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International survey on dry eye diagnosis by experts

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ABSTRACT

Purpose: To evaluate patterns and opinion from international experts with respect to dry eye disease (DED) diagnosis in clinical practice.
Methods: An online survey was distributed to worldwide DED experts. The use of diagnosis tests was evaluated including: symptoms questionnaires, functional tests, tear stability, tear volume, tear composition, surface damage and inflammation, and eyelid assessment. After the subjective importance of symptoms, tear break up time (TBUT), non-invasive TBUT, Schirmer's test, tear meniscus height, tear osmolarity, tear metalloproteinase 9, blepharitis assessment and non-contact meibography was evaluated according to likert scale.
Results: The survey was sent to 109 experts, and 77 completed the questionnaire (rate of response = 70.6%). Most of the participants were from North America (27%) and Europe (40%). A majority of respondents (73%) diagnose DED using clinical signs and symptoms, but not fulfilling a specific criteria. Seventy-six participants (98.7%) use symptoms questionnaires. All participants evaluate damage to ocular surface, and fluorescein staining is the most frequent method used (92%). Also, all the respondents perform meibomian gland and blepharitis assessment. On the other hand, only 69.8% evaluate tear composition, being osmolarity the most common test used (66.2%). Regarding to the importance of tests, TBUT ($p = 0.002$) and Schirmer's ($p = 0.021$) were found to be more important to experts from Europe than North America. No differences were found in any other test ($p > 0.05$).
Conclusions: This survey offers updated and day-to-day diagnostic clinical practice by DED worldwide experts. The results highlight the importance of symptoms and clinical signs, but not necessarily following a strict criteria.

1. Introduction

Dry eye disease (DED) is a multifactorial condition that affects a large proportion of the population globally [1]. DED diagnosis is based on symptoms and clinical signs, which were first defined by the National Eye Institute in 1995 [2]. This effort was followed by

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the Dry Eye Workshop I (DEWS I) in 2007, which defined DED as a disease caused by abnormalities of tears and the ocular surface characterized by inflammation of the ocular surface and increased tear osmolarity [3]. However, the definition has evolved with a better understanding of DED physiopathology and the consequent change in the diagnostic criteria. For example, in 2017, DEWS II proposed diagnostic criteria that should consider symptom questionnaires such as Ocular Surface Disease Index (OSDI) or Dry Eye Questionnaire (DEQ-5) and markers of homeostasis loss including ocular surface staining, non-invasive/fluorescein tear break-up time (TBUT), and elevated osmolarity [4]. To diagnose DED based on these criteria, a patient needs to present symptoms and at least lose one homeostasis marker. The DEWS has not been the only effort aimed at improving DED diagnosis. For instance, in 2006 the Japanese Dry Eye Society published diagnostic criteria that considered symptoms, tear function abnormalities (including the Schirmer's test and/or TBUT), and epithelial damage (presence of vital staining); for a definitive diagnosis of DED, patients were required to be positive for all three components. This definition evolved with the Japanese Dry Eye Society and Asia Dry Eye Society (JDES/ADES) consensus in 2016, which modified the previous criteria requiring only the presence of symptoms and unstable tear film defined as TBUT of <5 s for DED diagnosis [5]. Despite valuable input from these consensus groups, the application of these criteria may vary in clinical practice. DED diagnosis is still challenging due to the highly variable symptoms and signs, and some tools, such as tear osmolarity measurement systems, may not be available due to access or economic restraints [6–8]. Additionally, new technologies have been developed to facilitate less invasive and/or more accurate methods for evaluating tear function such as Matrix Metalloproteinase-9 (MMP-9), non contact Meibography, Topography, Aberrometry and Optical Coherence Tomography (OCT) [9]. Consequently, we decided to survey DED specialists globally to evaluate how DED is being diagnosed in real-world clinical practice around the world.

2. Methods

This anonymous survey was created on Google Forms and distributed by email for six weeks between June and July 2021. The selection criteria for the DED world expert clinician list included recognized DED specialists and corresponding/senior authors of DED publications in English between 2012 and 2020. The email address for each participant was obtained from the corresponding information declared in the articles and/or from contact information published in their clinical practices. Three reminder emails were sent to participants who had not responded every two weeks. A list of 109 DED specialists was obtained in the following proportions: Latin America and Caribbean (13.8%; n = 15), North America (30.3%; n = 33), Europe (32.1%; n = 35), Asia (16.5%; n = 18), Africa (2.7%; n = 3), and Oceania (4.6%; n = 5).

The survey included general questions, including the place of the main practice (public, academic, and/or private), country, and years of experience. Then, a question was asked to evaluate how DED was diagnosed in relation to DEWS II criteria in clinical practice with five possible options: i) following DEWS II criteria, ii) considering symptoms and signs but not fulfilling the DEWS II, iii) only DED symptoms, iv) only DED signs or v) using other criteria. The methods or tools mentioned in DEWS II for evaluating different DED aspects were assessed using the following categories: symptoms, visual functional tests, tear film stability, tear volume, tear composition, ocular surface damage, ocular surface inflammation, and eyelid and meibum assessment. In this section, questions were allowed for multiple answers. Subsequently, the subjective importance of DED diagnosis of symptoms, TBUT, non-invasive TBUT, Schirmer's test, tear meniscus height (TMH), tear osmolarity, MMP-9 (Inflammadry, Quidel Corporation, San Diego, CA, USA), blepharitis assessment, and non-contact meibography were evaluated according to a scale (never, rarely, sometimes frequently, and always). A detailed survey is available in Adnexa 1.

The data were analyzed using Stata Software 16.0 (Stata, College Station, Texas, USA). Descriptive statistics were used and categorical variable summarized by percentages. In addition, the subjective importance of DED tests was compared between geographical regions and place of main practice using Fisher's exact test. P value < 0.05 was considered statistically significant. This study was approved by the ethical committee of Centro de la Vision, Santiago, Chile, and the study procedures followed the tenets of the Declaration of Helsinki.

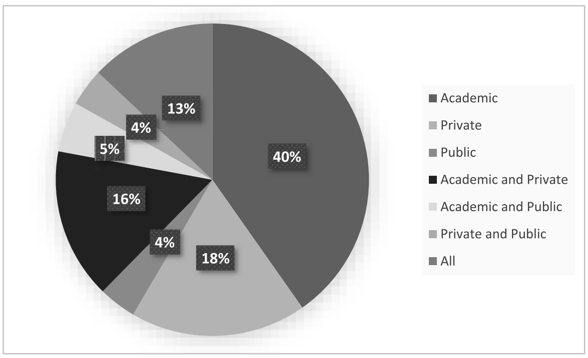

Fig. 1. Respondents place of practice.

3. Results

Seventy-seven DED experts responded to the survey at a response rate of 70.6% (77/109). The experts were predominately from Europe (42.6%; n = 32), followed by North America (27.3% n = 21), Latin America and Caribbean (13%; n = 10), Asia (11.7%; n = 9), Oceania (5.2%; n = 4), and Africa (1.3%; n = 1). The respondents were from 26 different countries. A total of 83.1% (n = 64) declared more than 15 years, 15.6% (n = 12) declared 10–15 years, and 1.3% (n = 1) declared 5–10 years of experience managing DED patients. In addition, most respondents (40%) worked in the academic health system only, and 38% worked in two or more areas (Fig. 1).

3.1. Dry eye disease diagnosis

Of the respondents, 72.7% (n = 56) considered symptoms and signs but did not necessarily fulfilled the DEWS II criteria for DED

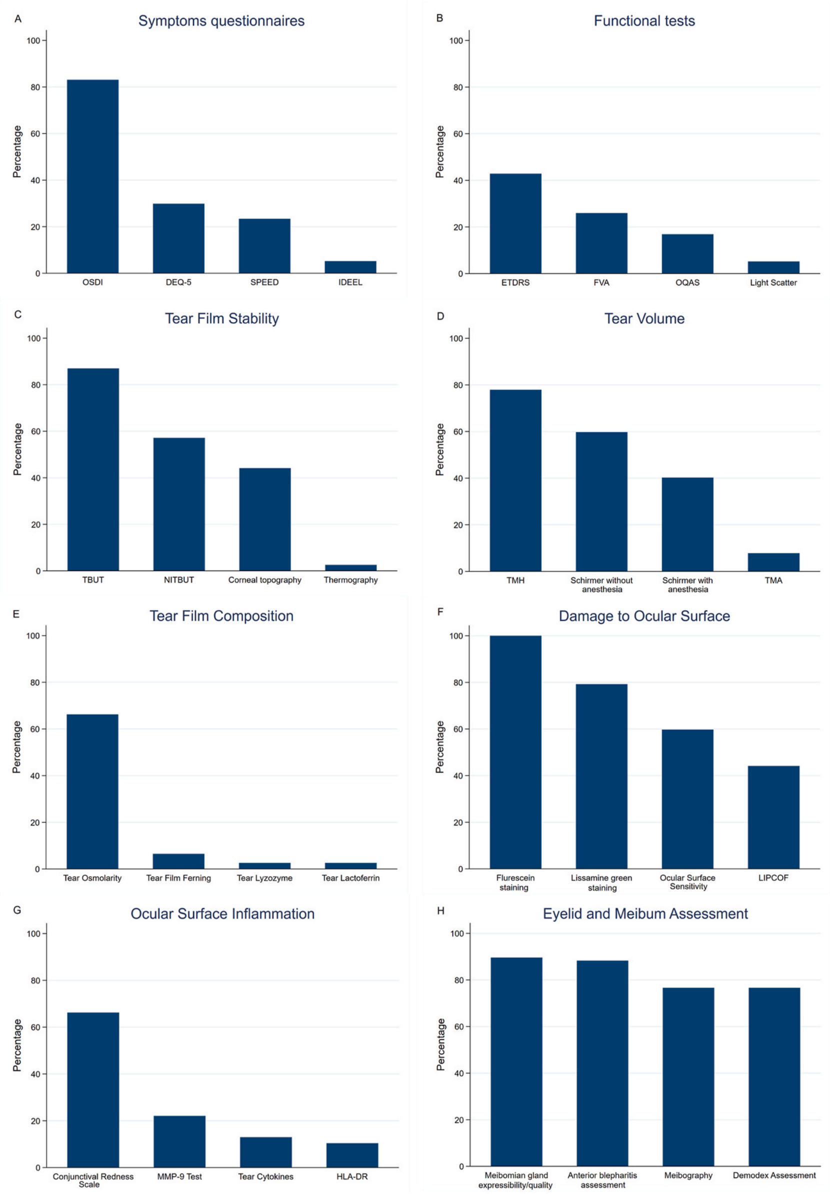

Fig. 2. Main preferences to evaluate dry eye disease according to each category*. * = Multiple answers were allowed for each category, OSDI= Ocular Surface Disease Index, DEQ-5 = Dry Eye Questionnaire-5, SPEED= Standard Patient Evaluation of Eye Dryness Questionnaire, IDEEL= Impact of Dry Eye in Everyday Life, FVA=Functioal Visual Acuity, OQAS = , TBUT = tear break up time, NITBUT = non invasive tear break up time, TMH: tear meniscus height, TMA = tear meniscus area, LIPCOF= Lid Parallel Conjunctival Folds, MMP-9 = matrix metalloproteinases, HLA-DR = human leucocyte antigen.

diagnosis in clinical practice, 24.7% (n = 19) used the DEWS II criteria, 1.3% (n = 1) used only symptoms, and 1.3% (n = 1) used other criteria.

The main preferences used to evaluate symptoms, visual functional tests, tear film stability, tear volume, tear composition, ocular surface damage, ocular surface inflammation, and eyelid and meibum assessments are summarized in Fig. 2 (A-H).

Regarding questionnaires for DED diagnosis, 96% (n = 74) of the experts admitted using them, and 71.4% (n = 55) declared using them "always or frequently". Most respondents used two or more questionnaires (51%, n = 38), while 22% (n = 17) used three or more questionnaires. The most popular questionnaire was the Ocular Surface Disease Index (OSDI) (83%, n = 64), followed by the Dry Eye Questionnaire (DEQ-5) (30%, n = 23) (Fig. 2A).

The visual functional tests were evaluated by 70% (n = 54) of respondents. The most popular test was ETDRS (42.9%) scale, followed by a variety of functional visual acuity (FVA; n = 20; 25.9%) test and the optical quality analysis system (OQAS; n = 10;

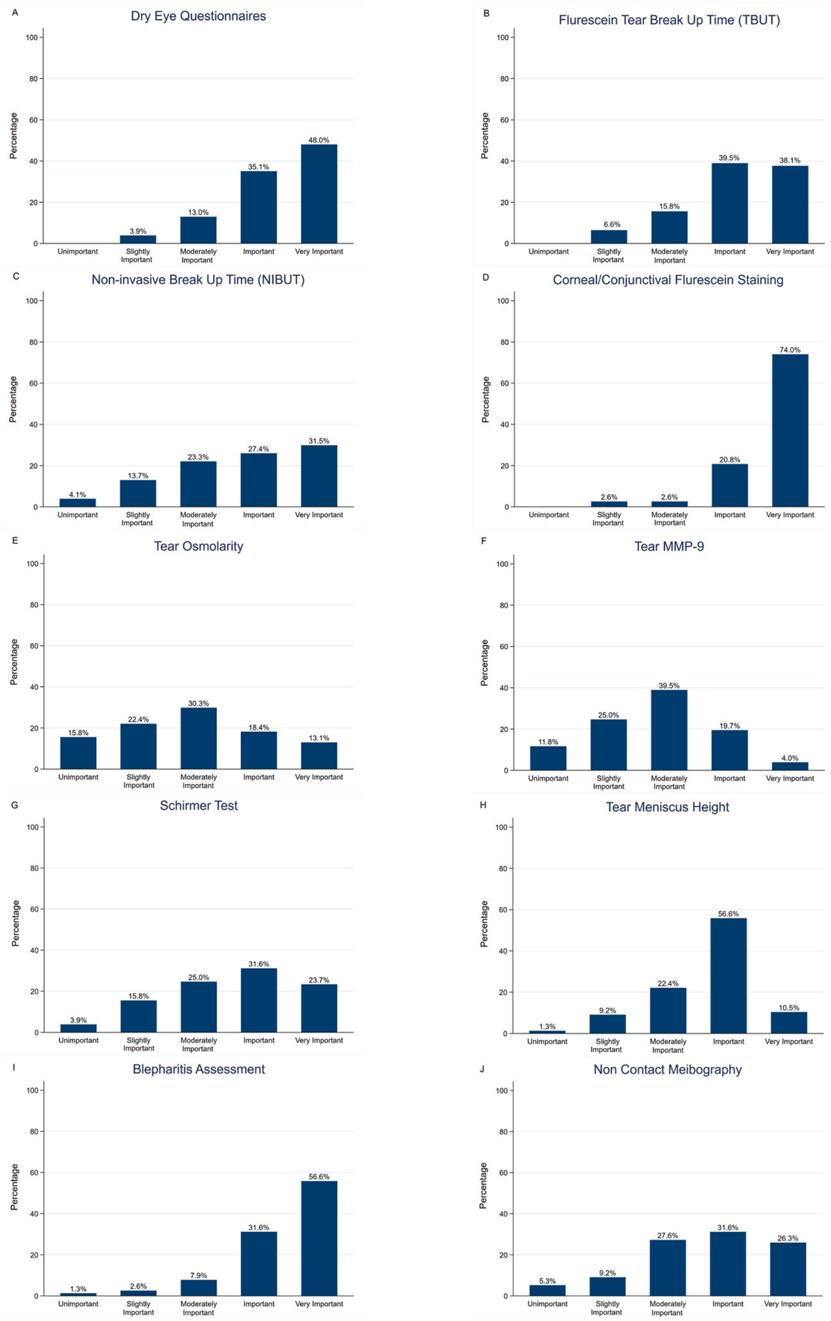

Fig. 3. Subjective importance of the different dry eye disease diagnosis tests. MMP-9 = matrix metalloproteinases.

12.9%) (Fig. 2B).

Regarding tear film stability (Figs. 2C), 96% of the participants reported using it, and the majority of respondents used TBUT (87%; n = 67), followed by non-invasive TBUT (niTBUT) (57%; n = 44), and corneal topography (42.8%; n = 33). In addition, 9.1% (n = 7) of the experts used niTBUT without TBUT.

Tear volume assessment (Fig. 2D) was used by 98.7% of the participants (n = 76). The tear meniscus height was performed by 77.9% (n = 60) of the experts. Other meniscus measurements, which are the tear meniscus area, tear meniscus curvature and tear meniscus depth, were utilized by 7.8% (n = 6), 6.5% (n = 5) and 1.3% (n = 1) of the respondents, respectively. On the other hand, Schirmer's test without anesthesia was performed by 59.7% (n = 46), while Schirmer's test with anesthesia was performed by 40.2% (n = 31). The proportion of experts who performed at least one type of Schirmer's test was 83.1% (n = 64).

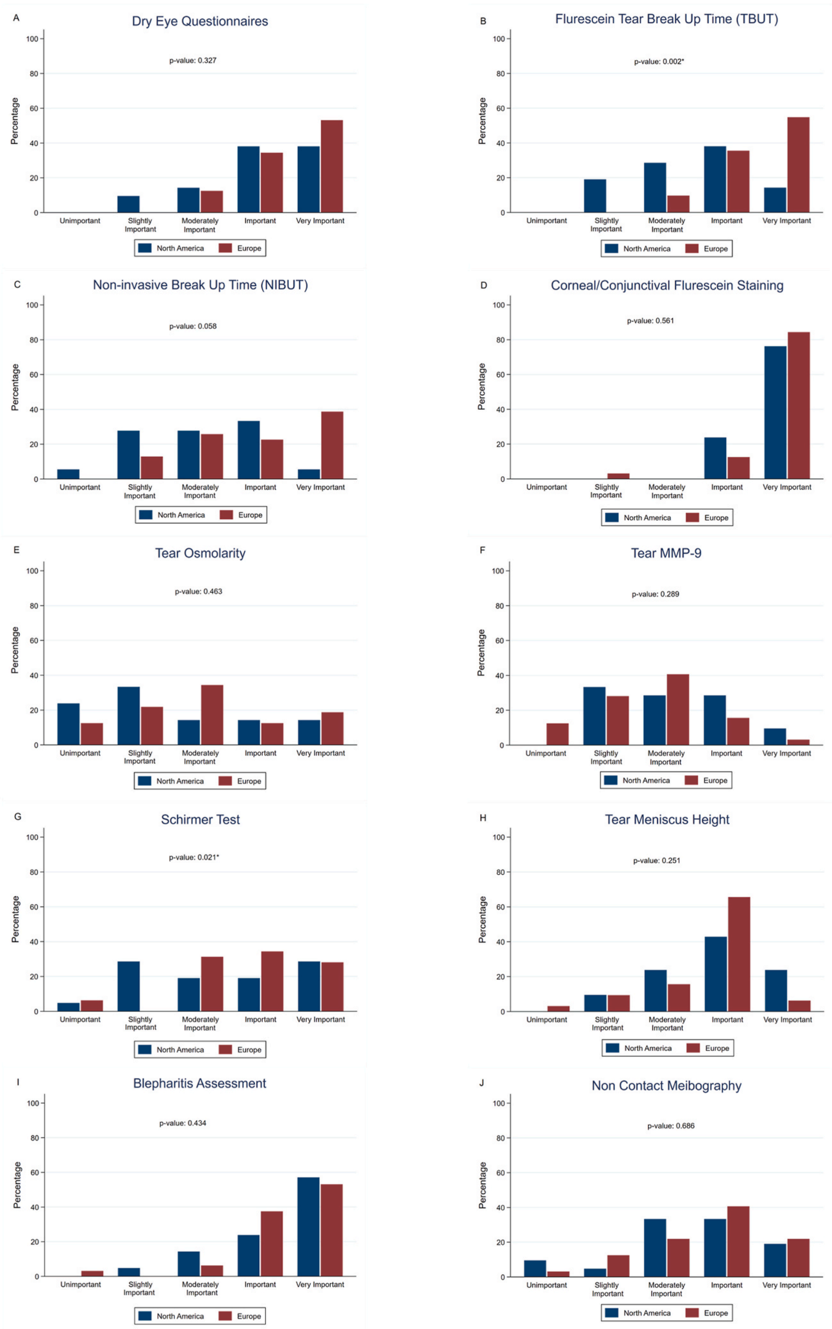

Fig. 4. Comparison between experts from Europe and North America with respect to dry eye disease diagnostic tests. * = statistically significant, MMP-9 = matrix metalloproteinases.

The tear film composition was the least frequently evaluated feature (68.9%, n = 53), with tear osmolarity being the most frequently used method (66.2%, n = 51). Other tests such as those for ferning, lactoferrin, and lysozyme were used by 6.5% (n = 5), 2.6% (n = 2), and 2.6% (n = 2), respectively (Fig. 2E).

Regarding damage to the ocular surface (Fig. 2F), all the respondents (100%; n = 77) performed corneal/conjunctival fluorescence staining. Ninety-two percent (n = 71) used a scale to grade staining; the National Eye Institute scale was the most frequently used (64.9%, n = 50), followed by the ocular staining scale (33.8%; n = 26). Conjunctival lissamine green staining was utilized by 82.4% (n = 61); Lid parallel conjunctival folds evaluation was used by 48% (n = 37); ocular surface sensitivity (Cochet-Bonnet) was used by 59.7% (n = 46); cornea *in vivo* confocal imaging was used by 42.8% (n = 33); conjunctival impression cytology was used by 27.2% (n = 21); and conjunctival *in vivo* confocal imaging was used by 9% (n = 7).

Ocular surface inflammation was evaluated by 81% (n = 63) of the experts. The majority used the conjunctival redness scale (66.2%, n = 51), followed by the MMP-9 tear test (33.8%, n = 26), tear cytokines (12.9%, n = 10), HLA-DR (10.4%, n = 8), and tear proteomics (9%, n = 7) (Fig. 2G).

Eyelid and meibum assessments (Fig. 2H) were performed by all participants (100%; n = 77). For instance, 89.6% of the experts (n = 69) evaluated meibomian gland (MG) expressibility and quality; finger compression was predominantly used (77.9%; n = 60), followed by the MG evaluator (Tears Science, USA) (19.4%; n = 15) and chalazia clamp (12.9%; n = 10). In addition, anterior blepharitis, Demodex, and lipid layer thickness assessments were performed by 81.8% (n = 63), 76.6% (n = 59), and 42.8% (n = 33), respectively. In addition, non-contact meibography was used by 85.7% (n = 66) of the respondents; Keratograph 5 M (Oculus, USA) was the most used (55.3%; n = 42), followed by Lipiview (Johnson and Johnson, USA) (37.7%; n = 29), Sirius Sheimpflug Camera (Schwind, Germany) (12.9%; n = 10), and Topcon BG-4M (Topcon, Japan) (9%; n = 7).

Fig. 3(A–J) summarizes the subjective importance of the different tests. In addition, North America and Europe had more respondents, and they were subsequently compared (Fig. 4A–J). TBUT ($p = 0.002$) and Schirmer's test ($p = 0.021$) were found to be more important to DED experts from Europe than those from North America (Fig. 4B and G respectively). No differences were observed in any of the other tests. (Fisher exact test $p > 0.05$). The experts who work in academic and non-academic environments were similarly compared, and no differences in the subjective importance were found (Fisher's exact test, $p > 0.05$).

4. Discussion

This International DED expert survey evaluated the current trends in the diagnosis of DED in clinical practice around the world. DED diagnosis is challenging because of the frequent poor correlation between symptoms and signs, which has resulted in different interpretations and definitions [10]. The diagnostic criteria for DED have changed over the years, and this has been attributed to better understanding of the disease and its physiopathology [5]. This information has been taken into account by different consensus, such as DEWS II and JDES/ADES consensus, with the lack of homeostasis and instability of the tear film as the main factors [5,11,12]. However, clinical practice may vary from theoretical concepts. For example, there is evidence of low repeatability of traditional DED tests, which may account for their current usage trends [10]. Several new technologies have been developed to facilitate less invasive and/or more accurate methods for evaluating tear function, but evidence of its applicability to daily activities is unknown [13]. To try to answer this question, we evaluated the preferences of the experts for DED diagnosis in clinical practice.

In our survey, the majority of the respondents made a DED diagnosis based on considerations of both symptoms and signs without necessarily fulfilling strict criteria. It is obvious from the results that symptoms are important, clearly demonstrated by the frequent use of symptom questionnaires. The most commonly used questionnaires are the OSDI and DEQ-5, which have been recommended by the DEWS II committee [4]. Both have shown good sensitivity and specificity for DED diagnosis and have been translated and adapted for several languages [14–17].

There was a consensus by all the participants on evaluating damage to the ocular surface, but also eyelid and meibum assessments. This may be explained by the presence of corneal/conjunctival staining, which seems to be a frequently assessed sign for diagnosis, and dysfunction of the MG has been described as a key feature of evaporative DED. MG expressibility and quality were evaluated by almost 90% of the responders. In addition, a similar proportion evaluated tear stability using TBUT while a low proportion used niTBUT. Ozulken et al. reported a good correlation between both tests when niTBUT was performed using the Sirius Topography device [18]. In contrast, Hong et al. found that the niTBUT values measured with Keratograph 5 M were significantly lower than the TBUT values [19]. Non invasive TBUT has the advantage of being non invasive; however, it may require more time and a device to do it. In addition, there is a need to evaluate diagnostic and severity grade cut-off values, as this has not been determined in large population studies to improve test performance [18,20]. On the other hand, TBUT is not usually standardized, as the amount of fluorescein used each time is not commonly measured which may lead to variable results [18].

Tear volume was also evaluated by almost all participants. The most popular test for tear volume was Schirmer's (I or II), followed by TMH. However, the proportion of respondents considering TMH as important or very important was higher than that of participants considering Schirmer's criteria for DED diagnosis. Furthermore, TMH has shown good repeatability and high sensitivity and specificity, especially with the use of OCT [21,22]. On the other hand, Schimer's test is easily accessible and cheap; however, it may be highly variable and is not usually helpful unless its value is extremely low [10,23].

From our data, the least popular test included in the DEWS II criteria is tear film osmolarity. Accurate measurement of tear osmolarity can be performed in the office as a minimally invasive procedure [23,24]. Although the proportion of experts using tear osmolarity is still high, certain issues prevent further use, e.g., disposable tips incur an additional fee which may be a barrier for a large scale implementation. In fact, costing may be an issue in many practices around the world where the test is not necessarly covered by an insurance system. Moreover, tear osmolarity is highly variable [25]. Although it has been considered as a diagnostic criterion [4, 26]; this variability may result in a low negative predictive value for DED diagnosis [27].

Regarding geographical differences, we were only able to compare the subjective importance attached by experts from North America and Europe because the other groups were not highly represented. We found that TBUT and Schirmer's test were more important to European DED experts. Although not an exhaustive explanation, both tests are classical and very low cost, and this may explain their extensive use in certain practices. Non invasive tests usually require additional devices with an extra cost which may be a barrier for massive implementation. There is no difference in the subjective significance of niTBUT and TMH, which are supposed to replace the former.

With respect to new technology implementation for DED diagnosis, non-contact meibography has become a frequent tool for evaluating MG morphology, and certain devices offer several diagnostic options, such as evaluation of lipid layer thickness and/or niTBUT [13]. Considering that evaporative dry eye is the most common form of DED, anatomical evaluation of MG seems to be helpful for the diagnosis, treatment and follow up of these patients [28]. Confocal imaging is another frequently used imaging technique. Approximately half of the experts used this technique to evaluate damage to the ocular surface. However the real practical impact is limited due to high cost, intra-observer and inter-observer variability and a small area of analysis which could be solved with future software and hardware improvement [29]. Regarding ocular surface inflammation, the availability of an in-office test to evaluate tear MMP-9 has promoted its use [9]. Although, inflammation is a key point in the management of DED patients, the qualitative nature of the test difficult its use for the evaluation of response to treatment. Moreover, tear cytokines, impression cytology, and tear proteomics are not commonly used in daily clinical practice, as it is in clinical trials or research setting, probably because they need more complex processes and/or facilities to be annalyzed. However, they will probably be further developed and hopefully more adopted in the future.

This survey had certain limitations. First, the representations of respondents were generally good; however, some areas, such as Asia, may have been underrepresented. Second, because of the subjective approach used to search for expert, some specialists and opinions may have been missed; for example, some experts may not have published recently on the topic. Also, contact information was obtained from published email addresses of each expert, with the risk of not being the most used and current account. Finally, most DED expert participants worked in an academic setting. There is a risk that experts refer mainly to study patients which may have resulted in bias. However, we found no differences in the subjective importance attached to different tests by experts with academic and non-academic backgrounds.

In conclusion, this survey offers updated information on day-to-day clinical practice by international experts, regarding DED diagnosis, . To our knowledge, this is the first attempt to evaluate trends in DED diagnosis globally, specially considering the availability of two important consensus such as DEWS II and JDES/ADES. The results highlight the importance of considering symptoms and clinical signs, especially those related to epithelial damage, tear film instability, and tear volume, without necessarily following strict criteria. We hope this survey results will provide important information to help setting-up new, but also review the structure of existing DED clinics globally.

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The authors declare that the research was conducted in the absence of any commercial or financial conflict of interest.

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Author contribution statement

Cristian Cartes; Margarita Calonge; Francisco Figueiredo: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Christian Segovia: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.heliyon.2023.e16995.

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