Dry eye disease: diagnostic myths and realities



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Disclosures

I am an inventor on patent relating to a new diagnostic method for dry eye.

My research laboratory has received funding from Allergan, Alcon, CooperVision and Azura Ophthalmics for anterior eye disease research, and research laboratory infrastructure support from Medmont.

Learning objective

 To understand current best practice for diagnosing and subtyping dry eye disease

Ocular Tear Film

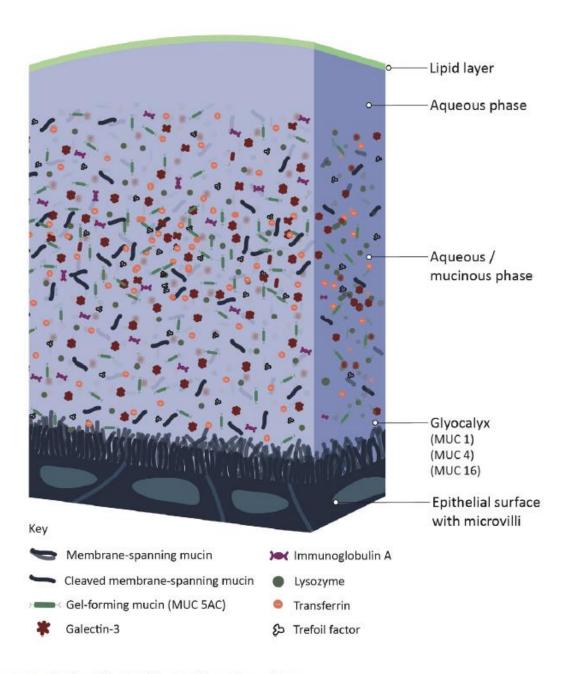


Figure 17: Current conceputalisation of tear film structure.

Definition of dry eye disease

2017 TFOS DEWS II definition

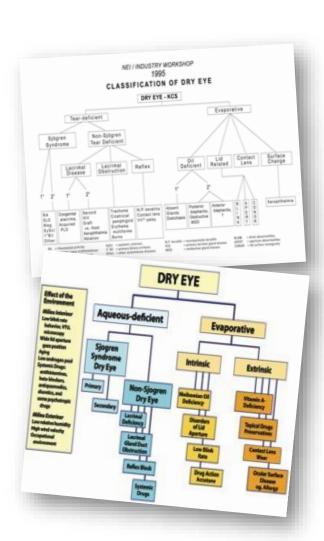
"Dry eye is a multifactorial disease of the ocular surface characterised by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play aetiological roles."

1. Definition and Classification

Classification of dry eye disease

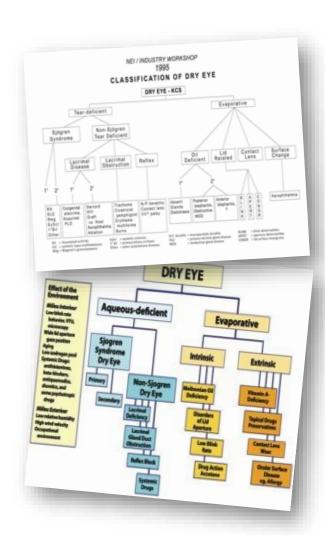
Main purpose was to improve patient care

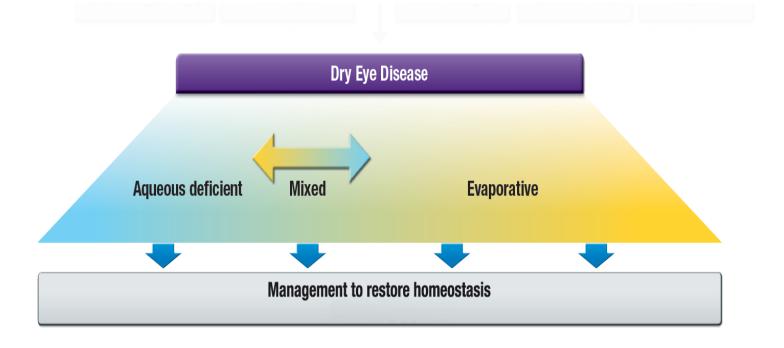
- Refine previous classification system
 - Include an option for a diagnosis of 'normal'
 - Accommodate patients with a conflict between signs and symptoms
 - Clarify dry eye subtype classification



Myth #1

Aqueous-deficient and evaporative dry eye are mutually exclusive





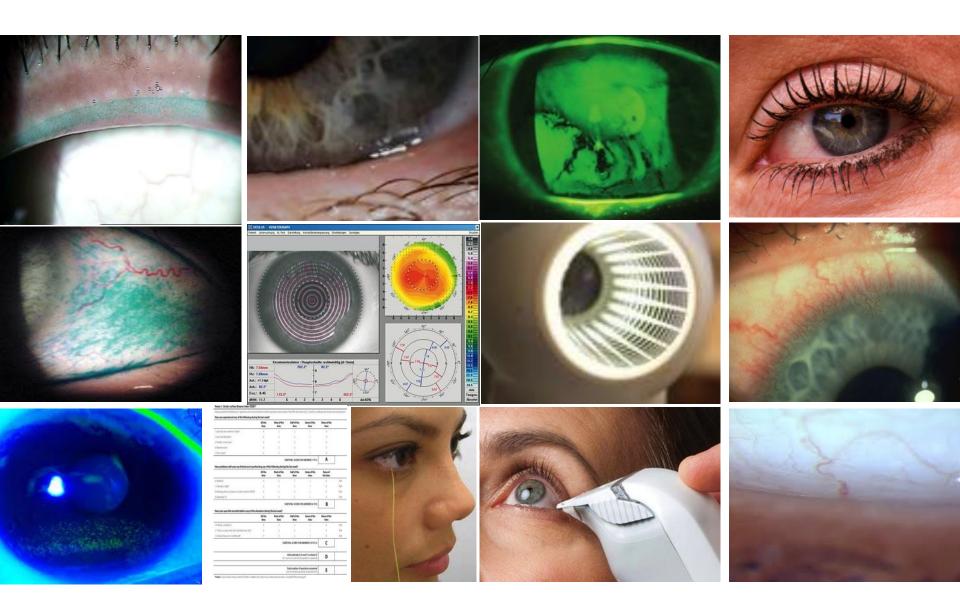


Myth #2

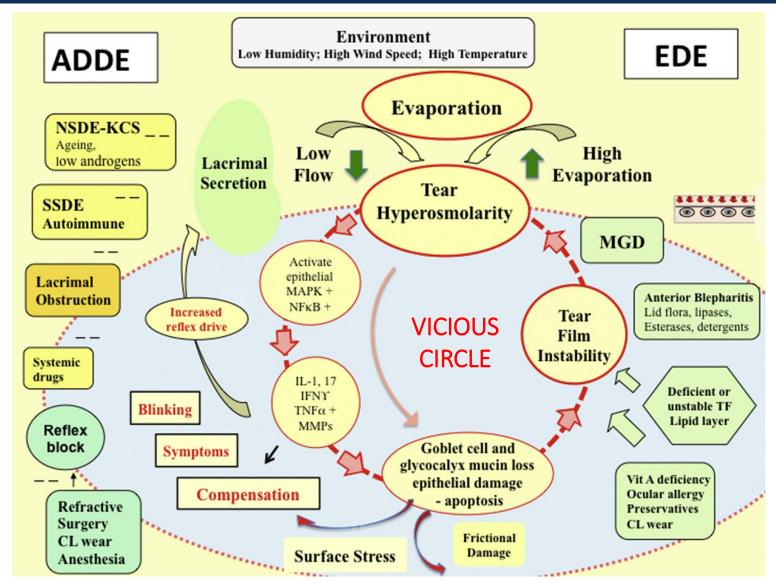
Dry eye can be diagnosed on the basis of corneal staining.

Dry eye diagnosis

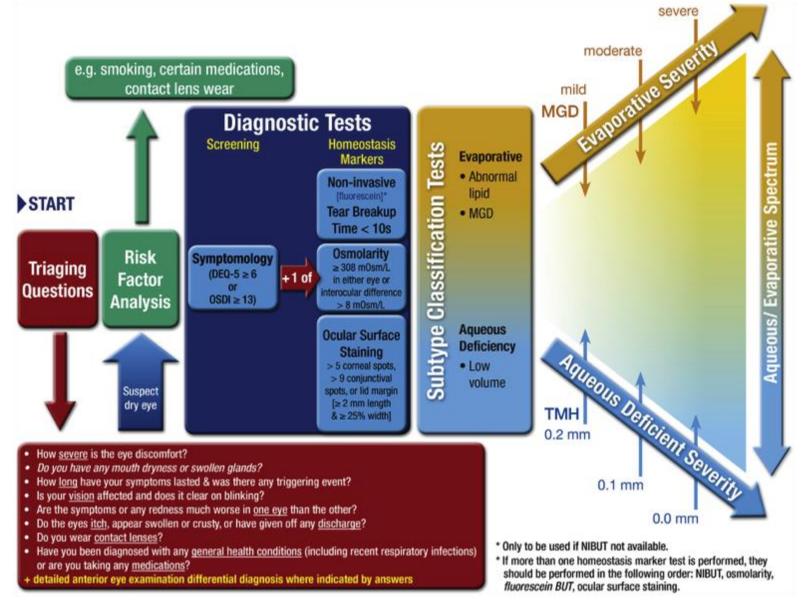




Pathophysiology of dry eye disease



TFOS DEWS II diagnostic algorithm



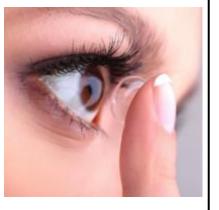
TFOS DEWS II diagnostic algorithm



"<u>TRT</u> before you Treat"

1. Triaging Questions: taking a thorough history

- How <u>severe</u> is the eye discomfort?
- Do you have any <u>mouth</u> dryness or swollen glands?
- How <u>long</u> have your symptoms lasted and was there any <u>triggering</u> event?
- Is your <u>vision</u> affected and does it clear on blinking?
- Are the symptoms or any redness much worse in one eye than the other?
- Do the eyes <u>itch</u>, are they swollen, crusty, or have they given off any <u>discharge</u>?
- Do you wear contact lenses?
- Have you been diagnosed with any general health conditions?
- Are you taking any <u>medications</u>?







2. Risk factor analysis

Non-modifiable

- Age (>40 yrs)
- Female sex
- Asian ethnicity
- Systemic conditions
 - Diabetes mellitus
 - Rosacea
 - Rheumatoid arthritis
 - Sjögren's syndrome
 - Thyroid disorders

Modifiable

- Medications
- Cigarette smoking
- Computer use
- Contact lens wear
- Environmental factors
 - Humidity, air currents/drafts, air conditioning

3. Diagnostic Tests

Screening

Homeostatic Markers

Non-invasive tear breakup time (NIBUT)* < 10s

<u>Symptomatology</u>

 $(DEQ-5 \ge 6 \text{ or } + 1 \text{ of }$ $OSDI \ge 13)$

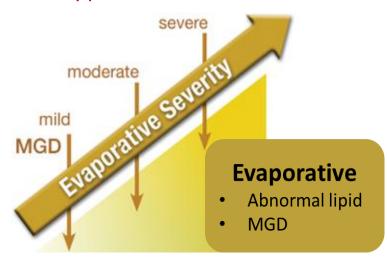
Tear osmolarity

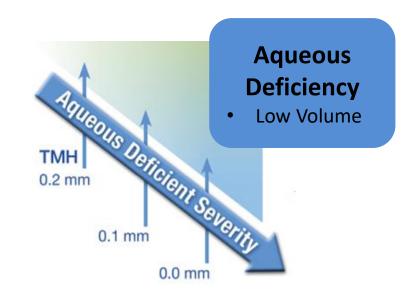
≥ 308 m0sm/L in either eye or interocular difference > 8 m0sm/L

Ocular surface staining

> 5 corneal spots > 9 conjunctival spots, or lid margin [≥ 2 mm length & ≥ 25% width]

Subtype Classification Tests

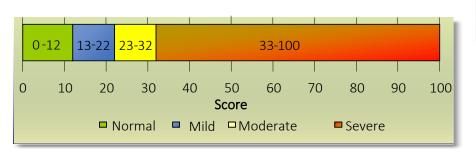




* Fluorescein is only to be used if NIBUT is not available and if so, after tear osmolarity.

OSDI survey

- 12-item survey
- Captures information over the past week relating to:
 - Vision-related functional impact
 - Symptom frequency
 - Ocular response to environmental risk factors
- Score stratifies symptom severity



Ocular Surface Disease Index

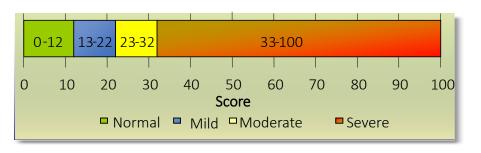
Have you experienced any of the following during the last week?	All of the time	01	lost f the ime	Half of the time	Some of the time	None of the time
1. Eyes that are sensitive to light?	4		3	2	1	0
2. Eyes that feel gritty?	4		3	2	1	0
3. Painful or sore eyes?	4		3	2	1	0
4. Blurred vision?	4		3	2	1	0
5. Poor vision?	4		3	2	1	0

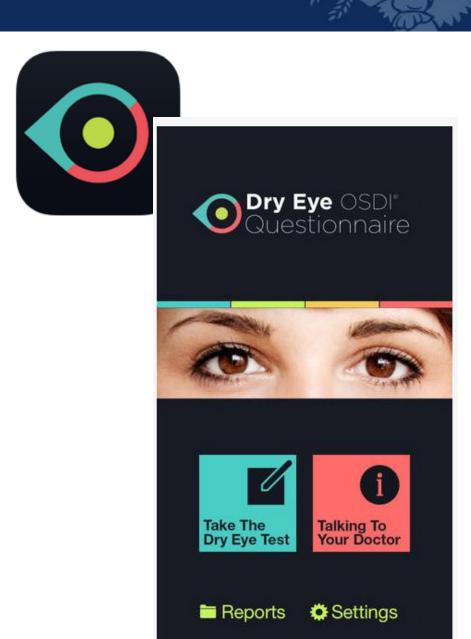
Have problems with your eyes limited you in performing any of the following <u>during the last week?</u>	All of the time		Most of the time	Half of the time	Some of the time	None of the time	N/A
6. Reading?	4		3	2	1	0	N/A
7. Driving at night?	4	П	3	2	1	0	N/A
Working with a computer or bank machine (ATM)?	4		3	2	1	0	N/A
9. Watching TV?	4		3	2	1	0	N/A

Have your eyes felt uncomfortable in any of the following situations during the last week?	All of the time	Most of the time	Half of the time	Some of the time	None of the time	N/A
10. Windy conditions?	4	3	2	1	0	N/A
11. Places or areas with low humidity (very dry)?	4	3	2	1	0	N/A
12. Areas that are air conditioned?	4	3	2	1	0	N/A

OSDI survey

- 12-item survey
- Captures information over the past week relating to:
 - Vision-related functional impact
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DEQ-5 survey



- Captures information over the past month relating to:
 - Frequency of watery eyes
 - Eye discomfort
 - Intensity of dryness during the day

Scoring

- Score ≥6: suspicion of dry eye
- Score ≥12: may indicate Sjögren's syndrome

DEQ 5

- Questions about EYE DISCOMFORT:
 - a. During a typical day in the past month, how often did your eyes feel discomfort?
 - 0 Never
 - 1 Rarely
 - 2 Sometimes
 - 3 Frequently
 - 4 Constantly
 - b. When your eyes felt discomfort, how intense was this feeling of discomfort at the end of the day, within two hours of going to bed?

Never have it	Not at All Intense				Very Intense
0	1	2	3	4	5

- Questions about EYE DRYNESS:
 - a. During a typical day in the past month, how often did your eyes feel dry?
 - 0 Never
 - Rarely
 - 2 Sometimes
 - 3 Frequently
 - 4 Constantly
 - b. When your eyes felt dry, how intense was this feeling of dryness at the end of the day, within two hours of going to bed?

Never have it	Not at All Intense				Very Intense
0	1	2	3	4	5

Question about WATERY EYES:

During a typical day in the past month, how often did your eyes look or feel excessively watery?

- 0 Never
- Rarely
- 2 Sometimes
- 3 Frequently
- 4 Constantly

Score: 1a+1b+2a+2b+3 = Total + + + + + =

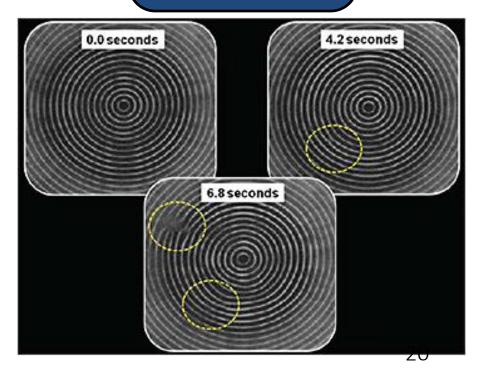
NIBUT

Tear instability is a major feature of all forms of dry eye disease

NIBUT

- Reflected grid from pre-corneal film
- Time (in seconds) for visible distortion of the reflected target
- Normative values vary slightly with instrumentation
- Average of 3 measures
- Poor correlation with NaFl TBUT

Non-invasive tear breakup time (<u>NIBUT</u>)* < 10s



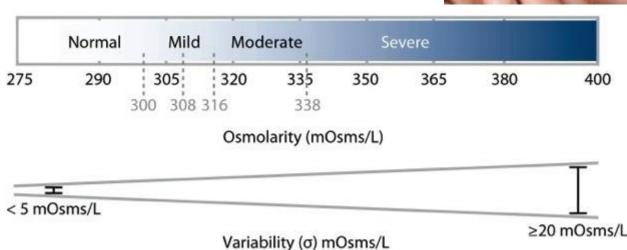
Tear osmolarity

- Objective index
- Can be used to monitor treatment
 - Reductions in osmolarity precede symptomatic improvement
 - Sensitivity: 73%; Specificity: 90%

Tear osmolarity

≥ 308 m0sm/L in either eye or interocular difference > 8 m0sm/L





Ocular surface staining

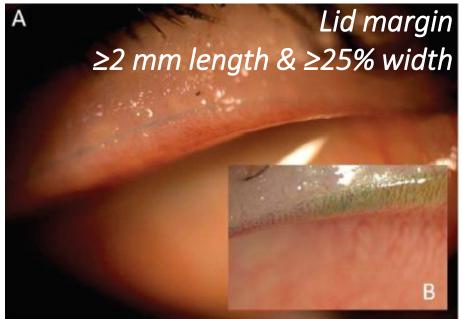


Fluorescein >5 spots

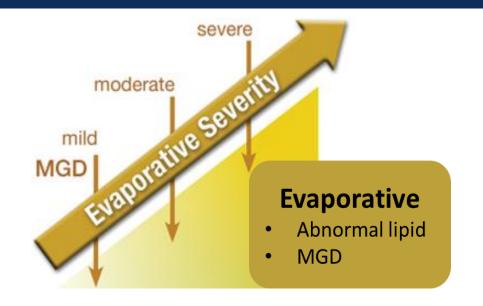
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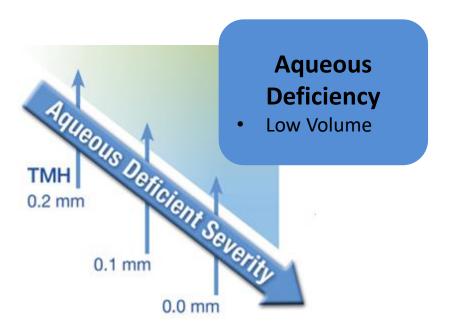




Subtyping classification tests



- MG evaluation
- MG expression
- Meibography
- Lipid layer thickness



- Tear meniscus height
- Schirmer test
- Phenol red thread test



Myth #3

Dry eye diagnosis... We have all the tests we need.

... Don't we?

What do our colleagues say?

Question	Optometrists' response
Most significant barrier(s) to optimal dry eye care	 Difficulty in achieving an accurate diagnosis (80%) Complexity of subtyping (70%)
<u>Limitations</u> of current diagnostic tests	 Lack of a single gold standard (75%) Test accuracy and repeatability (70%)

Accurate dry eye diagnosis is a challenge

- No single device for accurate and efficient triaging
 - Time consuming
 - Imprecise
 - Invasive



- Inaccurate diagnosis: most significant barrier to patients receiving optimal care
 - Patients seeking treatment may not receive the most appropriate treatment
 - Sub-optimal management

Unmet need: an accurate, rapid, point-of-care device for diagnosing tear film dysfunction

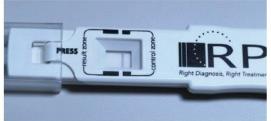
Next generation devices

TearLab Discovery

- Molecular diagnostics at point of care
- 100nL tear sample
- Tear osmolarity PLUS
 - MMP-9: evaporative dry eye
 - IL-1 Receptor Antagonist (IL-1RA): inflammatory marker for aqueous deficiency

Figure 4: (Top) Matrix metalloproteinase-9 testing application of test to the lower palpebral conjunctiva of a patient; (Bottom) A negative test result

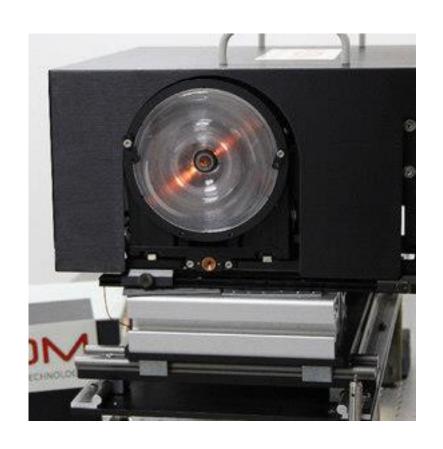




Next generation devices

Tear Film Imager

- Uses a halogen light to illuminate the ocular surface and analyses the spectrum of light reflected back
- Claims to enable direct imaging of muco-aqueous
- Quantifies: tear muco-aqueous layer thickness, lipid layer thickness, thickness change rate, and break-up time



The benefit of accurate dry eye subtyping

- Dry eye patients: delivering the right treatment to the right patient
 - Improved clinical care
 - "Actionable solutions" targeted to dry eye subtype
 - Enhanced quality of life and associated flow-on benefits

Aqueous-deficient	Evaporative
 Anti-inflammatories (e.g., corticosteroids) Immunomodulators (e.g., cyclosporine) Punctal occlusion Secretagogues Neurostimulation 	 Liposomal eye sprays Eyelid hygiene Antibiotics Meibomian gland warm compresses Thermal pulsation Intense pulsed light

Our solution: ADMiER

<u>A</u>coustically-<u>D</u>riven <u>Mi</u>crofluidic <u>E</u>xtensional <u>R</u>heometry

 Measures viscoelasticity ('stretchiness') of the tears

 Tears from people with dry eye disease have distinctive 'stretchiness' that differ from healthy tears



Prof Leslie Yeo



Dr Amarin McDonnell

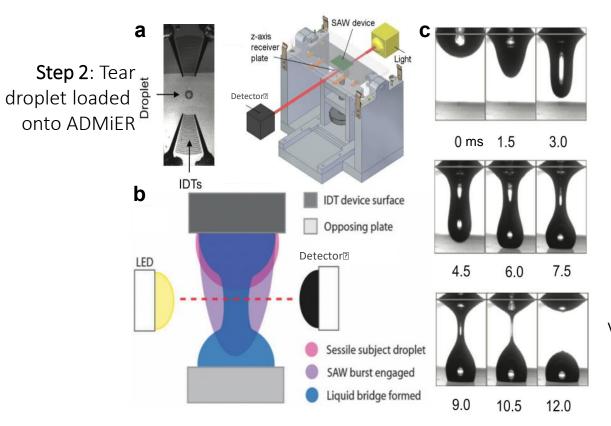


Our solution: ADMiER

Acoustically-Driven Microfluidic Extensional Rheometry



Step 1: Clinician non-invasively collects 1.5ul tear droplet



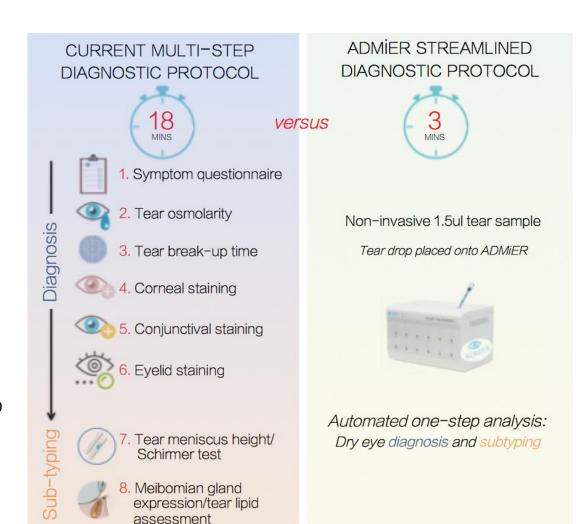
Step 3: Tear viscoelastic properties quantified.

Step 4: Viscoelasticity yields diagnosis.



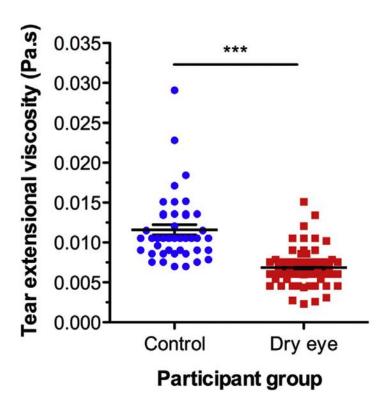
Clinical Proof-of-Concept

- Investigate ADMiER's diagnostic utility for:
 - 1. Disease Identification
 - 2. Severity Stratification
 - 3. Disease Subtyping
- Clinical study
 - Diagnostic-test accuracy
 - 103 participants
 - ADMiER vs current 8-step gold-standard diagnostic protocol



Clinical Proof-of-Concept

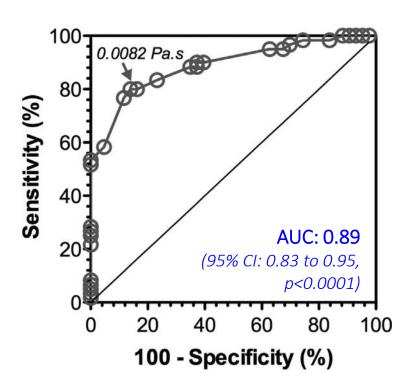
Tears from dry eyes have lower extensional viscosity than healthy tears



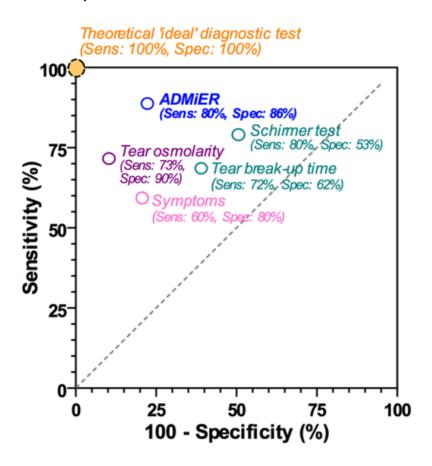
Tear film extensional viscosity in each group. Data are shown as mean \pm SEM, *** p < 0.0001.

Diagnostic accuracy

Receiver Operator Characteristic (ROC) curve analysis

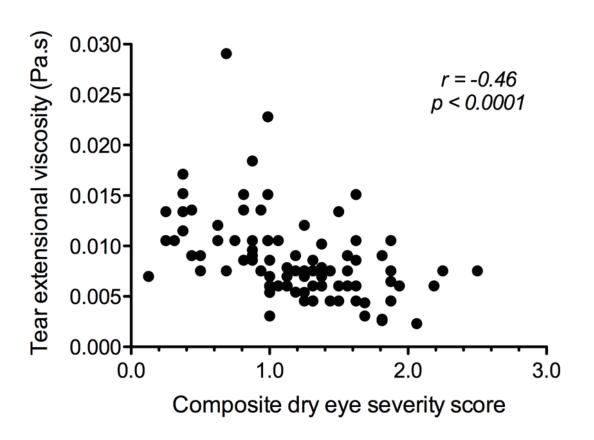


ADMiER has 80% sensitivity and 86% specificity vs current 8-step protocol



Severity stratification

Lower tear extensional viscosities relate to more severe dry eye disease







Summary

- TFOS DEWS II diagnostic approach is current best-practice
 - Comprehensive dry eye work-up in a dedicated visit

 Enhanced diagnostics are key to improving the identification and stratification of dry eye disease to inform appropriate management and optimising patient health outcomes

