence criteria for the classification of tests, equivalent to those applicable to clinical trials, are not available.

The final section asked the rapporteur to identify:

20) Test problems encountered;
21) Any proposed solutions;
22) The "forward look" section, inviting suggested improvements; and
23) A final box providing a glossary of terms.

The section headed "web video" indicates whether a video-clip is available via a web link; this section is currently under development. The intention is to illustrate use of the test in field conditions in order to assist potential researchers. In the longer term, it is also intended to add links to other materials, such as schemas for protocols, Clinical Record Forms, and manuals of operation for given tests. It is hoped that Industry will consider this to be an opportunity to release nonsensitive, nonproprietary material for incorporation into the program.

IV. DEFINITION OF DRY EYE DISEASE

It was important for the Diagnostic Methodology Subcommittee to have a clear idea about the definition and classification of dry eye in order to put the tests presented into their proper context. As reported elsewhere in this supplement, the Definition and Classification committee has defined dry eye disease as follows:

> *Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability, with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.*[1]

Currently, ocular symptoms are included internationally within all definitions of dry eye, although it is acknowledged that asymptomatic patients exist who exhibit some of the objective features of dry eye and may be entitled to the diagnosis. The Japanese criteria were an exception to this,[2] but these criteria were revised in 2005 and are summarized in Appendix 4.

The issue of symptomatology in the diagnosis of dry eye is important, as one approach to the diagnosis of dry eye is based solely on the use of validated symptom questionnaires, whose administration, both in population studies and in the clinic, offer a highly accessible diagnostic instrument available to the comprehensive ophthalmologist and to the dry eye specialist alike.

V. CLASSIFICATION OF DRY EYE DISEASE

For its assignment, the Diagnostic Methodology Subcommittee regarded dry eye as a chronic, symptomatic ocular surface disease, which may, however, occasionally be asymptomatic. Asymptomatic dry eye implies that in the absence of symptoms, some objective criteria of dry eye may still be satisfied, such as tear hyperosmolarity, the presence of interpalpebral ocular surface staining, reduced tear production, or tear instability. The presence of symptoms may not always be clearcut, particularly when they develop insidiously. A patient may accept the development of irritative or visual symptoms as a matter of course (eg, as a normal part of aging), so that of the symptoms are revealed only when a suitably structured questionnaire is applied.

Symptomatic ocular surface disease, (**SOSD**), is an umbrella term that includes:

1) Classical, *symptomatic dry eye*, as defined above, ie, patients experiencing the symptoms of dry eye and also exhibiting objective features of dry eye, however determined. In the current classification, this would include

both *aqueous-deficient dry eye* (**ADDE**) and *evaporative dry eye* (**EDE**), as previously described[3]:

2) *Symptomatic lid disease*, including meibomian gland dysfunction (**MGD**) and anterior blepharitis, in the absence of dry eye;

3) *Symptomatic conjunctivitis and keratitis* (eg, allergic conjunctivitis, infective and noninfective keratitis and conjunctivitis) in the absence of dry eye.

The term *symptomatic ocular surface disease* has features in common with the term *dysfunctional tear syndrome* (**DTS**), a term coined by the Delphi group,[4] except that the term DTS was introduced as a *replacement* for the term dry eye, whereas, as discussed here, dry eye is seen as one component of SOSD. Any conceived form of SOSD can be expected to have its asymptomatic counterpart.

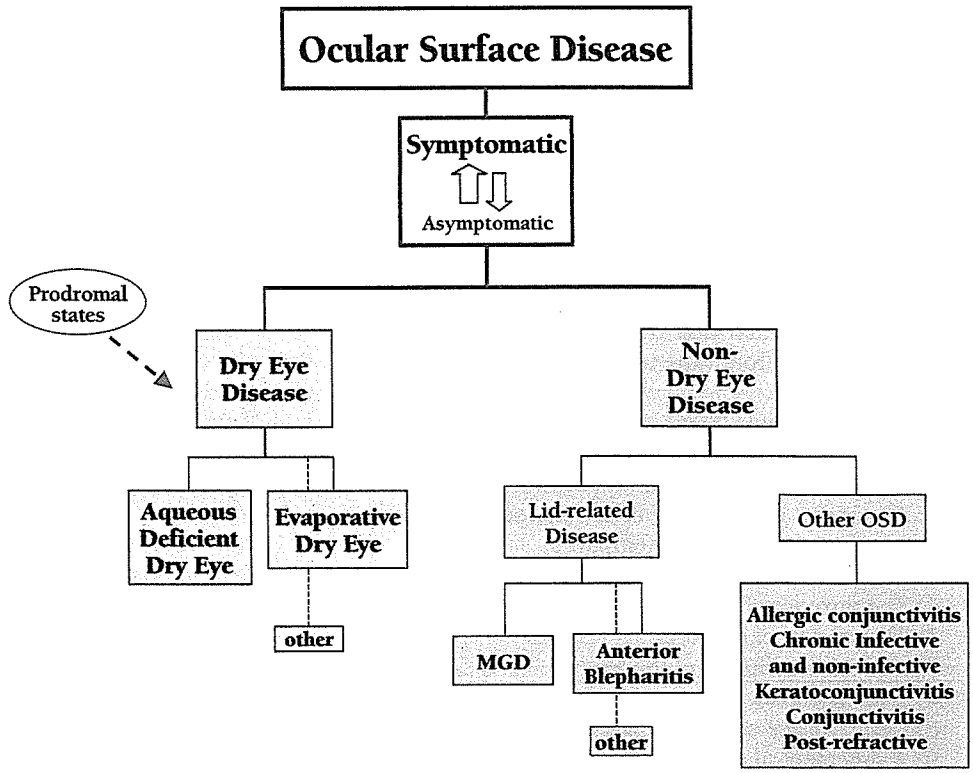

Figure 1. Schematic illustration of the relationship between dry eye and other forms of ocular surface disease. Ocular surface disease is either symptomatic or asymptomatic, but its various subgroups may coexist and interact. Therefore, a patient may suffer from both aqueous deficient and evaporative forms of dry eye, which will consequently be more severe than in the isolated disease. Also, dry eye may coexist with non-dry eye disease. (See text for further details; see also Chapter 1: Definition and Classification.[1]) OSD = Ocular surface disease; MGD = Meibomian gland dysfunction.

Dry eye is usually a symptomatic disorder that varies in severity and must be differentiated from other forms of SOSD. Severity ranges from a mildly irritative disorder of essentially nuisance value to the patient to a severely disabling disorder (eg, in Sjogren syndrome).[1] Although dry eye in its milder forms may respond to treatments that alleviate symptoms without modifying the disease process, recent pharmacological approaches are directed toward slowing, halting, or even reversing the disease process. Tests are therefore required that will discriminate between dry eye and its various subsets, identify precipitating factors, quantify disease severity, and demonstrate the effect of disease on a patients' quality of life.

It is also necessary to distinguish dry eye from other SOSD. Any classification scheme should address the differential diagnosis of dry eye, such as MGD occurring on its own and disorders such as allergic eye disease, chronic non-dry eye conjunctivitis, and infective conjunctivitis and keratoconjunctivitis. Meibomian gland dysfunction and these other conditions may cause or contribute to dry eye, but exist in their own right as either symptomatic or asymptomatic disorders.

Other individuals should be recognized who are "at risk" of developing dry eye but show no evidence of disease. They are related to, but fall outside, the SOSD group, as they show no objective signs of any ocular surface damage that might constitute disease. An example would be those refractive surgery patients with reduced tear stability (eg, as assessed by the tear stability analysis system [**TSAS**]), who have greater risk of post-LASIK symptomatic keratitis and have a slower recovery time than those without a preoperative tear film instability.[5] Environmental factors may also contribute to risk.[1]

A general classification of ocular surface disease, including dry eye, is illustrated in Figure 1.

VI. TESTS USED TO DIAGNOSE AND MONITOR DRY EYE DISEASE

A. Uses of Tests

Tests are used for a variety of purposes:

1) To diagnose dry eye in everyday clinical practice.
2) To assess eligibility in a clinical trial (ie, recruitment). Such tests used in recruitment, may also be used as primary, secondary, or tertiary end points in a trial.
3) To follow quantitative changes over the duration of a clinical trial (monitoring). These tests might differ from those employed in recruitment. For instance, they might simply monitor the pharmacological action of a drug under study, eg, stimulation of mucin production.

4) To characterize dry eye as part of a clinical syndrome, eg, as in the harmonized classification criteria of Sjogren syndrome[6] (See Section VIII, Table 6).
5) To follow the natural history of the disorder. This opportunity is limited for dry eye, because treatment is so common in the population. However, the natural history of treated patients is also of interest, although they represent a heterogeneous population.

B. Shortcomings of Tests for Dry Eye

1. Selection Bias

No "gold standard" exists for the diagnosis of dry eye. Thus, when a test, eg, Schirmer test or rose bengal staining, is being evaluated for efficacy, the test population may have been classified as affected or non-affected based on those same tests. Similarly, the performance of any "new" test may be compromised when the test is assessed in a population of dry eye patients who have been diagnosed using unestablished criteria.

When studies of test efficacy look at how the test defines affected and unaffected individuals using individuals from the sample from which the diagnostic cut-offs were derived, this potentially results in a higher sensitivity and specificity rating than would have arisen from an independent sample. Also, because of the multi-factorial nature of dry eye, variable test efficacy is likely to occur from study to study.

2. Spectrum Bias

When the study sample consists of patients with either very mild or very severe disease, results are compromised because the severity of the disease in the sample studied has been highly selected.

Certain ground rules are proposed for appraising the performance of tests for dry eye diagnosis reported in the literature (Table 2).

1) Accept efficacy values on samples from which the test cut-off was derived (as is the case in most reports).
2) Exclude data from studies with selection bias due to the test being part of the original dry eye diagnostic criteria (to avoid study results with high, ie, false, sensitivity and specificity values).
3) To avoid spectrum bias, study samples should be large enough to include a range of dry eye patients with various etiologies.
4) The choice of the cut-off value for diagnosis and the test itself, unless there is some special physiological reason, should be based on a consideration of the relative consequences of having too many false-positives or too many false-negatives. Generally, in a screening test for a serious or life-threatening condition, it is desirable to have a test of high sensitivity (high detection rate)—with few false-negatives—since failure to detect the condition early can be fatal. In a mass screening test for a less serious condition or for one whose early detection is not critical, *it may be more desirable* to have a high specificity to avoid overburdening the health care delivery system with too many false-positives.
5) For dry eye screening tests, it is suggested that sensitivity and the predictive value of a positive test (**PPV**, see below) be maximized, ie, avoid high false-negative rates by "over-diagnosing" dry eye through choice of cut-off/test. This is appropriate when the patient is to be further assessed with other tests to finally diagnose dry eye. However, low false-negative rates (choice of test or cut-off maximize sensitivity) should be balanced by an acceptable PPV.
6) In diagnostic tests, optimize overall accuracy (**OA**) and combine this with a high sensitivity and PPV.
7) Simplify comparisons of screening and diagnostic tests by using single and simple terms for measuring test efficacy.

C. Appraisal of Tests Used for Screening

The purpose of screening is prevention, and it aims to identify people at high risk of a disorder. It is implicit in the screening process that a treatment is available that will reduce the morbidity of the disorder in a cost-effective manner. Screening has been defined, among persons who have not sought medical attention, as the "systematic application of a test or enquiry to identify individuals at sufficient risk of a...disorder to benefit from further investigation or...preventive action..."[26] It is implied that the disorder has serious consequences and that a remedy is available that could reduce morbidity.

Inclusion of symptoms within the definition of dry eye has an awkward implication in the context of screening. To identify those at risk of developing the disorder or who have unrecognized disease, screening is characteristically carried out on asymptomatic individuals who have not presented themselves for diagnosis; those who are symptomatic already have the disease. This "at-risk" group is likely to be represented by asymptomatic subjects whose pathophysiological background favors the development of dry eye. Perhaps, their lacrimal secretory level or their meibomian lipid secretion or delivery is at the lower limit of normal, so that with time they will pass into a state of insufficiency. They may have an unstable tear film, or they may be in the prodromal stages of a disease (eg, exhibiting nonophthalmic features of primary Sjogren syndrome), whose natural history dictates that they will eventually develop dry eyes. Members of this diverse group of subjects could be precipitated into dry eye by a number of biological, pharmacological or environmental events, ie, hormonal changes, drug exposure, high air or wind speeds, irritants, low humidity, and high temperatures. Exposure to such influences might engender dry eye symptoms in an at-risk group at a lower threshold than in subjects not at risk of dry eye.

At-risk subjects could be identified by "stress tests," some of which are included among the test templates that accompany this report (**EDITOR: PROVIDE TFOS ACCESS INFO**). Whether or not such tests could or should become part of a "screening program" depends on whether

Table 2. Characteristics and current tests for dry eye

Test	Reference	Cut-off Value	Sensitivity (%)	FPR (%)	Specificity (%)	PPV*
Single Tests						
Questionnaires	†McMonnies[7]	Any	98	3	97	85
PRT	†Patel[8]	≤10mm	86	17	83	47
Rose Bengal	†Goren[9]	Any	25	10	90	31
Schirmer I	†Lucca[10]	<5mm/5min	25	10	90	31
Schirmer I	†Farris[11]	<3mm/5min	10	0	100	100
Schirmer I	†Bijsterveld[12]	<5.5mm/5min	85	17	83	47
Schirmer I	†Vitali[13]	<10mm/5min	83	32	68	31
F BUT	†Vitali[13]	<10s	72	38	62	25
NIBUT	†Mengher[14]	<10s	83	15	85	49
TMS-BUT	**†Goto[15]**	**<5s**	**98**	**37**	**63**	**32**
Evaporation Rate	†Khanal[16]	33 g/m²/h	51	4	96	84
Meniscus Height	†Mainstone[17]	≤0.35mm	93	33	67	33
Meniscus Radius	**†Yokoi[18,19]**	**≤0.25mm**	**89**	**22**	**78**	**42**
Tear Film Index	†Xu[20]	≤95	67	40	60	23
Tear Turnover Rate	†Khanal[16]	12%/min	80	28	72	79
Osmolarity	†Farris[21]	>312 MOsm/L	95	6	94	73
Osmolarity	†Tomlinson[22]	>316 MOsm/L	69	8	92	60
Osmolarity	†Tomlinson[22]	>316 MOsm/L	59	6	94	63
Osmolarity	†Tomlinson[22]	>312 MOsm/L	66	16	84	42
Osmolarity	†Tomlinson[22]	>322 MOsm/L	48	1	99	89
Osmolarity	†Khanal[16]	**317** MOsm/L	78	22	78	86
Osmolarity	†Sullivan B[23§]	>318MOsm/L	94	5	95	77
Lysozyme assay	**†van Bijsterveld[12]**	**dia <21.5mm**	**99**	**1**	**99**	**95**
Fleming	†Norn[24]	Area <0.06mm²/µl	94	25	75	40
Lactoferrin	†Lucca[10]	<90	35	30	70	17
Combined Tests (Parallel)						
Sch + RB	†Farris[21]	Any/<1mm/min	77	51	49	21
Sch + BUT	†Farris[21]	<1mm/min/<105	78	44	56	24
Sch + BUT + RB	†Farris[21]	<1mm/min/<105/Any	80	51	49	22
TTR + Evap + Osmol	†Khanal[16]	<12%/>33/ >317	100	34	66	81
Combined Tests (Series)						
Sch + Osmol	**†Farris[21]**	**<1mm/min; >312**	**25**	**0**	**100**	**100**
Lacto + Osmol	**†Farris[21]**	**> 90; >312**	**35**	**0**	**100**	**100**
TTR + Evap + Osmol	†Khanal[16]	< 12%; >33; >317	38	0	100	100
Discriminant function						
Osmol + Evap + Lipid	†Craig[25]	< 0.4	96	13	87	56
TTR + Evap + Osmol	†Khanal[16]	> –0.4	93	12	88	58

The table shows the effectiveness of a range of tests, used singly or in combination, for the diagnosis of dry eye. The tests included in the table are those for which values of sensitivity and specificity are available in the literature. The predictive values of these tests (positive, negative and overall accuracy) are calculated for a 15% prevalence of dry eye in the study population. The data shown here is susceptible to bias; selection bias applies to those studies shown in dark shading, in these, the test measure was part of the original criteria defining the dry eye sample group and spectrum bias applied to those studies (shown in light shading) where the study population contained a large proportion of severe cases. Both of these forms of bias can lead to an artificially increased test sensitivity and specificity. In most of the studies listed above the efficacy of the test was shown for the data from the sample on which the cut off or referent value for diagnosis was derived (indicated by a †), again this can lead to increased sensitivity and specificity in diagnosis. Ideally test effectiveness should be obtained on an independent sample of patients, such data is shown in studies indicated by the symbol ‡.

Table 2 continues on following page

Table 2. Characteristics and current tests for dry eye *(continued)*

KEY to symbols and abbreviations used in Table 2.

*	Assumes a dry eye prevalence of 15% in the population studied.
†	Efficacy calculated in the sample from which the cutoffs were derived.
‡	Efficacy calculated in an independent sample of subjects.
§	Unpublished data

Definitions and Abbreviations

BUT	Tear break-up time
dia	Diameter of the disc observed with the radial-immuno-diffusion Lactoplate method
Evap	Tear film evaporation rate
F BUT	Fluorescein tear break-up time
FPR	False positive rate. The proportion of normals identified incorrectly as +ve by the test (Specificity is: 100-FPR)
Lacto	Lactoferrin assay using the Lactoplate method
NIBUT	Non-invasive tear break-up time
NPV	Predictive value of a negative test result
OA	Overall accuracy of test results
PPV	Positive Predictive Value: the probability of truly having dry eye among those with a positive test result
PRT	Phenol red thread test
RB	Rose Bengal staining
Selection bias	Bias built into an experiment by the method used to select the subjects who are to undergo treatment
Sensitivity	Detection rate: the proportion of patients with disease who have a positive test result
Specificity	Proportion of normal people with negative test result
Spectrum bias	Bias due to differences in the features of different populations eg, sex ratios, age, severity of disease, which influences the sensitivity and/or specificity of a test
TMS-BUT	Tear break-up time measured with the Topographic Modeling System[15]
TTR	Tear turnover rate, often measured with a scanning fluorophotometer (Fluorotron)

any perceived therapeutic benefits would be economically justified. One such benefit might be to identify the suitability of individuals to work within a particular work environment, or to answer questions about the modifications of environments to avoid inducing symptomatic disease.

To be of value, a screening test should be simple, effective, applicable to a definable population, and cost-effective. In an effective screening program, a positive test ultimately leads to diagnostic tests, which, if positive, lead to timely treatment. Where a series of tests is required to achieve a definitive diagnosis and initiate effective treatment, it is possible to assess the performance of the combination of tests. This may include a series of screening tests followed by one or more diagnostic tests, some of which may be performed simultaneously to save time.

The screening performance (efficacy) of a test can be estimated according to three parameters: 1) the *Detection Rate* (**DR**) or Sensitivity, 2) the *False-Positive Rate* (**FPR;** specificity is: 100-FPR), and 3) the ***O**dds of being **A**ffected in those with a **P**ositive test **R**esult* (**OAPR**). (This is the same as the PPV, if expressed as a probability.) Before a test is adopted, estimates of all three components should be available.

The relationship between affected and unaffected members of a population and the test result achieved can be represented in tabular form (Table 3).

The Detection Rate (DR) is the percentage of affected individuals who test positive. It is also referred to as the *sensitivity* of the test. The DR must be estimated using values from a continuous series of patients with the disorder, with no omissions.

$$DR = \frac{a}{a+c}$$

The False Positive Rate (FPR) is the percentage of unaffected individuals in a population who test positive. The FPR is usually estimated in a large series of apparently unaffected individuals.

Table 3. Relationship between affected and unaffected members of population and test result achieved

		Presence of Disease				
		Yes	No	Sum		Population
Diagnostic Test Result	Positive +	a	b	a+b	=	total testing positive
	Negative –	c	d	c+d	=	total testing negative
Totals		a+c = total truly affected	b+d = total truly unaffected	a+b+c+d	=	total population

$$FPR = \frac{b}{b+d}$$

The FPR, subtracted from 100, is also known as the *specificity* of the test.

The DR and FPR represent key characteristics of a test. Both are required for an assessment of its efficacy. The ideal test will have a high DR and a low FPR (ie, high specificity). The DRs and FPRs for a number of tests used in dry eye diagnosis are presented in Table 2.

The third parameter is dependent on the prevalence of the disorder in the population studied. This is *The **O**dds of being **A**ffected in those with a **P**ositive test **R**esult* (OAPR [or PPV]). This is expressed as an odds value, eg, 1:3 or 1:100, etc. It can also be expressed as a percent probability (which in these cases would be: 1/4 × 100 = 25%, or 1/101 × 100 = 0.99%).

$$OAPR = \frac{a}{a+b}$$

D. Appraisal of Tests Used for Diagnosis

Diagnostic tests are applied to symptomatic or asymptomatic patients to obtain a diagnosis and, by inference, to exclude other diagnoses. A successful diagnosis can serve several functions, paramount of which is the opportunity for therapy. Therapy can ameliorate the symptoms of a disease, retard its progression, or produce a cure. Arrival at a successful diagnosis may also serve other functions, for instance, in relation to the natural history and prognosis of a disease, knowledge of which is of value to both patient and doctor. Also, a diagnosis, by excluding other diseases, may usefully indicate that a feared diagnosis is not present and that other kinds of therapy are not indicated.

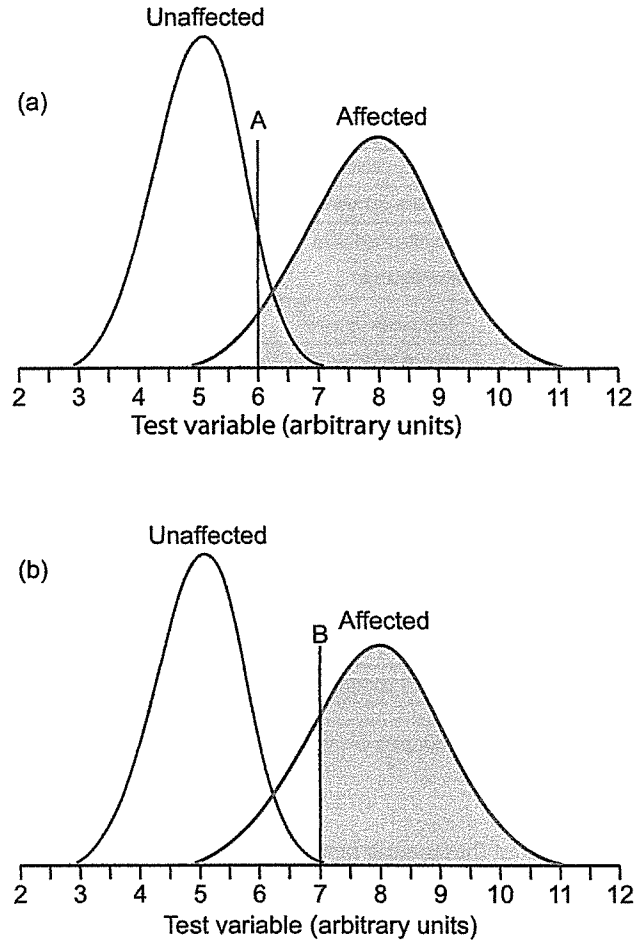

Figure 2. Illustrates how selection of the cutoff value influences the FPR and DR. See text for details.

1. Selecting a Cut-off Value

Test data may be qualitative (categorical, eg, with or without epiphora), semi-quantitative (ordinal, eg, grading by corneal staining), or quantitative (continuous, eg, the Schirmer test result in mm, intraocular pressure). For a test offering continuous data, it is appropriate to select a cut-off value to discriminate between affected and unaffected subjects. This may involve a trade-off between the DR and FPR, depending on the distribution of test values between these two groups. The DR and FPR are dependent on the selected cut-off values, and this is influenced by the overlap of values between affected and unaffected subjects. For instance, if there is no overlap in values between unaffected and affected subjects, then the cut-off will lie between the two data sets. However, where there is an overlap of values, which is usually the case, a cut-off must be chosen somewhere in the region of overlap.

The concept of choosing a cut-off is illustrated in the Figures 2a and 2b, which represent the situation in a hypothetical disorder in which the test variable is higher in the affected than in the unaffected population.[27] An example might be a staining score. When distributions are presented in this way, then the area to the right of the cut-off under the *unaffected* curve, provides the FPR, while the area to the right of the cut-off under the *affected* curve, gives the DR. Moving the cut-off to the right (as in Figure 2b) reduces the FPR but also reduces the DR.

2. The Likelihood Ratio

A useful way of expressing the interaction of DR and FPR is by calculating the *Likelihood Ratio* (**LR**), which is the ratio of those areas. The LR is a measure of the number of times individuals with positive results are more likely to have the disorder compared with individuals who have not been tested. A successful screening test might have an LR in the range of 5 to 25.

3. Calculating the OAPR

The OAPR is a valuable parameter that represents the average chance of being affected for all individuals with a positive result by the test. It expresses the odds of the number of *true positives* to the number of *false positives*. For a given population, the OAPRs of different tests for the same condition may be compared directly with one another. There are two ways to calculate the OAPR (examples taken from Wald[26] and Wald and Cuckle[27]).

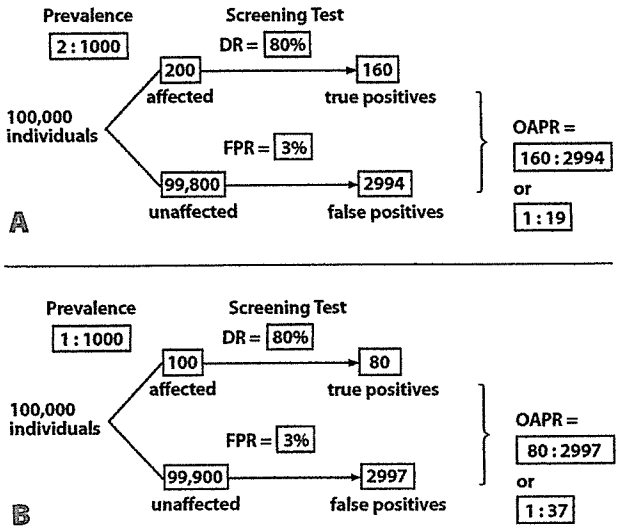

Figure 3. The influence of disease prevalence on the OAPR. See text for details.

The first method uses a flow chart to estimate test performance.

Considering the total number of individuals identified as positive by a test within a defined population, a proportion will be true positives (determined by the DR of the test), and the remainder will be the false positives (determined by the FPR). The OAPR is the ratio of these two numbers, ie, OAPR = True Positives: False Positives.

Note that OAPR is influenced by the prevalence of the condition in the population studied.

If the test has a DR of 80% and an FPR of 3% then there are 160 true positives (80/100 x 200), and 2994 false positives (3/100 x 99,800) in the population. The OAPR can then be calculated as follows:

$$\text{OAPR} = \frac{\text{Number of true positives} = 160}{\text{Number of false positives} = 2994} = 1{:}19$$

The equivalent PPV is 5% [ie, 1/1+19 = 1/20 = 5%] (Figure 3A).

With the same DR and FPR rates, but a prevalence of 1:1000, there are 100 affected and 99,900 unaffected.

In that case the test identifies 80 true positives and (3/100 x 99,900=) 2297 false positives, giving an OAPR that is twice that of the previous example:

$$\text{OAPR} = \frac{\text{Number of true positives} = 80}{\text{Number of false positives} = 2997} = 1{:}37$$

It can be seen that the OAPR falls as the prevalence falls (Figure 3B). The second method to calculate the OAPR uses the likelihood ratio. For a given population, the OAPR can be calculated by multiplying the LR by the prevalence of the disorder (expressed as an odds), ie, OAPR = LR x Prevalence as an odds [eg, 1:1000; 1:2000].

In the example given in Figure 4A, with a cut-off at 7, the DR is 80% and the FPR is 1%. In this case the LR is (80%/1%) = 80, and if the prevalence of the disorder is 1 per 1000 (ie, an odds of 1:999 or nearly the same as 1:1000), then:

$$\text{the OAPR} = 80 \times 1{:}1000 = 80{:}1000 = 1{:}1000 = 1{:}12.5$$

The two methods of calculating the OAPR are applicable to groups of subjects and are, therefore, of public health significance. However, it is also possible to calculate the OAPR for an *individual* with a particular positive result. This is illustrated in Figure 4B. In this situation, the LR for that individual is given by the height of *the affected population distribution curve* at the point of their test value, divided by the height of *the unaffected population distribution curve* at the same point. In the example given above, where the test value is 7 arbitrary units, the LR ratio is a/b = 12/1 = 12. Note that the vertical units are also arbitrary. Therefore, the OAPR for that individual is:

$$\text{OAPR} = \text{LR} \times \text{Prevalence as an odds [eg, 1:1000]}$$
$$= 12 \times 1{:}1000 = 12{:}1000 = 1{:}1000/12 = 1{:}83.$$

This individual has a relatively low risk of being affected.

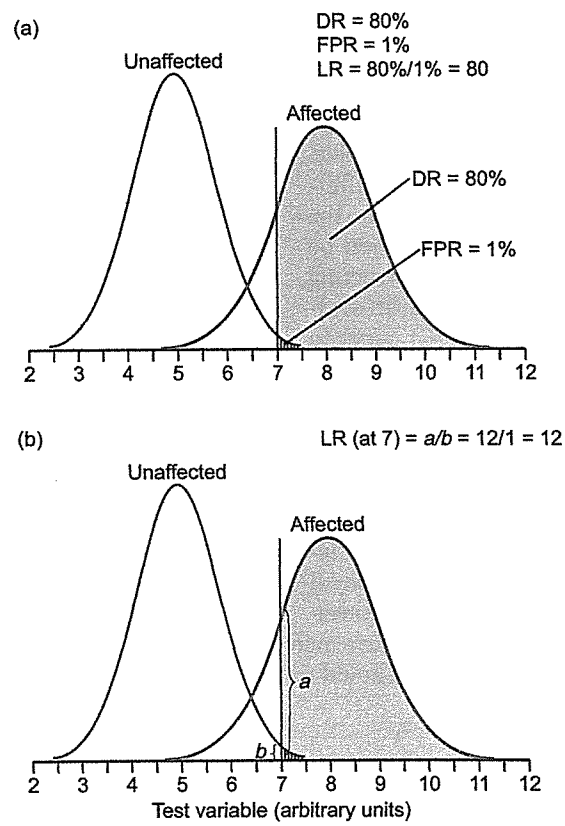

Figure 4. Calculation of the OAPR using the likelihood ratio. (a) For a group, (b) for an individual. See text for details.

VII. A PROTOCOL FOR EVALUATING DRY EYE DIAGNOSTIC TESTS

The following protocol is suggested as a model for evaluating diagnostic tests for dry eye. It is proposed that:

1) The diagnostic test will be applied to a study sample of normal subjects and patients with dry eyes, as defined by symptoms, and the "traditional" ophthalmological tests, Schirmer I, tear film breakup time (**TBUT**), and ocular surface staining.

2) The values obtained for the new diagnostic test in the two samples will be determined, frequency distributions of data will be compiled, and an initial cut-off value, distinguishing affected from non-affected, will be set at the intercept of the two frequency curves.

3) The sensitivity, specificity, and predictive values of a positive and negative test result and the overall accuracy of the test will be determined for this cut-off value.

4) A range of different cut-off values for the test statistic can then be analyzed by constructing a receiver-operator characteristic (**ROC**) curve to maximize the sensitivity and the specificity of the diagnostic test.

5) The proposed cut-off value thus determined for the test will then be assessed for its efficacy on a new, *independent sample* of normal and dry eye patients. An iterative process may then be required to arrive at a final cut-off value.

This approach should provide the best estimate of test performance.

Table 4A. A sequence of tests used in the clinic or in dry eye trials

Group	Assessment	Technique
A	Clinical history	Questionnaire
	Symptoms eg, dry eye	Symptom questionnaire
B	Evaporation rate	Evaporimetry
C	Tear stability	Non-invasive TFBUT (or NIBUT)
	Tear lipid film thickness	Interferometry
	Tear meniscus radius/volume	Meniscometry
D	Osmolality; proteins lysozyme; lactoferrin	Tear sampling
E	Tear stability	Fluorescein BUT
	Ocular surface damage	Grading staining fluorescein; lissamine green
	Meniscus, height, volume	Meniscus slit profile
	Tear secretion turnover	Fluorimetry
F	Casual lid margin oil level	Meibometry
G	Index of tear volume	Phenol red thread test
H	Tear secretion	Schirmer I with anesthesia
	Tear secretion	Schirmer I without anesthesia
	"Reflex" tear secretion	Schirmer II (with nasal stimulation)
I	Signs of MGD	Lid (meibomian gland morphology)
J	Meibomian gland function	MG expression Expressibility of secretions Volume Quality
	Meibomian physicochemistry	Oil chemistry
K	Ocular surface damage	Rose bengal stain
L	Meibomian tissue mass	Meibography

From: Foulks G, Bron AJ. A clinical description of meibomian gland dysfunction. *Ocul Surf* 2003: 107-26.
Test invasiveness increases from A to L. Intervals should be left between tests. Tests selected depend on facilities, feasibility and operational factors.

Table 4B. A practical sequence of tests

Clinical history
Symptom questionnaire
Fluorescein BUT
Ocular surface staining grading with fluorescein/yellow filter
Schirmer I test without anesthetic, or I with anesthetic, and/or Schirmer II with nasal stimulation
Lid and meibomian morphology
Meibomian expression
Other tests may be added according to availability

Further narrative information is provided in a template on the DEWS web site, entitled "A sequence of tests."
From Foulks G, Bron AJ. A clinical description of meibomian gland dysfunction. *Ocul Surf* 2003: 107-26.

VIII. RECOMMENDATIONS OF THE DIAGNOSTIC METHODOLOGY SUBCOMMITTEE: PREFERRED SCREENING AND DIAGNOSTIC TESTS FOR DRY EYE

The following recommendations are based on the commentary provided above and on the test data presented in Table 2. Readers are reminded that when a battery of tests is performed, these should be performed in the sequence that best preserves their integrity (Table 4). The tests discussed below are presented with this in mind.

A. Current Tests

For nearly half a century, a tetrad of diagnostic tests has been universally applied to assess symptoms, tear stability, ocular surface staining, and reflex tear flow.

1. Symptom Questionnaires

Over time, a number of symptom questionnaires have been developed for use in dry eye diagnosis, epidemiological studies, and randomized controlled trials (**RCTs**), which have received some psychometric or other validation and are available to practitioners for use in their clinics. The most important of these have been summarized elsewhere in this issue, where the necessity for reproducibility and the ability to measure severity and change ('responsiveness') have been emphasized.[28] According to their length and composition, such questionnaires explore different aspects of dry eye disease in varying depth, ranging from diagnosis alone, to the identification of precipitating factors and impact on quality of life. The time taken to administer a questionnaire may influence the choice of questionnaire for general clinical use, and, with this in mind, the number of questions administered in various questionnaires is listed in Table 5.

These questionnaires have been validated to differing extents, and they differ in the degree to which the dry eye symptoms assessed correlate with dry eye signs. For example such correlations were identified by the extensive Dry Eye Questionnaire (**DEQ**) of Begley et al,[34] but not by the questionnaire developed by Schein et al[30] or, to any great extent, in the study McCarty et al.[36]

Table 5. A protocol for evaluating dry eye diagnostic tests

Report	Questions administered	Reference
Womens' Health Study (WHS)	3	Schaumberg et al[29]
International Sjogren's Classification	3	Vitali et al[6]
Schein	6	Schein et al[30]
McMonnies	12	McMonnies and Ho[31]
OSDI	12	Schiffman et al[32]
CANDEES	13	Doughty et al[33]
Dry Eye Questionnaire (DEQ)	21	Begley et al[34]
IDEEL (3 modules, 6 scales)	57	Rajagopalan et al[35]

The Diagnostic Methodology Subcommittee concluded that the administration of a structured questionnaire to patients presenting to a clinic provides an excellent opportunity for screening patients with potential dry eye disease. Clinic time can be used most efficiently by utilizing trained auxiliary staff to administer the questionnaires. Selection of a specific questionnaire will depend on practical factors, such as available staffing, and also the intended use of the data collected, eg, whether it will be used for diagnosis alone, recruitment to a clinical trial, or as a guide to treatment.[1]

Symptomatology questionnaires should be used in combination with objective clinical measures of dry eye status, as illustrated below.

2. Grading Ocular Surface Staining

In clinical trials in some countries, it is current practice to grade staining of the cornea using fluorescein dye and to grade staining of the conjunctiva using lissamine green. This is done for reasons of visibility and is discussed in detail elsewhere.[37] It is, however, possible to detect and score staining on both the cornea and conjunctiva together, using fluorescein alone, if fluorescence is viewed through a yellow barrier filter (eg, Wratten 12).[38]

Three systems for quantifying staining of the ocular surface are in current use, the van Bijsterveld system,[12] the Oxford system,[37] and a standardized version of the NEI/Industry Workshop system,[3]—for instance, the version developed for the CLEK study and used in the assessment of clinical methods for diagnosing dry eye.[38] The Oxford and CLEK systems use a wider range of scores than the van Bijsterveld system, allowing for the detection of smaller steps of change in a clinical trial. The CLEK system, which assesses several zones of the cornea, has the advantage of scoring staining over the visual axis, providing the opportunity to relate surface changes to changes in visual function. No studies have been published that indicate that one grading system is innately better than another, but interconversion of the van Bijsterveld and Oxford scores has been estimated in an unpublished comparative study (J. Smith, personal communication).

Selection of a diagnostic cut-off for recruitment to a clinical trial is influenced by the need to identify a score that is sufficiently high to be able to demonstrate a response to treatment, but is sufficiently low to permit the recruitment of adequate numbers. Some workers have used a van Bijsterveld cut-off of ≥ 3 in recruiting dry eye patients for clinical studies. For dry eye diagnosis within the framework of Sjogren syndrome, a cut-off of ≥ 4 was derived by the American-European consensus group in a large multicenter study. [6]

3. Tear Film Stability—Tear Film Break-Up Time (TFBUT)

Details of test performance are given in the relevant templates, (**EDITOR: INSERT TFOS ACCESS INFO**) including the need for application of a standard volume of fluorescein and the use of a yellow barrier filter to enhance the visibility of the break-up of the fluorescent tear film. The established TFBUT cut-off for dry eye diagnosis has been < 10 seconds since the report of Lemp and Hamill in 1973.[39] More recently, values lying between ≤ 5 and < 10 seconds have been adopted by several authors, possibly based upon the 2002 report of Abelson et al,[40] which suggested that the diagnostic cut-off falls to < 5 seconds when small volumes of fluorescein are instilled in the conduct of the test (eg, using 5µl of 2.0% fluorescein in that study—many clinical trials adopt the practice of pipetting small, fixed volumes of dye). At present, sensitivity and specificity

data to support this choice have not been provided, and the population in that study has not yet been defined. Refinement of this kind of data would comprise a welcome addition to the literature. Selecting a cut off below < 10 seconds will tend to decrease the sensitivity of the test and increase its specificity.

4. Reflex Tear Flow—the Schirmer Test

The Schirmer test score (length of wetting after 5 minutes) is commonly treated as a continuous variable, but it is more properly termed a pseudocontinuous variable, as wetting length values are generally taken as the nearest integer or half integer rather than as continuous fractions of a millimeter.

The Schirmer test without anesthesia is a well-standardized test that is currently performed with the patient's eyes closed.[6] There is wide intrasubject, day-to-day, and visit-to-visit variation, but the variation and the absolute value decrease in aqueous-deficient dry eye, probably because of the decreased reflex response with lacrimal failure. The diagnostic cut-off employed in the past was ≤ 5.5 mm in 5 minutes, based on the van Bijsterveld study,[12,41] and the studies of Pflugfelder et al[42,43] and others[6] have made a case for using ≤ 5 mm. More recently, many authors and clinical trialists have adopted a cut-off of < 5 mm although the basis for this shift is unclear. Lowering the cut-off decreases the detection rate (sensitivity) but increases the specificity of the test. The van Bijsterveld study, although a model study in many ways, suffered from selection bias and, therefore, a refinement of this value, using appropriate studies, is needed (see above). In the meantime, it is reasonable to carry out the Schirmer test using a cut-off of ≤ 5 mm in 5 minutes.

Table 6. Revised international classification criteria for ocular manifestations of Sjogren syndrome

I. Ocular symptoms: a positive response to at least one of the following questions: 1. Have you had daily, persistent, troublesome dry eyes for more than 3 months? 2. Do you have a recurrent sensation of sand or gravel in the eyes? 3. Do you use tear substitutes more than 3 times a day?
II. Oral symptoms: a positive response to at least one of the following questions: 1. Have you had a daily feeling of dry mouth for more than 3 months? 2. Have you had recurrently or persistently swollen salivary glands as an adult? 3. Do you frequently drink liquids to aid in swallowing dry food?
III. Ocular signs: that is, objective evidence of ocular involvement defined as a positive result for at least one of the following two tests: 1. Schirmer's I test, performed without anaesthesia (≤5 mm in 5 minutes) 2. Rose bengal score or other ocular dye score (≥4 according to van Bijsterveld's scoring system)
IV. Histopathology: in minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialoadenitis, evaluated by an expert histopathologist, with a focus score ≥1, defined as a number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm^2 of glandular tissue[18]
V. Salivary gland involvement: objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests: 1. Unstimulated whole salivary flow (≤1.5 ml in 15 minutes) 2. Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitary or destructive pattern), without evidence of obstruction in the major ducts[19] 3. Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer[20]
VI. Autoantibodies: presence in the serum of the following autoantibodies: 1. Antibodies to Ro(SSA) or La(SSB) antigens, or both

Reprinted with permission from: Vitali C, Bombardieri S, Jonnson R, et al. Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 2002;1:554-8.

5. Tear Osmolarity

The place of tear osmolarity measurement in dry eye diagnosis is well established, and its adoption has several attractions. There is considerable value in assessing a parameter that is directly involved in the mechanism of dry eye. Tear hyperosmolarity may reasonably be regarded as the signature feature that characterizes the condition of "ocular surface dryness."[1] Furthermore, in several studies, as illustrated in Table 2, development of a diagnostic osmolar cut-off value has utilized appropriate methodology, using an independent sample of dry eye patients. Thus, the recommended cut-off value of 316 mOsm/l can be said to be well validated.[22]

In the past, although the measurement of tear osmolarity has been offered as a "gold standard" in dry eye diagnosis,[11] its general utility as a test has been hindered by the need for expert technical support; thus, its use has been confined to a small number of specialized laboratories. The feasibility of this objective test is greatly enhanced by the imminent availability of a commercial device that will make the technology generally available (see below).[23,45]

6. Combined Tests in Current Use

In various RCT settings, different authors have adopted different approaches to the recruitment of dry eye patients, on an *ad hoc* basis, usually requiring subjects to satisfy entry criteria including a symptom or symptoms together with one or more positive signs (eg, a positive TFBUT test, staining grade, or Schirmer test).

The best example of the validated use of a combination of tests in dry eye for diagnosis is provided by the classification criteria of the American-European consensus group.[6] These criteria require evidence for a single ocular symptom and a single ocular sign for the diagnosis of dry eye as a component of Sjogren syndrome, as summarized in Table (Table 6).

B. Future Tests

Looking to the future and based on the currently available data (Table 2), the use of various tests, singly or in combination, can be considered as adjunctive approaches to dry eye screening and diagnosis. They are summarized briefly below:

1. Screening Tests for Dry Eye Disease

Screening tests should maximize sensitivity and "dry eye overdiagnosis." Such tests include single measures of meniscus height (using appropriate technology), tear ferning; or parallel combinations of tear turnover rate (**TTR**) + evaporation + osmolarity, or weighted combinations (by discriminant function analysis) of osmolarity + evaporation + lipid classification or TTR .

Because a screening test should be rapid and simple, the preference might be for a meniscus height or radius measure.

2. Diagnostic Tests for Dry Eye Disease

Diagnostic tests should combine high overall accuracy with good sensitivity. As noted above, the measurement of tear osmolarity may turn out to be the single most important, objective test in the diagnosis of dry eye. Alternative candidates as objective tests include 1) the parallel combination of TTR + evaporation + osmolarity, or the weighted combination (by discriminant function analysis) of osmolarity + evaporation + lipid classification or TTR.

The most effective test candidates are complex and not easily applicable, clinically. This might suggest noninvasive TFBUT as the clinical alternative.

Certain combinations of dry eye-related tests have been used to predict the risk of contact lens intolerance in patients presenting for fitting with hydrogel contact lenses.[1,44]

Table 7. A selected list of some emerging technologies

Invasiveness	Comment	Reference
Non-Invasive	Symptom questionnaires (also see Table 2)	
	Schein	Schein et al[30]
	OSDI	Schiffman et al[32]
	DEQ	Begley et al[34]
	IDEEL	Rajagopalan et al[35]
	Utility assessment	Buchholz et al[45]
Non- to Minimal	*Optical sampling*	
	Meniscometry	Yokoi et al[46]
	Lipid layer interferometry	Yokoi et al[47]
	Tear stability analysis system	Kojima et al[48]
	High speed video—tear film dynamics	Nemeth et al[49]
	OCT tear film and tear film imaging	Wang et al[50]
	Confocal microscopy	Erdelyi[51]
	Tear fluid sampling	
	Strip meniscometry	Dogru et al[52]
	Sampling for proteomic analysis	Grus et al[53]
	Osmolarity eg, OcuSense	Sullivan[54]
Moderate	Meibomian sampling; Meibometry	Yokoi et al[55]
	Meibography	Mathers, et al[56]
Invasive non-stress	Staining: new dyes. Digital photography of surface staining	Note: These techniques may reflect steady state conditions at the time of sampling, even though they disturb the steady state with respect to downstream tests.
	Impression and brush cytology—coupled to flow cytometry	
	Lacrimal scintigraphy	
Stress Tests	Functional visual acuity	Ishida et al[57]
	Controlled Adverse Environment (CAE)	Ousler et al[58]
	S-TBUD (Areal BUT while staring)	Liu et al[59]
	Forceful blink test (Korb)	Korb[60]

DEQ = Dry Eye Questionnaire; IDEEL=Impact of Dry Eye on Everyday Life; OCT =Ocular Coherence Tomography; OSDI =Ocular Surface Disease Index; S-TBUD=Staring Tear Breakup Dynamics.

C. Emerging Technologies

The purpose of this section is to review those diagnostic technologies that show promise for advancing our ability to investigate, monitor, or diagnose dry eye disease in the future. Many of these technologies are described within the web-based diagnostic test templates, and some are at a nascent stage. Such tests start life as prototype instruments that are used by investigators within a research environment. Some of these never see broader application as inexpensive, easy-to-use tools that can be used in the clinical setting. There is particular interest is in those technologies that might be adapted and adopted for everyday clinical use. The tests discussed here are summarized in Table 7. The new technologies are at various stages of development. Some are elaborations of old technologies and some are entirely new.

Most technologies sample the eye in some fashion, and it is useful to consider whether that sampling process is noninvasive, minimally invasive, or invasive. In tear sampling, a non- or minimally-invasive technique has the major advantage that it captures data from the surface of the eye without significantly inducing reflex tearing. Reflex tearing has been a major obstacle to the interpretation of aqueous tear-sourced data from the earliest days of tear research. There are evident advantages to the capturing of data that represent the steady state, whether these are physiological data or pathologic data.

The problem of reflex tearing has, of course, greatly influenced the interpretation of tear compositional data. For this reason, techniques that gather information from the tear film by processing reflected light or images from the tear film surface have a particular attraction as representing the "true" state of the ocular surface. This would include techniques such as interferometry, meniscometry, high-speed videotopography and optical coherence tomography (**OCT**). Some of these techniques offer the opportunity of delivering on-line data to a data capture system, allowing processing of the dynamic behavior of the tear film. In the same way, the capturing of images of cells and other materials at the ocular surface on-line seems to represent an opportunity to view the steady state.

It is the view of the Diagnostic Methodology Subcommittee that access to the steady-state presents less of a sampling problem when data are directly acquired from the ocular surface (eg, sampling cells or mucin from the ocular surface by impression cytology or brush cytology), as the sample makes an instantaneous statement about the steady state. Here, however, there may be problems in interpreting the sample because of the variable and partial nature of the sampling procedure. These problems can be handled in part by standardization. Also, although such sampling may take a "snapshot" of the steady state, such procedures (ie, impression cytology), because they are invasive, will influence subsequent sampling events. Therefore, they may need to be placed at the end of a series of tests.

It is our expectation that the sampling of expressed meibomian lipid is likely to reflect the steady state condition of the meibomian glands at the time of collection. Here we encounter other kinds of difficulties; for instance, the expressed material is all presecretory and, therefore, it does not fully reflect the nature of lipids delivered to the tear film, and in the case of meibomian gland dysfunction, the expressed material is likely to be increasingly contaminated with keratinized epithelial debris. For this reason, many publications refer to this expressed material as "meibomian excreta" or "meibum." Nonetheless, such expressed material, whether secretion or excreta, is likely to reflect the steady state of the meibomian and ductular product.

In summary, the Diagnostic Methodology Subcommittee concludes that in studying the ocular surface, there is a reasonable opportunity to obtain steady-state information about ocular surface cells and the meibomian gland and duct status. For studying the tear film, the greatest opportunity lies in the use of noninvasive techniques involving the sampling of optical radiation reflected from the tear film. However, even with noninvasive techniques, we must be cautious, as a gradual change has been observed in meniscus curvature by meniscometry in subjects sitting in apparently stable room conditions over a matter of several minutes, suggesting that it is very easy to induce minor degrees of reflex tearing under "test" conditions. Consequently, such techniques hover in a gray zone between non- and minimally-invasive in character. On the other hand, we anticipate that the designation of "minimally invasive" may be reasonably applied to direct sampling of tears under circumstances where sample volumes are in the low nanolitre range. This relates to sampling for proteomic analysis and to the depression of freezing point and "lab-on a-chip" methods for estimating tear osmolarity.

In considering noninvasiveness, it is important to note that there have been significant advances in the development of questionnaires to diagnose dry eye, identify precipitating or risk factors and explore quality-of-life implications. Nonetheless, even questionnaires are not truly non-invasive, since whenever people are observed within a study, their behavior or performance is altered (the "Hawthorne effect"[61]).

Although emerging technologies have focused on the development of noninvasive techniques to observe the steady state conditions of dry eye, there is one area where the invasive test plays a useful role. This relates to various stress tests for dry eye diagnosis, which aim to subject the eye to some sort of stress that will reveal a predisposition to dry eye. Such stress tests include the staring tear breakup dynamics (**S-TBUD**) test, forced closure test, and use of a controlled adverse environment (**CAE**).

In general, the recommended approach favors technologies that allow changes in tears at the ocular surface to be detected while causing the least disturbance to tear film dynamics during sampling. Proteomic and related techniques are examples of these. Such non- or minimally-invasive technologies offer improved acceptability to the patient and the possibility of assessment at something close to the steady-state. In addition to disturbing the tear film and altering the accuracy of the test, an invasive test is more likely to influence the outcome of another test performed sequentially, perhaps as part of a battery of tests. Some minimally invasive technologies are already in place and require only further refinement, such as the development of micro-processor-controlled systems to capture and represent data. In other technologies, the induction of reflex tearing at the time of tear sampling still exists as a problem to be overcome.

IX. SUMMARY OF RECOMMENDATIONS

A. Diagnosis of Dry Eye Disease

Two factors influence our recommendations of diagnostic tests for dry eye. First, many candidate tests derive from studies that were subject to various forms of bias (Table 2). This means that the cut-offs that they propose may be

unreliable. Second, several tests with excellent credentials are not available outside of specialist clinics. We therefore offer here a pragmatic approach to the diagnosis of dry eye based on the quality of tests currently available and their practicality in a general clinic, but we ask readers to apprise themselves of the credentials of each test by referring to Table 2.

1) Seven sets of validated questionnaires, of differing length, are listed in Table 5 (refer to the website and the report of the epidemiology subcommittee for further details). (**EDITOR: INSERT WEB SITE INFO**). We recommend that practitioners adopt one of these for routine screening in their clinics, keeping in mind the qualitative differences between the tests.
2) The dry eye component of the international classification criteria for Sjogren syndrome requires one ocular symptom (out of three) and one ocular sign (out of two) to be satisfied (Table 6).[6]
3) Tear Evaluation

   a) Tear osmolarity: Although techniques to measure tear osmolarity are currently inaccessible to most practitioners, the development of commercial instruments may make such measurements feasible in the near future. As an objective measure of dry eye, hyperosmolarity is attractive as a signature feature, characterizing dryness. A number of studies, including the study of an independent sample, suggest a diagnostic cut-off of ≥ 316 MOsm/L.

   b) Non-invasive TFBUT: If the studies shown in Table 2 that are potentially susceptible to selection or spectrum bias are ignored, the simple clinical alternative for dry eye diagnosis might be noninvasive TFBUT measurements that give moderately high sensitivity (83%) with good overall accuracy (85%).

   c) Tear function: The tear function index (**TFI**) has been used in the diagnosis of dry eye as a component of Sjogren syndrome. It is the quotient of the Schirmer value and the tear clearance rate, and a standard kit is available (see web template). The sensitivity of the test is cited as 100% with a cut off of < 40.[62]
4) Better test performance can be achieved when tests are used in combination, either in series or in parallel and the opportunity should be taken to review some of the standard tests cited above, using large, independent populations of subjects.

B. Monitoring Dry Eye Disease.

Many of the tests used to diagnose dry eye are also used to monitor its progress, either in the clinic or within clinical trials. Additional tests, many of them referred to in this DEWS Report or presented on the website (**EDITOR: INSERT TFOS SITE INFO**) can be used to follow the progress of the disease. In the future, these may include increasingly sophisticated techniques applied to tiny tear volumes with minimal invasiveness. Such tests will help to identify important changes in the native and inflammatory components of the tears in dry eye.

X. SUMMARY AND CONCLUSIONS

The purpose of this report was to review the literature and develop a resource of tests used in dry eye diagnosis and monitoring. These are displayed as templates on the TFOS website (**EDITOR: INSERT WEB INFO**), and a selection is presented herein. To give guidance as to their selection and interpretation, we have indicated some of their shortcomings and sources of bias. Our aim has been to facilitate standardization and validation. In general, most symptom questionnaires in current use have been well validated, whereas objective tests have lagged behind, both in validation and in their use of diagnostic cutoffs derived from poorly defined sample populations. These deficiencies are remediable and will be a stimulus for future research. As we emphaisze here, in considering emerging technologies, the way forward will be with new, minimally invasive techniques that sample the eye and preserve its steady state.

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Appendix 1. Alphabetical listing of tests used to diagnose and monitor dry eye

Allergy conjunctival eosinophils
Allergy conjunctival provocation test
Allergy tear IGE
• • •
Basal tear volume
Brush cytology
• • •
CCLRU—Hyperemia and other grading scales
Conjunctivochalasis
• • •
Fluorescein permeability
Flow cytometry
• • •
Endocrine markers report
EQ-SD (questionnaire)
• • •
Ferning
Forceful blink test
Functional visual acuity
• • •
Grading staining—Nichols CLEK B
Grading staining—Oxford scheme
Grading staining—van Bijsterveld
• • •
Hamano thread test
• • •
IDEEL
Impression cytology
• • •
Lacrimal biopsy
Lid margin disease criteria
LASIK-induced neuro-epith line-dry eye
• • •
Meibography
Meibomian gland expression
Meibomian lipid analysis
Meibomian lipid sampling
Meibomian microbiology
• • •
NEI-VFQ25
NIBUT
• • •
Ocular protection index
Osmolarity OcuSense overview
Osmolarity—Depression of freezing point
Osmolarity OcuSense—Sullivan
Osmolarity—Vapor pressure
• • •
Rheumatic criteria
• • •
SBUT
Schirmer I European criteria 1994
Schirmer I Farris
Schirmer I Nichols
Schirmer I van Bijsterveld
Schirmer Pflugfelder A
Schirmer Pflugfelder B
Scintigraphy
SF-36
Sicca index
Sjogren syndrome—Direct sialometry
Sjogren syndrome—Salivary-scintigraphy
Sjogren syndrome—Sialography
Sjogren syndrome—Hematology
Sjogren Serology—Martin
SSI (Sjogren Syndrome Index)—Bowman
Symptoms DEQ (questionnaire)
Symptoms McCarty (questionnaire)
Symptoms McMonnies (questionnaire)
Symptoms OSDI (questionnaire)
Symptoms Schein (questionnaire)
Staining exam form-1 from Nichols
• • •
TBUD
Tear evaporation—Tsubota
Tear flow fluorimetry
Tear lipid interferometry
Tear meniscus height
Tear meniscus radius—Yokoi
Tear protein profiles
Tear stability analysis system
Tear turnover fluorimetry
Tear volume fluorimetry
Tests used in combination
  Combined tests—Afonso 1999
  Combined tests—Bjerrum 1997
  Combined tests—European criteria 1994
  Combined tests—Nichols 2004
  Combined tests—Pflugfelder 1998
  Combined tests—Shimazaki 1998
  Combined tests—van Bijsterveld 1969
Tear film breakup time (TFBUT)
Thermography
Time-trade-off approaches to dry eye severity