New Technology

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DR.BLOOMENSTEIN's Disclosure

- Presenter is on speakers panel of Alcon, Allergan, AMO, Bausch + Lomb, RPS, Reichert, Tear Lab
- President of MRB Eye Consultants
- Past-President of the Optometric Council on Refractive Technology (OCRT)
- Board Member of Ocular Surface Society of Optometry
- Presenter has NO financial interest in any products mentioned

Laser Assisted Cataract Surgery

- Traditional Cataract Surgery
  - Capsulotomy size directly related to Effective Lens Position
  - Corneal incisions are manually executed and imprecise
  - High level of phaco power can be associated with post-op complications

Cataract Complications

- PCO 10-30%
- CME transient 2-10%
- Vitreous loss 1-5%
- Corneal endothelial cell loss 4-10%
- Retinal detachment 0.6-1.7%
- CME persistent 1-2%
- IOL Malposition 0.3%
- Need for Corneal Transplant 0.3%
- Endophthalmitis 0.1%

Femtosecond Laser Technology

- LenSx:
- LensAR:
- Optimedica:
- Technolas:
- Nidek:

Femtosecond Cataract Surgery Capabilities

- Keratome Incision
- Paracentesis *
- Limbal Relaxing Incisions
- Anterior Capsulotomy
- Anterior Capsule Polishing *
- Nuclear Sectioning
- Posterior Capsulotomy *
- Vitreolysis *

* *Future application

Femtosecond Cataract Surgery: FDA Approved

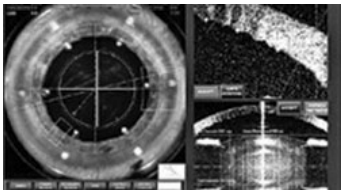
- LenSx: Capsulotomy, Incision, Fragmentation
- LensAR: Fragmentation, Capsulotomy
- Victus: B & L Technolas: Capsulotomy, Incisions, Fragmentaion and Lasik Flap
- Optimedica pending
- Nidek pending

Where and When to Use

- Pros and Cons of Femoseond Technology
  - Premium IOL
    - Toric
    - Multifocal
    - Monofocal IOL
  - Costs associated with technology

Intraoperative Wavefront aberrometry

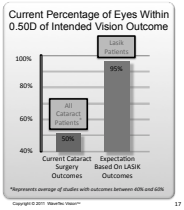
- Standard and premium IOL calculations
  - Monofocal
    - .25Diopter steps
  - Multifocal
  - Accommodating
  - Toric



ORA

Optiwave Refractive Analysis
Wavetec Vision

Current Surgery Tools Unable to Support Future Expectations



- Historical IOL power formulas have modest success, ~50% within 0.5 diopter (D)
- >40% of patients dissatisfied: need glasses or request secondary enhancement surgery
- Surgeons bear cost of post-surgery enhancement procedures, which can reduce procedure profit by up to 50%
- Patients paying out-of-pocket for premium lenses expect spectacle-free, LASIK-like results
- Surgeons need refractive measurement when it matters most – intra-operatively

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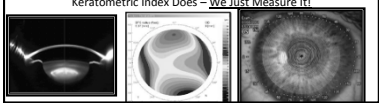
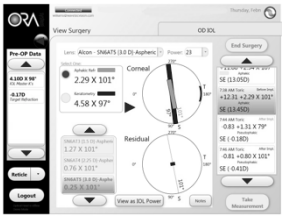
"True"Aphakic Refractive Cylinder vs Corneal

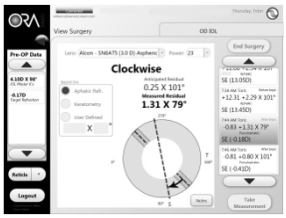
- After Phaco Incision has been Made
- Measurement Combines **Anterior and Posterior** Contributions into a Single Value
- Measures line of sight not Apex
- REFRACTIVE Cylinder not Kerotometric Cylinder
- Makes No Assumptions About Index Changes like the Keratometric Index Does – We Just Measure It!



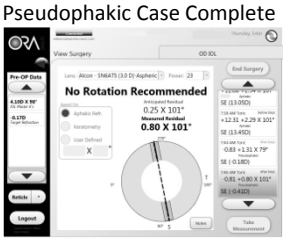
Aphakic Reading



Pseudophakic Verification

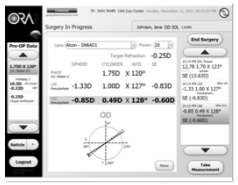


Pseudophakic Case Complete



LRI Application

- Most effective in Pseudophakic
- Least effective in phakic
- Titrate LRI to target



ORA Post LASIK Challenge

	Patient 1	Patient 2	Patient 3	Patient 4
ORA System's IOL Power Calculation	25.0 D	22.5 D	21.5 D	18.5 D
Patient's Post-Op Refraction	+0.25 D	-0.12 D	-0.25 D	-0.25 D
Surgeon 1 IOL Recommendation	24.5 D	20.5 D	20.0 D	18.0 D
Refractive Error	+0.45 D	+1.30 D	+0.75 D	+0.10 D
Surgeon 2 IOL Recommendation	24.5 D	21.0 D	22.5 D	19.0 D
Refractive Error	+0.45 D	+1.00 D	-0.90 D	-0.55 D
Surgeon 3 IOL Recommendation	24.5 D	22.0 D	21.0 D	19.5 D
Refractive Error	+0.45 D	+0.20 D	+ 0.10 D	-0.85 D

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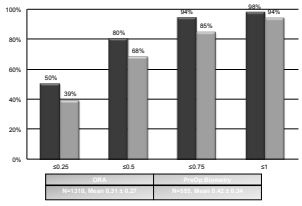
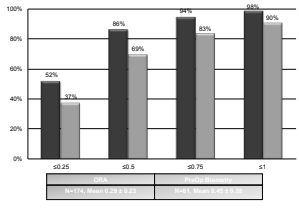
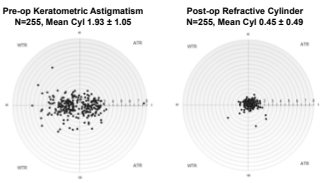
Standard Cases
Absolute Prediction Error



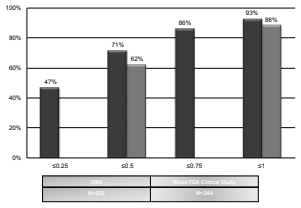
Standard Toric Cases
Absolute Prediction Error



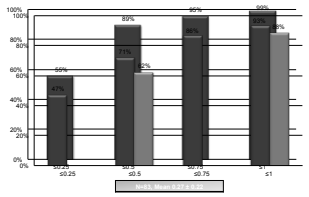
Standard Toric Cases
Cylinder Reduction



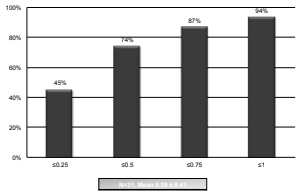
Standard Toric Cases
Post Op Cylinder Distribution



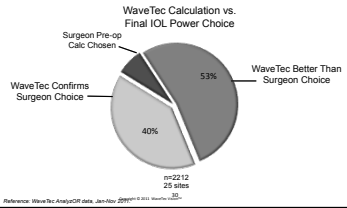
Post Myopic LASIK
Absolute Prediction Error



Post Hyperopic LASIK
Absolute Prediction Error

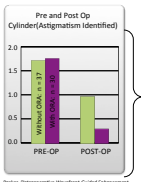


On-Demand Measurement Impacts 93% of Surgeon's IOL Decision-Making



Reference: WaveTec AnalyzeOR data, Jan-Nov 2011

Case Studies: ORA Improves Accuracy, Reduces Surgical Enhancements & Follow-up Costs



Surgeon	Number of ORA Procedures	Reduced Enhancement/ Revision Rate With ORA: Prior to ORA	With ORA
K. Assil, MD	1,042	20%	3%
E. Donnenfeld, MD	478	35%	8.5%
S. Lane, MD	278	10%	5%
M. Packer, MD	217	16%	3%
D. Tran, MA	556	17%	6%
R. Weinstock, MD	798	10%	6%
W. Wiley, MD	1278	15%	3%
M. Woodcock, MD	1630	10%	2.5%
Average	784	17%	5%

Packer, "Intraoperative Wavefront-Guided Enhancement of LRI's – A Retrospective Study" ,ICRS May 2010

Modhori, "Wavefront-Guided Custom Cataract™ Surgery A New Value Proposition for Cataract Surgeons" SMQ Strategic 2011

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ORA

- Increases Accuracy of Post-Surgical Outcomes
  - Improved Premium IOL Outcomes
- Higher Level of Technology
- Increased Cost to Patients
- Increased Time in O.R.

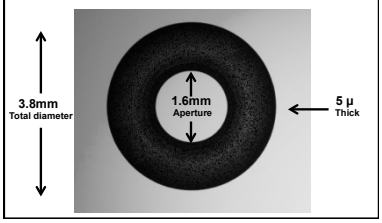
The AcuFocus™ KAMRA™ Inlay

The KAMRA inlay is limited by United States law to investigational use and not available for sale in the United States.

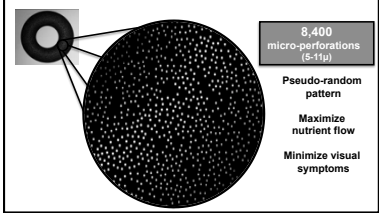
Key Milestones & Developments

- Over 9000 inlays implanted worldwide
- US IDE enrollment complete (507 patients)
  - Follow-up out to 24 months
- Combination with LASIK has expanded the application of the KAMRA inlay from emmetropes to ametropes
- New technology to ensure accurate centration

Inlay Design



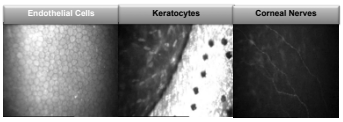
Inlay Design



Proven Biocompatibility & Stability

- Verified by testing to FDA standards of ISO 11979 and 10993, including a 6-month rabbit corneal implant study
- Validated by clinical study results in over a 1000 subjects and extensive OCT studies
- Corneas are quiet after surgery and do not respond to the inlay material
- Photostability testing demonstrates exceptional UV resistance for the material to last a lifetime in vivo

PVDF is Biocompatible and Well Tolerated in the Intracorneal Space

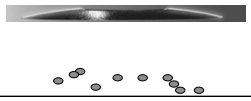


Corneal Nutrition

- The corneal epithelium has the highest metabolic rate of any corneal cells
- The nutritional requirements of the cells in the cornea are supplied from the aqueous humor
- Important to allow for free flow of glucose and other metabolites to ensure corneal epithelial health

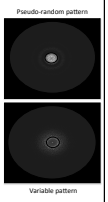
Corneal Nutrition

- Diffusion holes cover approximately 5% of the inlay area
- The hole pattern of the inlay allows proper diffusion of metabolites to support the health of all areas of the corneal epithelium



Light Transmission

- Allowing too much light transmission through a corneal inlay can degrade visual acuity and may cause night vision disturbances
- The KAMRA™ inlay allows:
  - Light transmission of only 5% in order to reduce symptoms of glare and halos
  - The perforations are arranged in a pseudo-random pattern to minimize diffraction which can contribute to night vision complaints

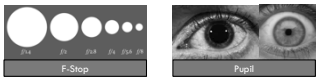


Foundations in Photography

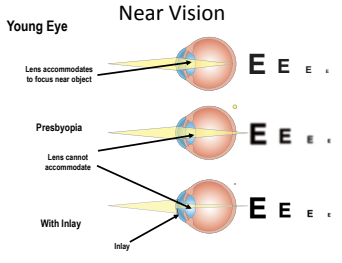
- A photographic lens aperture is used to adjust the amount of light reaching the film or image sensor.
- Depth of field is a function of both the aperture and focal length of the camera lens
- Smaller apertures (larger F-Stop numbers) produce a longer depth of field

Correlating "F-Stop" to Pupil Size

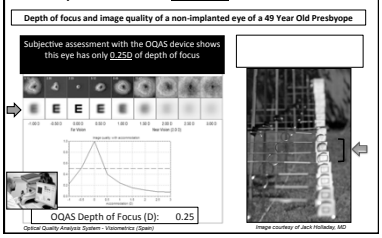
- The pupil is the aperture of the human eye
- The iris is the diaphragm that serves as the aperture stop
- The entrance pupil can range from 2 mm to 8 mm depending on lighting conditions and iris response



Near Vision



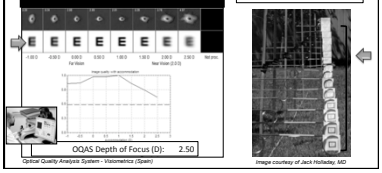
Depth of Focus *without* Correction



Depth of Focus *with* the Inlay

Depth of focus and image quality of the inlay implanted eye of a 49 year old presbyope

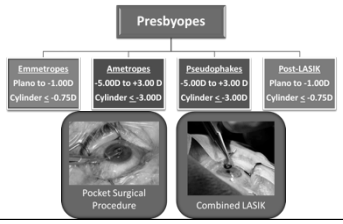
Subjective assessment with the OQAS device shows the eye with the inlay has >2.50D of depth of focus



Optical Quality Analysis System - Visiometrics (Spain)

Image courtesy of Jack Holladay, MD

Broad Application



Implantation Strategy

- The KAMRA™ Inlay is implanted MONOCULARLY in the NON-DOMINANT eye
- The fellow eye (dominant eye) may be emmetropic or ametropic
  - For ametropic eyes a LASIK procedure can be performed on the same day as inlay implantation

Pocket Procedure Overview

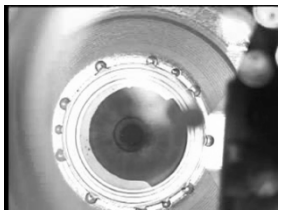
- A corneal pocket is small channel into the stroma
  - Approximately only 4.5 mm wide by 9.0 mm in length
- Technology requirements:
  - Femtosecond laser
  - High quality microscope
- Procedure time approximately 5-10 minutes

Objective Patient Selection Criteria Pocket Procedure

Pre-Op Measure	Recommendation
Age	45 - 65
Spherical Equivalent	Plano to -1.00 D
Cylinder	≤ 0.75 D
K's	N/A
Axis	Correlates with location of sidecut axis
Corneal thickness	> 500 microns
Residual bed	> 250 microns

- ✓ Stable refraction for minimum of 1 year
- ✓ No dry eye
- ✓ No ocular pathology

Pocket Surgical Procedure



Possible Paradigm Shift

- Objective Lab Measurements of Ocular Surface Disease

CLIA Wavier for In-Office Lab Testing

- TearLab
- Adneo-Plus
- Additional Testing in Future
- Optometric Scope of Practice Laws

What is Dry Eye Disease?

Definition:

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.

DEWS Report, Ocular Surface April 2007 Vol 5 No 2

Tear Hyperosmolarity- the Central Mechanism Causing Ocular Surface Inflammation, Cell Damage and Symptoms in Dry Eye Disease

DEWS Report, 2007

Tear hyperosmolarity stimulates a cascade of inflammatory events
- *Inflammatory tear cytokines and MMPs*
- *Apoptotic cell death*
- *Reduced and altered tear mucins*
- *Reduced lubrication*
- *Up-regulation of HLA-DR expression on surface cells*
- *Disruption of epithelial junctions*
- *Intra-cytoplasmic changes in surface cells*

Tear osmolarity tracks severity of disease linearly and tracks response to therapy and is tightly linked to tear film instability

Hyperosmolarity in Dry Eye Diagnosis

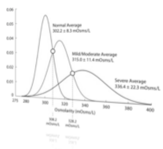
Dry Eye Diagnosis

Santosh Khanal,[1] Alan Tomlinson,[1] Angus McFadyen,[2] Charles Diaper,[3] and Kannu Ramaesh[4]

PURPOSE. To determine the most effective objective tests, applied singly or in combination in the diagnosis of dry eye disease.

METHODS. Two groups of subjects—41 with dry eye and 32 with no ocular surface disease—had symptoms, tear film quality, evaporation, tear turnover rate (TTR), volume and osmolarity, and meibomian gland dropout score assessed.

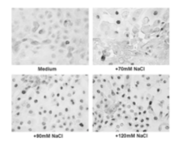
CONCLUSIONS. Tear osmolarity is the best single test for the diagnosis of dry eye, whereas a battery of tests employing a weighted comparison of TTR, evaporation, and osmolarity measurements derived from discriminant function analysis is the most effective. (*Invest Ophthalmol Vis Sci.* 2008;49:1407–1414) DOI:10.1167/iovs.07-0635



Hyperosmolarity & Ocular Surface Damage

Hyperosmolarity-Induced Apoptosis in Human Corneal Epithelial Cells Is Mediated by Cytochrome c and MAPK Pathways

Lihui Luo, MD,†‡ De-Quan Li, MD, PhD,* and Stephen C. Pflugfelder, MD**



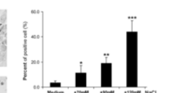


FIGURE 1. ApopTag ISOL assay in representative fields showing the increased ISOL-positive apoptotic cells in corneal epithelial cultures exposed to high-osmolarity saline-added media (+70, 90, or 120 mM NaCl) for 24 hours, compared with cells cultured in normal medium. The percentage of positive cells in each group (n = 5) is shown in the graph. *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$ compared with control medium.

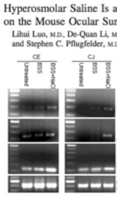
Liu H. Invest Ophthalmol Vis Sci. 2009;50:3671–3679

Hyperosmolarity as a Pro-inflammatory Stress

Hyperosmolar Saline Is a Proinflammatory Stress on the Mouse Ocular Surface

Lihui Luo, M.D., De-Quan Li, M.D., PH.D., Rosa M. Corrales, PH.D., and Stephen C. Pflugfelder, M.D.

Eye & Contact Lens 31(5): 186–193, 2005



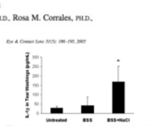


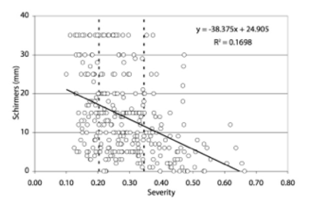
FIG. 1. IL-1β concentration in tear fluid washings of mice before (untreated) and after treatment with balanced salt solution (BSS) or hyperosmotic saline solution (HOSS) (BSS+NaCl) for 2 days by enzyme-linked immunosorbent assay (n = 12 for each group). Data are mean and standard deviation (error bars) of three separate experiments with four mice per group (*P<0.0001 by analysis of variance). Post-hoc analyses with Tukey multiple comparisons test showed that the concentration for the HOSS treatment group was significantly higher than that for the untreated control and BSS treated groups (P<0.001).

Osmolarity as a Gold Standard

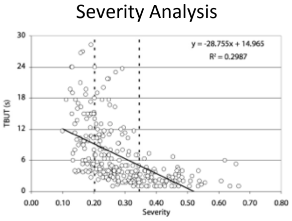
The measurement of tear film osmolarity arguably offers the best means of capturing, in a single parameter, the balance of input and output of the lacrimal system. It is clear from the comparison of the diagnostic efficiency of various tests for DED, used singly or in combination, that osmolarity provides a powerful tool in the diagnosis of DED and has the potential to be accepted as a gold standard for the disease.

Alan Tomlin[redacted]University, UK

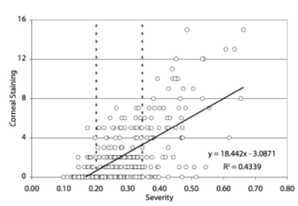
Schirmer Strip Severity Analysis



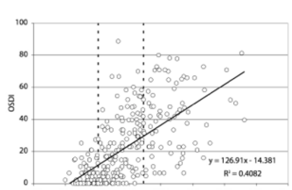
Tear Film Breakup Time (TBUT) Severity Analysis



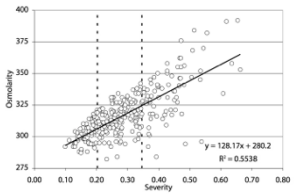
Corneal Staining Severity Analysis



Symptoms (OSDI) Severity Analysis



Osmolarity Severity Analysis



Osmolarity in the Diagnosis of Dry Eye Disease

Clinical Test	PPV
Osmolarity	87%
Schirmers	31%
TBUT	25%
Staining	31%
Meniscus Height	33%

- Osmolarity is the "gold standard" test for Dry Eye
  - 45 years peer reviewed research
  - Osmolarity has been added to definition of Dry Eye
  - Global marker of Dry Eye, indicating a concentrated tear film

Source: DEWS Report, Ocular Surface April 2007 Vol 5 No 2. & Tomlinson A, et. al., IOVS 47(10) 2006

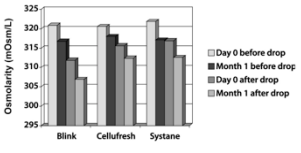
Osmolarity Testing

Osmolarity Testing

Utility of TearLab™ in Clincal Trials & Disease Management

- Osmolarity is a compelling choice for primary efficacy endpoint
  - Quantitative
  - Operator independent
  - Noninvasive (done at beginning of test sequence)
- **Inclusion Criteria are Critical**
  - One eye > 328 mOsms/L, Opposite eye > 316 mOsms/L
  - Different signs don't correlate in the general population
- Test TearLab™ Osmolarity before any other test
- Perform daily quality control
- Discontinue use of artificial tears at least 2 hours before testing

Tracking Therapeutic Efficacy with the TearLab™

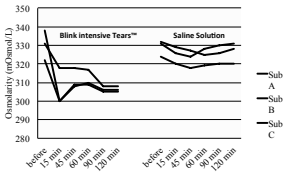


N ~ 20 each group. Each group showed a significant reduction in osmolarity, OSDI, fluorescein staining, aberrometry. Subjective questionnaire showed preference for Blink. Blink significantly lowered osmolarity as compared to Cellufresh or Systane ($p < 0.0001$)

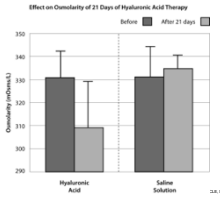
T. Alberti, U. Benelli, C.Posarelli
Dept. of Neurosciences - Section of Ophthalmology, University of Pisa, Italy

Measuring Impact of HA vs. Saline on Tear Film

Dept. of Optics and Optometry University of Salento Italy

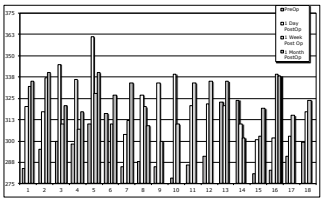


Relative Therapeutic Efficacy of HA vs. Saline



D.R. Dept di Optometria, Università del Salento

LASIK & OSMOLARITY



Place for Conventional Testing????

-
-
-
-

Improving the Diagnosis, Management, and Treatment of Infectious Conjunctivitis

Case

"Weeping, creeping and glass"

The Patient

A 44 y.o. "super cool" male
Presented to office with complaints of
- "My eye hurts and it is uncomfortable"
- "My eye is a little red and seems inflamed"

A physician
- Self-treating
- Self-diagnosing
- All about himself

Super Cool Patient

Patient has no known medical problems
- Mild head ache/jaw pain

No medications
No allergies
"This is the first time this has happened"
"Nobody else has this problem"
However...

Super Cool Patient Noticed

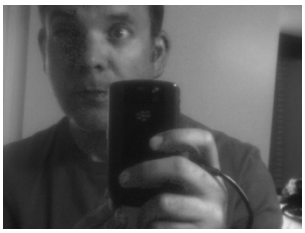
The "Eye"

- Chemosis
- Glassy appearance
- Teary eye
- Mild swollen lids
- No C/F
- No papillary rxn
- Mild follicular

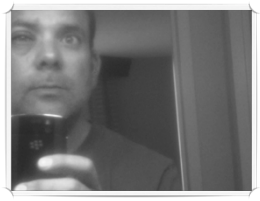
The Patient....

What's your diagnosis?

Iritis?
Episcleritis?
Bacterial Conjunctivitis?
Allergic Conjunctivitis?
Viral Conjunctivitis?



Not getting better....



Adenoviral Conjunctivitis

- Represents the most common external ocular infection[1]
- Most frequent virus isolated from the conjunctiva[2]
- Prevalence varies based on time of year and geographic location[3]
- Adenovirus is associated with significant morbidity and high healthcare costs
- 20-65% of all conjunctivitis cases are viral[2]
  - As many as 90% of these may be Adenovirus[3]

[1] Gordon JS. The Cornea 3rd ed 1998; 215-227. [2] Mastrangelo FB, Miller D, Alfonso E. Arq Bras Oftalmol 2007; 70:189-194. [3] Infectious Agents Surveillance Report 1995;16:97-98.

Adenovirus Transmission

- Can live on inanimate surfaces for 4-5 weeks [1]
- Attack rates from 10-50% [1]
- Stable to adverse chemical and physical conditions
- Can shed for 14-16 days after initial symptoms (**contagious**!)[2]
- Common modes of transmission:
  - Hand-to-eye
  - Airborne respiratory droplets

[1] O'Brien TP, Jeng BH, McDonald M, et al. Med Hec Opin. 2004 Aug;25(8):1953-61. [2] Chalita MR, Hofling-Lima AL, Parentkos A Jr, et al. Am J Ophthalmol. 2004 Jan;137(1):43-51.

Spread of Disease

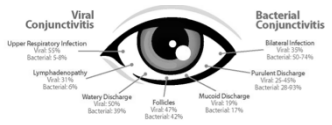
- Antibiotics are ineffective against treating the viral form of the disease but are prescribed in up to 95% of conjunctivitis cases[1]
- This leads many patients to return to school, work, or daycare while still contagious

A proper diagnosis and patient education can help stop the spread of infection!

[1] Everitt H, Little P. Fam Pract 2002;19:658-660.

Misdiagnosis

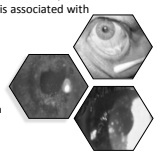
- Misdiagnosis occurs in ~50% of conjunctivitis cases[1]
- Significant overlap of signs and symptoms[1-3]



[1] O'Brien TP, Jeng BH, McDonald M, Raizman MB. Curr Med Rev Opin 2009;25(8):1953-1961. [2] Fitch CP, Rapoza PA, Owens S. Ophthalmology 1989;96:1215-1220. [3] Gigliotti F, Williams WT, Hayden FG. J Pediatr 1983;98:531-536.

Morbidity

- Unlike bacterial conjunctivitis, which is usually self-limiting, Adenoviral conjunctivitis is associated with significant morbidity such as:
  - Decreased visual acuity or light sensitivity from persistent subepithelial infiltrates[1]
  - Chronic dry eye
  - Visual loss from conjunctival foreshortening and symblepharon formation (conjunctival scarring)[2]

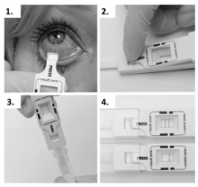


[1] Butt AL, Chodosh J. Cornea 2006;25:199-202. [2] Hammer LH, Perry HD, Donnenfeld ED, Rahn EK. Cornea 1990;9:338-340.

AdenoPlus

- Detects all known serotypes of Adenovirus
- Rapid – 10 minute results
- Easy to use – can be performed by a nurse or technician
- In-office (point-of-care) test
- Low cost – no additional equipment required
- One time use – disposable
- Accurate – high sensitivity and specificity
- Limit of detection – 6 ng/ml

How to Use AdenoPlus: Four-step Process



1. Use a "dab and drag" motion in 6-8 locations on the palpebral conjunctiva (lower eyelid) to collect a tear sample.
2. Snap the sample collector into the test cassette and press firmly where indicated.
3. Dip the test cassette into the provided buffer vial for 20 seconds. Replace the cap.
4. Read the results: 2 lines (**1 red, 1 blue**) = positive, 1 line (**blue**) = negative

AdenoPlus Clinical Trials™

A prospective, multicenter, masked, sequential, clinical trial was performed at a combination of private ophthalmology practices and academic centers.

The study enrolled 128 patients presenting with a clinical diagnosis of acute viral conjunctivitis.

Thirty-one patients were confirmed positive for Adenovirus by viral cell culture.

N = 128		Cell Culture	
		+	-
AdenoPlus	+	28	4
	-	3	93
Sensitivity		**90%** (28/31) 95% CI [74.2-98.0]	
Specificity		**96%** (93/97) 95% CI [89.8-98.9]	
Negative Predictive Value		97% (93/96) 95% CI [91.1-99.3]	
Positive Predictive Value		88% (28/32) 95% CI [71.0-96.5]	

Problems with Steroid Treatment

Although it may make the patient feel better…

- Risk of HSV (~3-21% of pink eye)[1,2]
- Increase infectivity and viral replication of Adenovirus[3-6]
- Prolongation of Adenoviral positive cultures[3-6]
- Result: increase potential spread of Adenovirus[3-6]
- Medical-legal issues

[1] Morangan F.B., et al. American Journal of Ophthalmology, 2004. 137(3): 450-458. [2] Frost M, Semczuk K. KlinOczna, 2005. 107(7-9): 418-420. [3] Gaynor BD, Chidambaram JD, Cevallos V, et al. Br J Ophthalmol. 2005 Sep;89(9):1097-9. [4] Mura H, Suzuki T, Kawamura Y, et al. Diagn Microbiol Infect Dis. 2006 Nov;56(3):297-303. [5]Uchio E, Takeuchi S, Itoh N, et al. Br Ophthalmol. 2000 Sep; 84(9): 968-72. [6] Silverman M, Brenemen B. Conjunctivitis. Available at: http://www.emedicine.com/emerg/topic110.htm.

Healthcare Economics

Appropriate use of the RPS Adeno Detector/ AdenoPlus can **reduce the costs associated with acute conjunctivitis by 40%** through:

- Reducing levels of inappropriate antibiotic use
- Reducing further local spread of the disease

A study showed that this translates to U.S. health insurer savings of as much as **$467 million** annually.

[1] Udeh B, et al. Am J Med Sci. 2008. 336(3):256-264.

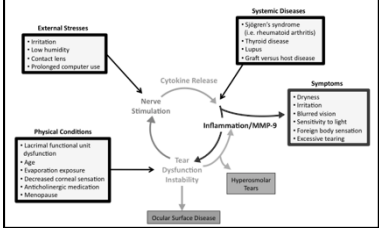
Improving the Diagnosis, Management, and Treatment of Inflammatory Dry Eye

What is MMP-9?

- Matrix metalloproteinases (MMP) are proteolytic enzymes that are produced by stressed epithelial cells on the ocular surface [1]
- Non-specific inflammatory marker
- More sensitive diagnostic marker than clinical signs [1]
- Correlates with clinical exam findings[1]
- Normal range between 3-41 ng/ml
- Ocular surface disease (i.e. dry eye) demonstrates elevated levels of MMP-9 in tears[1]

[1] Chotikavanich S, de Paiva CS, Li de Quan, et al. Invest Ophthalmol Vis Sci 2009; 50(7): 3203-3209.

Cycle of Inflammation



Normal Levels of MMP-9

Literature supports that the normal levels of MMP-9 (ng/ml) in human controls range from 3-41 ng/ml

Study	Normal Controls	Average MMP-9 Levels (ng/ml)	Standard Deviation (ng/ml)	Upper Range (ng/ml)
Acera et al 2008	18	23.6	17.4	41.0
Chotikavanich et al 2009	16	8.4	4.7	13.0
Solomon et al 2001	17	7.2	2.1	9.0
Leonardi et al 2003	10	10.5	0.2	11.0
Lema et al 2009	20	6.9	1.4	8.0
Honda et al 2010	28	22.7	14.0	37.0
Markouli et al 2010	38	11.6	15.2	N/A
Total/Avg/Range	**147**	**12.9 ng/ml**	–	**41.0 ng/ml**

MMP-9 and Dry Eye Severity[1]

Patient's Dysfunctional Tear Syndrome Level	Average MMP-9 Level	Statistical Significance vs Normal
Normal (n=18)	**8.39 ng/ml**	**NO**
Severity Level 1 (n=15)	**35.57 ng/ml**	**NO**
Severity Level 2 (n=11)	**66.17 ng/ml**	**YES**
Severity Level 3 (n=9)	**101.42 ng/ml**	**YES**
Severity Level 4 (n=11)	**381.24 ng/ml**	**YES**

Positive Result = Chronic Dry Eye

≥ 40 ng/ml

[1] Chotikavanich S, de Paiva CS, Li de Quan, et al. Invest Ophthalmol Vis Sci 2009; 50(7): 3203-3209.

InflammaDry

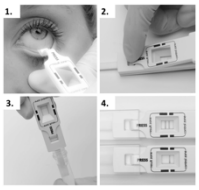
- Detects elevated levels of MMP-9 in tear fluid
- 10 minute in-office results
- Easy to use – can be performed by technicians or nurses
- Disposable – no additional equipment required

Limit of Detection: the normal level of MMP-9 in human tears ranges from 3-41 ng/ml

- **Positive** test result = MMP-9 ≥ 40 ng/ml
- **Negative** test result = MMP-9 <40 ng/ml

InflammaDry is CE Marked and commercially available in Europe. At this time InflammaDry is pending 510(k) review by FDA and is not commercially available in the U.S.

How to Use InflammaDry: Four-step Process



1. Gently dab the Sample Collector in 6-8 locations on the palpebral conjunctiva (lower eyelid) to collect a tear sample. Do not use a dragging motion.
2. Snap the sample collector into the test cassette and press firmly where indicated.
3. Dip the test cassette into the provided buffer vial for 20 seconds. Replace the cap.
4. Read the results: 2 lines (**1 red, 1 blue**) = positive, 1 line (**blue**) = negative

InflammaDry Clinical Trial

N = 206		Clinical Criteria	
		+	–
InflammaDry	+	**121**	**4**
	–	**22**	**59**
Sensitivity		**85%** (121/143)	
Specificity		**94%** (59/63)	
Overall Agreement		**87%** (180/206)	

Other Methods for Dry Eye Diagnosis[1]

Dry Eye Testing Method	Sensitivity	Specificity
Schirmer Tear Test	42%	76%
Tear Break Up Time	92%	17%
Corneal Staining	63%	89%
Questionnaire	89%	72%
TearLab Osmolarity[2,3]	64-73%	71-92%

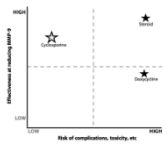
InflammaDry Sensitivity Specificity

[1] Versura P, Frigato M, Cellini M, et al. Diagnostic performance of tear function tests in Sjogren's syndrome patients. Eye (Lond). 2007;21:229-37.
[2] TearLab Performance Data – 510(k) Clearance. [3] Lemp MA, Bron AJ, Baudouin C, et al. Tear osmolarity in the diagnosis and management of dry eye disease. Am J Ophthalmol 2011;151:792-798.

Treatment of Dry Eye

Treatment of Dry Eye

- Elevated MMP-9 may predict which patients will respond to anti-inflammatory therapy
- Patients who test positive can be treated with one of the following:[1-3]
  - Cyclosporine, Steroid, or Doxycycline

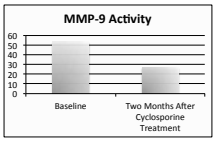


[1] De Paiva CS, Corrales RM, Villarreal AL, et al. Exp Eye Res 2006; 83(3): 526-535. [2] Gumbi C, Genc I, Sarac O, et al. Current Eye Research 2010; 35(9): 771-777. [3] Li DQ, Zhou N, Zhang L, et al. Invest Ophthalmol Vis Sci 2010; 51(11): 5623-5629.

Cyclosporine and MMP-9

MMP-9 expression was evaluated by immuno-histochemistry. The mean percentage of MMP-9 expression of the conjunctival epithelial cells was significantly decreased.

MMP-9 expression was evaluated semi-quantitatively by measuring cytoplasmic staining for MMP-9.



N=24 eyes of patients with thyroid orbitopathy-related dry eye

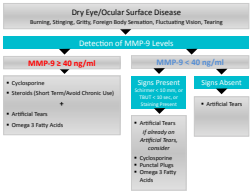
[1] Gumbi C, Sarac O, Genç, et al. Ocular surface and dry eye in Graves' disease. Curr Eye Res 2011; 36: 8-13.

Detecting Elevated Levels of MMP-9

Identifying elevated levels of MMP-9 facilitates better management of:

- Patients who present with signs or symptoms of dry eye
- Patients having ocular surgery such as LASIK or cataract surgery

Dry Eye/Ocular Surface Disease Patient Management



Ocular Surgery Complications

If elevated levels of MMP-9 are not tested and confirmed to identify and treat dry eye prior to ocular surgery, the following complications may occur:

- Less accurate pre-surgical measurements lead to worse visual acuity outcomes[1]
- Mild dry eye becomes severe dry eye[2]
- Asymptomatic dry eye becomes symptomatic chronic dry eye[2]
- Poor epithelial healing[3]
- Epithelial ingrowth[3]
- LASIK flap slippage[3]

[1] Trattler W, Goldberg D, Reilly C. Incidence of concomitant cataract and dry eye: prospective health assessment of cataract patients. Presentedat: World Cornea Congress; April 8,2010; Boston,MA. [2] Ambrosio R. J Refract Surg 2008; 24:396-407. [3] Fournie PR, Gordon GM, Dawson DG, et al. Arch Ophthalmol 2010; 128:426-434.

Clinician Benefits

Potential benefits of detecting elevated levels of MMP-9 and initiating treatment to optimize the ocular surface:

- Clinical advantage
  - Better outcomes
  - Reduced complications
  - Safer and better patient care
- Marketing advantage
  - Differentiates from competition
  - Optimal preoperative screening and perioperative management
- Economic advantage
  - Less complications
  - Less follow up/repeat visits for "unhappy" patients

ORA

Ocular Response Analyzer

Reichert, NY

Elasticity

Elasticity: The property of a substance that enables it to change its length, volume, or shape in direct response to a force, and to recover its original form upon the removal of the force.

Strain (deformation) is directly proportional to stress (applied force), independent of the length of time or the rate at which the force is applied.

Viscosity and Damping

Viscosity: Resistance of a fluid (liquid or gas) to a change in shape, or movement of neighboring portions relative to one another. The more viscous a fluid is, the more it resists flow.

Honey, for example, has a greater viscosity than water.

Resistance to an applied force depends primarily on the speed at which the force is applied.

Damping: restraining of vibratory motion, such as mechanical oscillations, by dissipation of energy. Viscous fluids or gasses are employed to accomplish this.

Visco-Elastic System

An Automotive "Strut" Assembly

- Coil Spring: Static Resistance (Elasticity)
- Shock Absorber: Viscous Resistance (Damping)

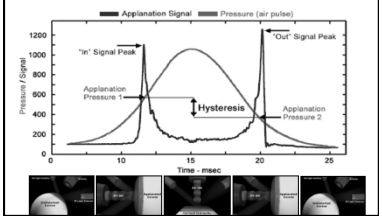
The Cornea is a Visco-Elastic System

Basic Parameters

ORA
- **IOP** - Goldmann Correlated IOP
- **IOP** - Corneal Compensated IOP
- **CH** - Corneal Hysteresis
- **CRF** - Corneal Resistance Factor

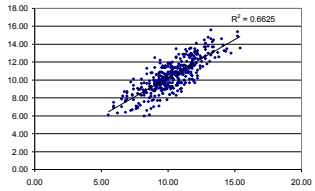
7CR Correlated IOP
IOP - Corneal Compensated IOP
- **IOPG** - Goldmann

Applanation Signal Plot

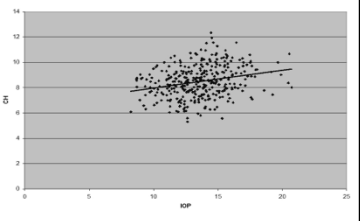


Corneal Hysteresis:
A New Ocular Parameter

Right/Left Eye Hysteresis

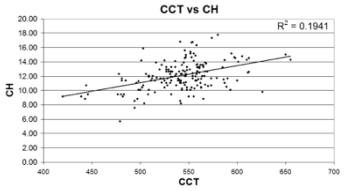


IOPG vs CH - 339 Normal Eyes



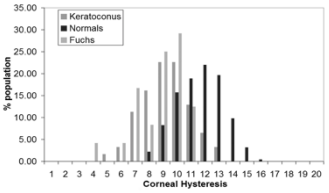
Data courtesy New England College of Optometry

CCT vs. CH - 184 normal eyes



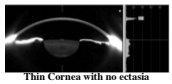
Data courtesy New England College of Optometry

CH in Corneal Pathologies



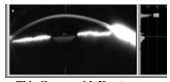
Data courtesy Shah, Brandt, Pepose, Castellano

CH in Corneal Pathologies



Thin Cornea with no ectasia

CCT 455
CH 11.2
CRF 10.8

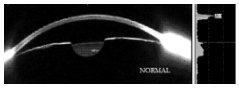


Thin Cornea with Keratoconus

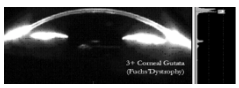
CCT 500
CH 8.1
CRF 7.9

Data courtesy Renato Ambrosio, MD - ASCRS 2006

CH in Corneal Pathologies



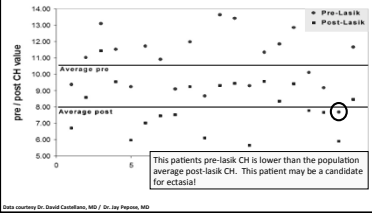
CCT 605
CH 11.3
CRF 10.7



CCT 597
CH 8.4
CRF 7.2

Data courtesy Renato Ambrosio, MD - ASCRS 2006

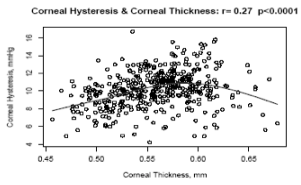
Pre / Post Lasik



Data courtesy Dr. David Castellano, MD / Dr. Jay Pepose, MD

The Cornea and IOP measurement

The problem with CCT-based IOP adjustment



Data courtesy Harry Quigley, Wilmer Eye Institute

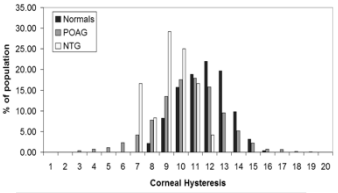
Why CCT-based IOP correction is flawed

Corneal Resistance to bending is not dependant thickness, but on material properties

Thick and thin is WRONG. Think weak and strong

CH and Glaucoma

CH distribution - Normals & Glaucoma



Glaucoma subjects have lower CH than normals, especially those who are still progressing in the disease.

Data courtesy New England College of Optometry and Mitsugu Shimmyo, MD

Thank you…..