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Letter to Editor RE "Diagnosing dry-eye: Which tests are most accurate?"

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We read with interest the recent paper by Eric Papas concerning the appropriate testing for diagnosing dry eye [1], and were concerned by the comment that *"Confronted with these insights, clinicians might be forgiven for concluding that it would be better (and cheaper) to toss a coin instead of following the current TFOS DEWS II recommendations."* which could be taken out of context, even though the article goes on to state *"This would be unfair however, since the guidelines actually specify the diagnostic hurdle as being the presence of "symptoms and at least one positive result of the markers of homeostasis"*. [2].

We certainly agree with the author that diagnosis is central to the role of any clinician and consensus is critical to the patient (for clarity and consistency between clinicians), to the clinician (for consistency with fellow eye care professionals and to inform the treatment approach) and to regulators (for accurate prevalence estimation and allocation of resources). However, merely relying on sensitivities and specificities, which is the modelling approach undertaken in this manuscript, is fundamentally flawed, as outlined in the Tear Film and Ocular Surface Society (TFOS) Diagnostic report (section 5)[2]. That sensitivity and specificity are not appropriate for diagnostic reasoning has also been identified by authors outside of the ophthalmic field [3,4]. This is primarily because there is no 'gold standard' test/techniue to compare the diagnosis against. The criteria by which the 'disease' group is chosen will lead to spectrum and selection bias (excluding individuals that do not fit the 'healthy' or 'disease' criteria set and recruiting a 'disease' group with more severe disease will lead to artificially raised sensitivity and specificity) and selection bias (when efficacy of metrics that were used in the selection and differentiation of subjects are directly compared to a novel test that was not used as part of the inclusion criteria) [2]. This will lead to much of the variability evident in the author's table 2 [1], highlighting the problem when there is no consensus around the definition/diagnosis of a disease. Moreover, the high heterogeneity in the methodology and reference standards of individual diagnostic studies included in the modelling may significantly compromise the clinical utility and applicability of the trends highlighted by the current study, which would therefore warrant judicious interpretation.

Some signs are also found to occur during later and more severe stages of the disease, such as ocular surface staining [2,5], and may therefore be associated with higher diagnostic specificity. Thus, the author recommending *"that this criterion be specified in diagnostic guidelines for dry eye disease"* [1] is biased toward patients with longstanding disease. The paper [1] refers multiple times to a 'correct' diagnosis, but this is impossible to define unless unified criteria have been applied, which is not the case across the range of studies reviewed. In addition, the parameters modelled will vary depending on how the tests are performed. In regard to ocular surface staining, specific examples might include fluorescein volume [6] and instillation location for assessing fluorescein breakup time and corneal staining, as well as the illuminating light spectrum and observational cut-off filter [7]; also whether lissamine green or fluorescein are used for conjunctival staining [8].

The modelling in this paper confirms that single tests will be less accurate [1], which is unsurprising. As the disease diagnosis must align with its definition (and the TFOS DEWS II definition includes both signs and symptoms [9]), the TFOS DEWS II diagnostic criteria requires **at least** two predefined criteria from a limited range of options to be met for a diagnosis to be made [2]. Adding multiple tests (performed consistently) will improve the sensitivity and specificity in making a diagnosis, but at the risk of fewer clinicians having the time, expertise and equipment to make that diagnosis.[2] As signs and symptoms are acknowledged not to be strongly correlated in dry eye disease [2], it will also exclude a large number of people with dry eye, such that the highly sensitive and specific diagnosis will not, in fact, be 'correct'! [2].

Hence, clinicians would absolutely **NOT** *"be forgiven for concluding that it would be better (and cheaper) to toss a coin"*[1] and should still follow the well-established and carefully selected TFOS DEWS II diagnostic recommendation [2] until such time as improved consensus

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criteria are developed.

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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