Innovations in EyeCare

Paul M. Karpecki, OD, FAAO

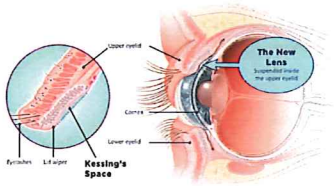
Medical Director, KEPLR Vision
Kentucky Eye Institute, Lexington KY
UPike KY College of Optometry
Chief Clinical Editor, Review of Optometry

Paul M. Karpecki, OD, FAAO
Financial Disclosures:

AI Optics
Aerie Pharmaceuticals
Akorn
Alcon Labs
Aldeyra
Allergan/Abbvie
Allysta pharmaceuticals
Amaros
Avellino Labs
Azura Pharmaceuticals
Bausch + Lomb
BioTissue
BlephEx
Bruder Healthcare
Bruno Vision Care
Cambium Pharma
Dompe
Eyedaptic
Eyedetec
Eyegate
Eyenovia
Eyevance
Gobiquity
Healthe
Hue.AI
iCare USA
Imprimis
Ivantis
Iveena
Jobson/Web MD
Johnson & Johnson Vision
Kala pharmaceuticals
KEPLR Vision
Konan Medical
Lacrisciences
LenTechs
Lombart/Marco
Maculogix
Mallinckrodt
Mitotech
Neurolens
Novaliq
Novartis
Oasis Medial
Oculus
OcuMedic
Ocuphire
Omega Ophthalmics
OcuSoft
Orasis
Osmotica
Oyster Point
Quark Pharmaceuticals
RegenerEyes
Reichert
Rendia
RxSight
Science Based Health
Sentiss Pharma
Sight Sciences
Silk Technologies
Sun Pharmaceuticals
Surface Biopharma
Tarsus Medical
TearClear
TearLab
TecLens
Visant Medical
Visionix
Vital Tears

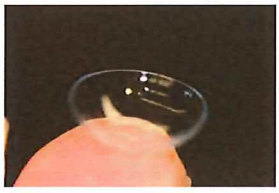
Contact Lens Technology: Suspended contact lens

- Recent advances in material, engineering knowledge, and manufacturing techniques allow for suspension of soft lenses
- Uses the anatomy of the upper lid as inspiration for a unique design feature that allows for suspension
- This feature along with other characteristics of the design allow for translational eye movement behind a rotationally stable lens
- From co-inventor Dr. Joe Barr: "The lens is designed to work like a translating gas permeable lens"
- A patented idea: 2 patents granted and 3 pending
  - Granted: USPTO #10,598,957
  - Granted: USPTO #10,191,302

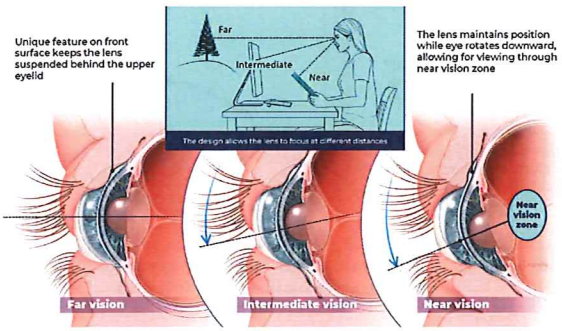


Apioc Lens Design

- Lid attached
- Rotationally stable
- 3+ mm of translation
- Comfortable lens design with multiple successful hours of wear



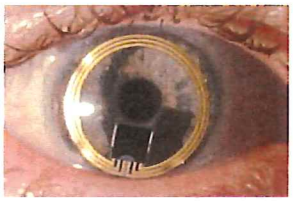
The MOA allows for Translational eye movement behind a rotationally stable lens



New lens standard parameters

- Distance Power
  - -12.00 to +6.00
- Add Power
  - Full range of add powers (+0.75 to +2.50)
- Astigmatism/Cylinder Powers
  - -0.25 to -2.50 DC
  - Axis 1 to 180°
- Easy to Fit
  - 2 base curve radii fit 98% of subjects in clinical trials (n=166)
  - No seg-height adjustment

Sensimed Triggerfish lens: Diurnal IOP measurements

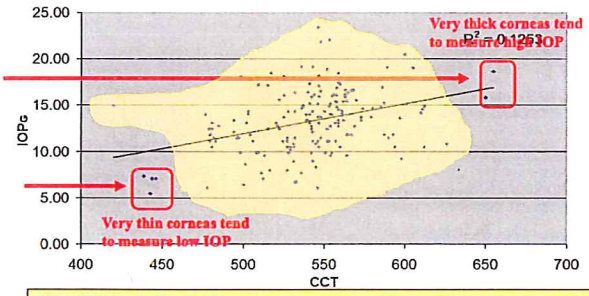


Corneal Biomechanics

Ocular Response Analyzer is the only instrument capable of measuring the biomechanical properties of the cornea

- CH is independently predictive of glaucoma visual field progression rate
- CH is predictive of response to IOP reduction medication
- CH facilitates the "corneal compensated" IOP (IOPcc): an IOP measurement that is less influenced by corneal properties than other tonometers, including Goldmann.
- This is superior to CCT-based adjustment formulas.

CCT based IOP adjustments are invalid

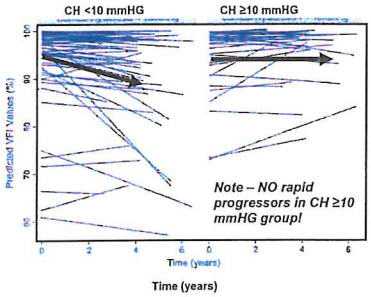


SCATTER in the data makes accurate mathematical "adjustment" of IOP impossible for individuals!

Data courtesy Shah, Brandt, Pepose, Castellano

Corneal Hysteresis in Glaucoma

Predictive of Progression in Prospective, Longitudinal Study (DIGS)



Time (years)

- Univariate model: each 1 mmHg decrease in CH was associated with a 0.25%/year increase in rate of VFI decline (*P*<0.001)
  - By comparison, each 1 mmHg higher baseline GAT IOP was associated with a 0.11%/year faster rate of VFI loss (*P*<0.001)
- In the multivariate model, CH was >3X more associated with rate of VF progression than CCT (17.4% vs 5.2%)
- The relationship between CH and IOP is complex:
  - For eyes with lower CH, the impact of IOP was significantly larger than in eyes with higher CH levels.

The prospective longitudinal design of this study supports the role of CH as an important factor to be considered in the assessment of risk for glaucoma progression

Medeiros FA et al. *Ophthalmology*. 2013;120:1533-1540

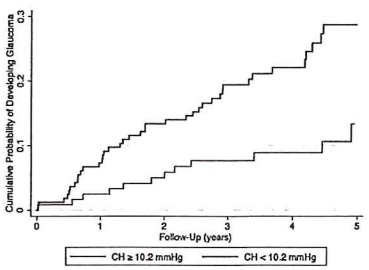
Corneal Hysteresis in Glaucoma

Predictive of conversion to Glaucoma in pre-perimetric Glaucoma Suspects

Purpose: To investigate the role of CH as a risk factor for <u>development</u> of glaucoma in a prospective longitudinal study.

Results: Fifty four (19%) of the 287 eyes developed repeatable visual field defects during a 4 year follow-up.

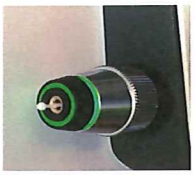
CH was *independently* predictive of conversion to glaucoma even when adjusted for age, IOP, and CCT.



Each 1mmHg lower CH was associated with an increase of 21% in the risk of developing glaucoma during follow up

A Prospective Longitudinal Study to Investigate Corneal Hysteresis as a Risk Factor for Predicting Development of Glaucoma
AJOPHT 10365 – in press
Author Block: Felin Zhu , Alberto DinizFilho, Linda M. Zangwill , Felipe A. Medeiros

Contact tonometer: Intelligent Positioning Assistant

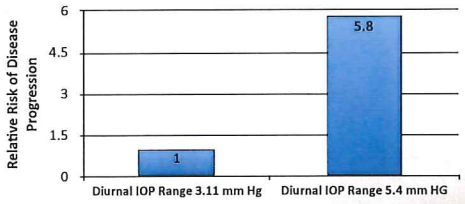


Green light on the probe base indicates correct vertical alignment

The probe should point perpendicularly to the center of the cornea (the reflection of the light ring is seen symmetrically inside the sphere of the pupil).

Red light on the probe base indicates incorrect vertical alignment of the tonometer.

Self-Monitoring Makes a Difference



Arsani S, Zeimer R, Wilensky J, et al. Large diurnal fluctuations in intraocular pressure are an independent risk factor in patients with glaucoma. *J Glaucoma*. 2000;9:134-142.

Corneal Modulation

- Contact lens reshaping technology after instillation of drops that can alter the cornea collagen structure
- Approved in Mexico and now working on US FDA approval

One subject's 8 month sings difference map. Upper left, section 1 shows a subject's before TVT topography image. Lower left, section 2 shows a subject e after image which is very similar. The difference between the two images becomes obvious only in the Instantaneous Difference map, seen in section 3 on the right side.

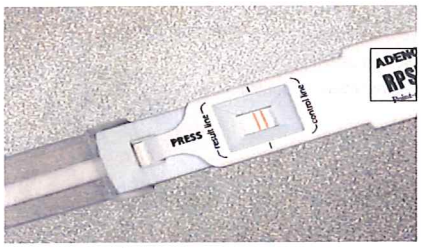
Point-of-Care Diagnostics

Quidel Adeno Plus Detector™

Reading & Interpreting the Results

Positive Results:

The ***Results Line and Control Line*** are **RED** in the result window, indicating that Adenovirus antigen ***is present***.

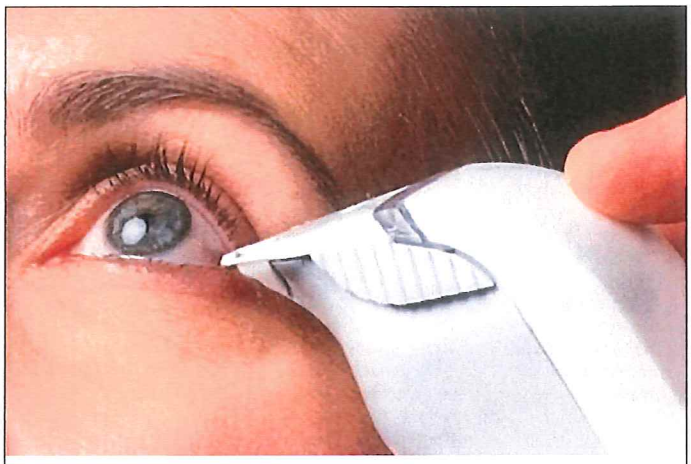


MMP-9

Reading & Interpreting the Results

Measures the presence of MMP-9 on the ocular surface
5 minute test
Point-of-Care
Measures 40 units and above
Positive or negative
Directs inflammation treatment

Osmolarity Reader & Pens



Tear Collection

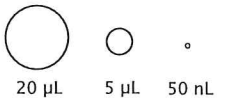
Osmolarity in the Diagnosis of Dry Eye Disease

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

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

Precision @ 50 nL

- < 2% coefficient of variation @ 50 nanoliters
  - Glucose ≥ 5.0% CV @ 5 microliters
  - Cholesterol > 4.0% CV @ 20 microliters

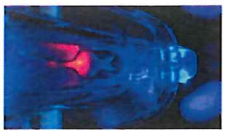


- Safe, simple collection
  - No reports of corneal or conjunctival trauma in 468 eyes [TearLab™ FDA 510(k) submission]
- Winner 2009 MDEA for In Vitro Diagnostics

Source: Kimberly MM et. al., Clinica Chimica Acta 364 (2006), Volles DF et. al. Pharmacotherapy 18:1 (1998).,

Future of Tear Biomarker Analysis:
TearLab Next Generation Platform

- Quantitative
- Ability to measure
  - Osmolarity
  - Inflammation biomarkers
  - Allergy biomarkers
  - Specific drug related biomarkers
- Rapid testing (< 2 minutes)
- Multiplexed biomarkers
- EHR Integration
- Clinical Application:
  - Normalization using osmolarity
  - Customized chips with designed sensitivity & specificity



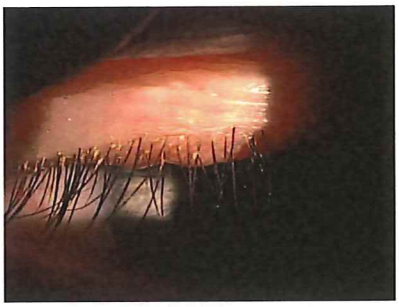
Next Generation Platform

- When?
  - 510k submission earlier this year
  - If approved would be Fall of 2021
    - First test will have osmolarity + 1 or 2 additional markers
    - Likely to be focused on inflammation
    - New iterations possible every 6 months

What's the first piece of equipment I need to purchase to create a dry eye clinic?

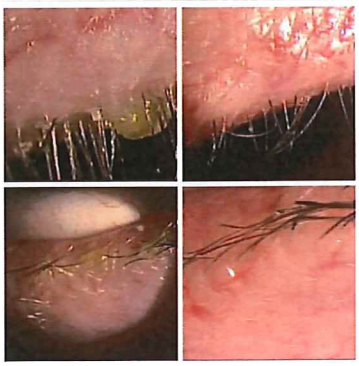
Slit Lamp Imaging System

25



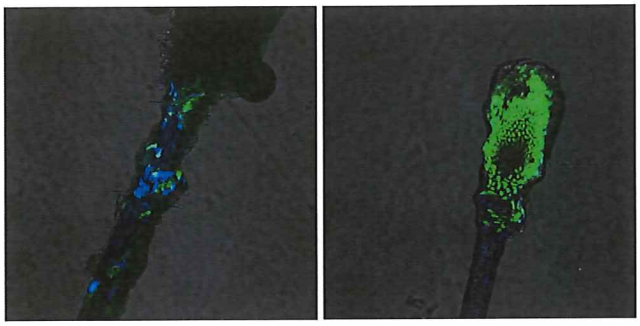
27

Blepharoexfoliation

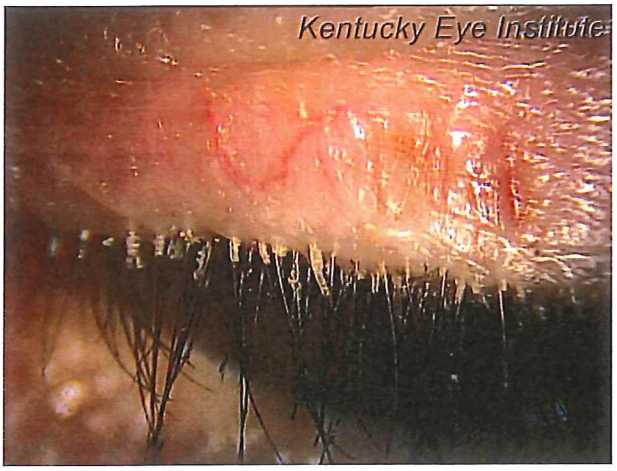


29

Bacterial Biofilm in Lash Follicles



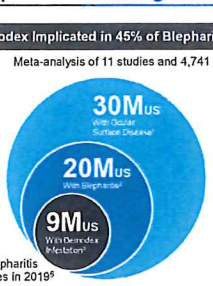
30



Blepharitis is a Large Unserved Market in Ophthalmology

Demodex Implicated in 45% of Blepharitis Cases[3]

Meta-analysis of 11 studies and 4,741 pts[3]



Blepharitis Routinely Causes	Eyelids to become red, irritated and itchy, with debris on the eyelashes[1]
Blepharitis Can Lead To	Blurring of vision, missing or misdirected eyelashes, and inflammation of other eye tissue, particularly the cornea[4]
Blepharitis and Surgery	60% of patients preparing to undergo cataract surgery have mild to moderate blepharitis[5]
Contact Lens Drop-out	#1 reason people discontinue contact lens wear is discomfort[5]
Prescription Treatment	None

Demodex is an Underlying Cause of Blepharitis and MGD

2 Species of Mites Contribute to Blepharitis

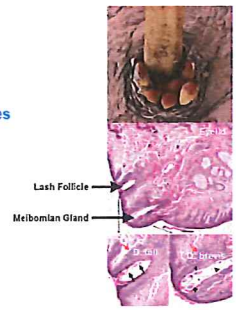
- *Demodex folliculorum*: eyelash follicles
- *Demodex brevis*: meibomian glands in eyelid

Demodex Implicated in 45% of Blepharitis Cases

- Meta-analysis of 11 studies and 4,741 pts[1]

Easily and Rapidly Diagnosed at Slit Lamp

- Cylindrical dandruff, or collarettes, are pathognomonic for *Demodex*[3]

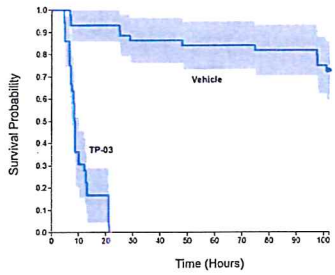


TP-03 is a Novel Drug to Treat Demodex Blepharitis by Eradicating Mites and Collarettes

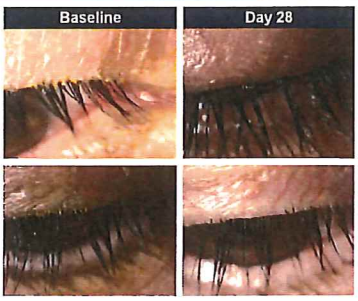
Product Form	Multi-dose eye drop solution bottle, preserved
Indication for Use	Treatment of Demodex Blepharitis
MOA	Paralysis and death of Demodex mites
Diagnosis	Collarettes on slit lamp examination
Dosing	BID for 6 weeks
Efficacy	Collarette cure, mite eradication, other secondary endpoints
Safety	Very clean to-date (mild transient stinging in < 10% of patients)

Mercury Study: TP-03 Works by Killing Mites

Ex-vivo mites extracted from the lashes of blepharitis patients

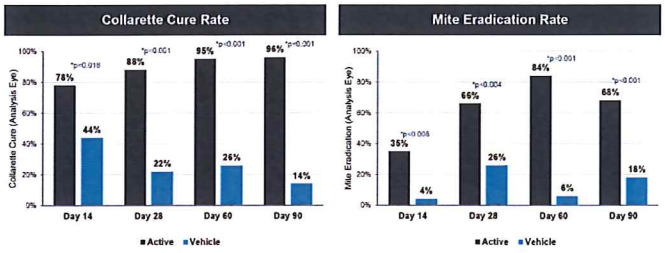


Cure of Collarettes with BID use of TP-03

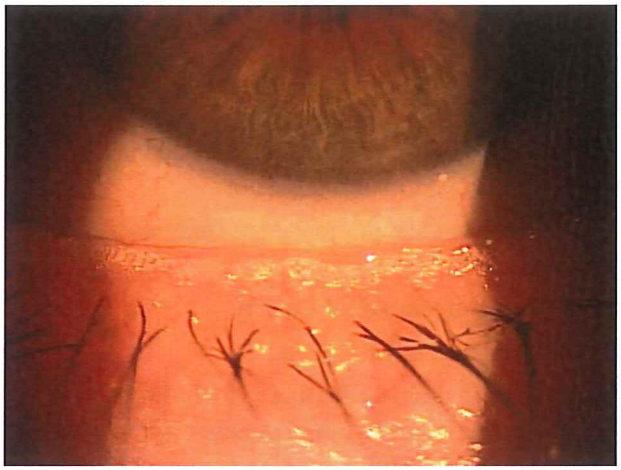


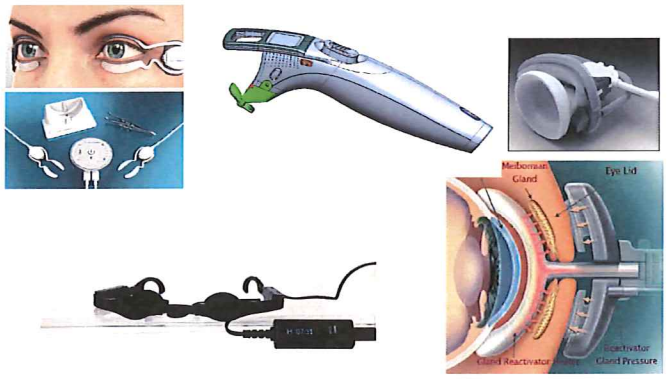
Jupiter Phase 2b Study:
High Collarette Cure Rate and Mite Eradication Rate

FDA-requested primary and secondary endpoints



37





IPL and LLLT

- Intense Pulsed Light Therapy/Low Level Light Therapy
- Clear association between DED and lid margin inflammatory disease
- Widely accepted as a treatment for dermatological rosacea
- More than 80% of patients with rosacea have MGD
- 20% have ocular signs first

40

IPL/LLLT

1. MGD/EDED
2. DEMODEX
3. Ocular Rosacea
4. CHALAZION
5. HORDEOLUM

TREATMENT: Demodex

IT CONSISTS OF A PHASE 1 (WITH A SPECIFIC BLUE LIGHT MASK) AND A PHASE 2 (WITH THE STANDARD SUPPLIED RED LIGHT MASK)

PHASE 1 – BLUE MASK

Blue light stimulates porphyrins and creates an anti-bacterial action.

PHASE 2 – RED MASK

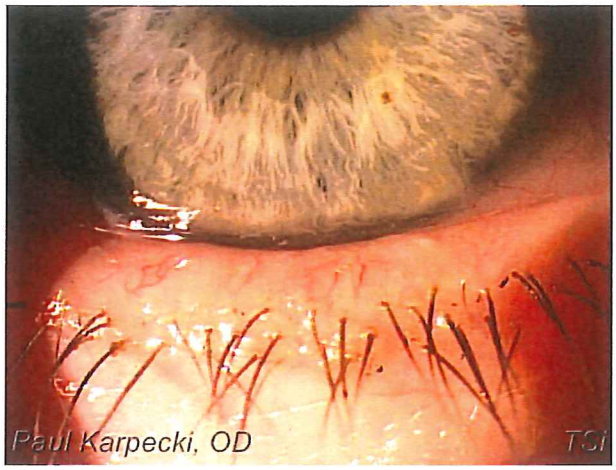
Red light stimulates ATP by increasing and improving cellular activity, it reduces inflammation and oedema and works on Meibomian glands.

72

IPL and LLLT

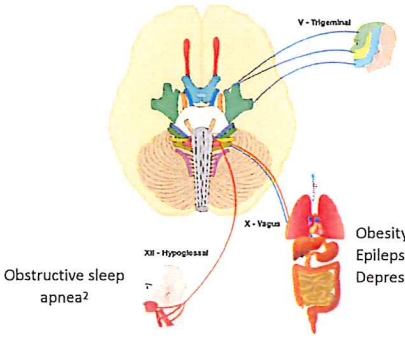
- Telangiectatic vessels and skin erythema release inflammatory mediators
- IPL targets the abnormal erythematous blood vessels
- Affects mitochondrial activity
- Temperature effect on glands?
- Photomodulation affecting cytochrome C or activating fibroblasts and collagen synthesis

43



CRANIAL NERVE STIMULATION

TARGETING NUMEROUS DISEASE CONDITIONS



Migraine prevention[1]

Obesity[3]
Epilepsy[4]
Depression[4]

Obstructive sleep apnea[2]

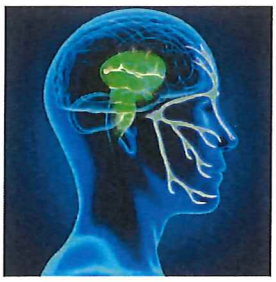
Image adopted from Netters.[5]

1. Zhu and Marmura. *Curr Neurol Neurosci Rep.* 2016; 2. FDA website. Accessed 2016; 3. FDA website. Accessed 2016; 4. FDA website. Accessed 2016.

TRIGEMINAL NERVE (CN V)

BRANCHES AND FUNCTION

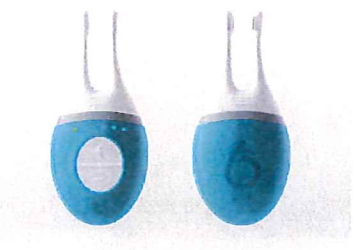
- Largest cranial nerve (CN V) with 3 divisions[1,2]
  - Ophthalmic nerve (V1)
  - Maxillary nerve (V2)
  - Mandibular nerve (V3)
- Ophthalmic nerve (V1) comprises 3 branches[1,3]
  - Lacrimal nerve
  - Nasociliary nerve
  - Frontal nerve
- Ophthalmic nerve innervates the lacrimal functional unit (LFU), including[4-6]:
  - Lacrimal gland
  - Meibomian glands
  - Goblet cells



1. Tewfik. Medscape website. Accessed 2016; 2. Morton et al. In: Morton et al, eds. *The Big Picture: Gross Anatomy.* 2011. Accessed 2016; 3. Waxman. In: Waxman SG. eds. *Clinical Neuroanatomy.* 2013. Accessed 2016. 4. Kossler et al. *Ophthal Plast Reconstr Surg.* 2015; 5. Beuerman et al. In: Pflugfelder et al, eds. *Dry Eye and Ocular Surface Disorders.* 2004; 6. Dartt. *Ocul Surf.* 2004.

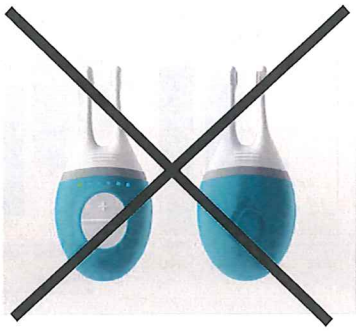
Neurostimulation Technology

- Tear stimulant for aqueous deficient dry eye
- Inserted in nasal canal
- Wireless stimuli to create tears



48

DISCONTINUED



49

A NOVEL NEUROSTIMULATION APPROACH WITH SONIC ENERGY

Drug free, home use, fast onset of action with sustained effect

Handheld, battery powered device with no disposable component

Externally applied

Doctor prescribed, 15s Training

** Investigational Device, Not FDA Cleared

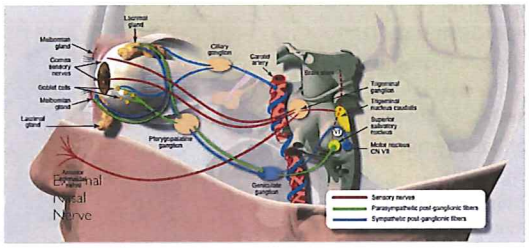
50

TAKEAWAYS FROM TRIALS

- Array of positive endpoints reflects broad mechanism of action of neuromodulation
- Effective for aqueous tear deficiency and meibomian gland disease
- Acute, sub acute, and chronic benefits to the ocular surface
- Outstanding safety profile
- High value product for dry eye

51

ACTIVATES CENTRAL REFLEX WHICH RESULTS IN ACTIVATION OF LACRIMAL FUNCTIONAL UNIT



52

OC-01/OC-02 for the Treatment of Signs and Symptoms of Dry Eye Disease (DED) Administered Via a Nasal Spray

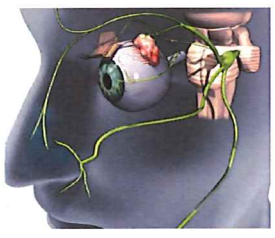
- OC-01 and OC-02 are being developed to directly address loss of tear film homeostasis in DED and are delivered as a nasal spray.
- Drug candidates bind to nicotinic acetylcholine receptors (nAChRs), which are located on the trigeminal nerve accessible within the nasal cavity, to stimulate tear film production.
- Trigeminal parasympathetic pathway is well characterized with nerves that innervate the lacrimal functional unit (LFU) including cornea, conjunctiva, accessory lacrimal glands, meibomian glands, and goblet cells[1,2,3]

53 ©2018 Oyster Point Pharma, Inc.

1van der Werf, F. R. A. N. S., Baljet, B., Prins, M. A. A. R. T. E. N., & Otto, J. A. (1996). Innervation of the lacrimal gland in the cynomolgous monkey: a retrograde tracing study. Journal of anatomy, 188(Pt 3), 591.
2LeDoux, M. S., Zhou, Q., Murphy, R. B., Greene, M. L., & Ryan, P. (2001). Parasympathetic innervation of the meibomian glands in rats. Investigative ophthalmology & visual science, 42(11), 2434-2441.
3Dartt, D. A., Mccarthy, D. M., Mercer, H. J., Kessler, T. L., Chung, E. H., & Zieske, J. D. (1995). Localization of nerves adjacent to goblet cells in rat conjunctiva. Current eye research, 14(11), 993-1000.

Trigeminal-Parasympathetic Pathway & DED

- The parasympathetic nervous system (PNS) controls tear film homeostasis
  - 34% of basal tear production is due to inhaled air through the nasal passage[1]
- Efferent parasympathetic nerves innervate the lacrimal functional unit (LFU) including cornea, conjunctiva, accessory lacrimal glands, meibomian glands, and goblet cells[2,3,4]
- Intervention @ the trigeminal-parasympathetic pathway represents a novel approach to producing complete tear film in patients with Dry Eye Disease (DED)

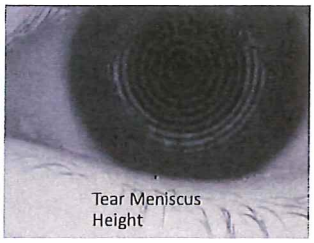


54 ©2018 Oyster Point Pharma, Inc.

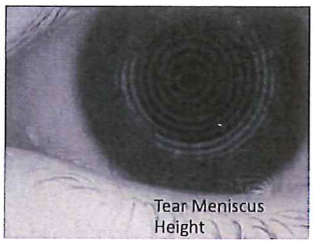
1Gupta A, Heigle T, Pflugfelder SC. Nasolacrimal stimulation of aqueous tear production. Cornea. 1997 Nov;16(6):645–8.
2van der Werf, F. R. A. N. S., Baljet, B., Prins, M. A. A. R. T. E. N., & Otto, J. A. (1996). Innervation of the lacrimal gland in the cynomolgous monkey: a retrograde tracing study. Journal of anatomy, 188(Pt 3), 591.
3LeDoux, M. S., Zhou, Q., Murphy, R. B., Greene, M. L., & Ryan, P. (2001). Parasympathetic innervation of the meibomian glands in rats. Investigative ophthalmology & visual science, 42(11), 2434-2441.
4Dartt, D. A., Mccarthy, D. M., Mercer, H. J., Kessler, T. L., Chung, E. H., & Zieske, J. D. (1995). Localization of nerves adjacent to goblet cells in rat conjunctiva. Current eye research, 14(11), 993-1000.

Before and 15 seconds After Administration of OC-02 Nasal Spray

OC-02 Before Administration



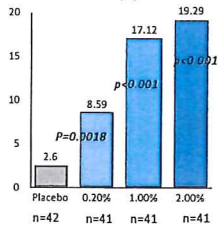
OC-02 15 Seconds After Administration



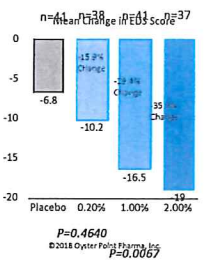
55

OC-02 Phase 2b Results Demonstrate Significant Improvement in Both Signs and Symptoms of Dry Eye and Clear Dose Response

Mean Change in Schirmer's Score (N=165)



Mean Change in Eye Dryness Score (N=165)

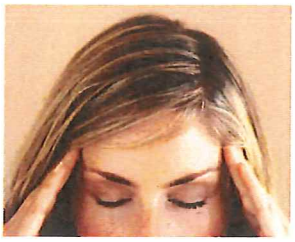


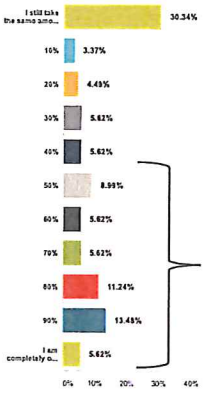
56

- OC-02 was well-tolerated with no ocular adverse events or drug-related serious adverse events.
- The most common adverse events were typical of nasal sprays and included cough, sneezing, and nose and throat irritation.
- These events were predominantly mild, transient and self-limiting.

Trigeminal Dysphoria

- Symptoms
  - Primary Symptoms
    - Frequent Headaches
      - 3+ days per week
    - Neck Pain/Stiffness
  - Secondary Symptoms
    - Dry eyes
    - Fatigue with near work
    - Photophobia, especially at night
      - headlights





70% off of at least some medications at 90 days

52% of patients off of 50% or more of their headache medications

No reported side effects

58

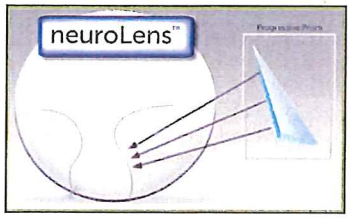
Research confirmed

- Pursuits and Saccadic eye movements
  - Sends it proprioceptive signal via the trigeminal nerve
    - Ophthalmic branch
- Trigeminal Nerve (V) :
  - Stimulation of Ophthalmic branch
    - Frontal headaches (sinus headaches)
    - Terminates in lower brain stem (back of head headaches /neck pain)
    - Cornea sensation (Dry Eye)

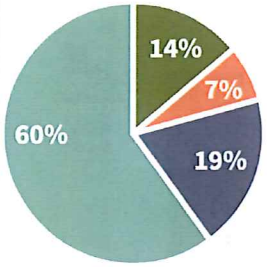
59

The Solution: Contoured Prism

- Synchronizes binocular vision at all distances, eliminating need for compensating eye movements.
- Progressive prism technology, using measurements from SightSync
- Built into spectacle lenses with patient's Rx



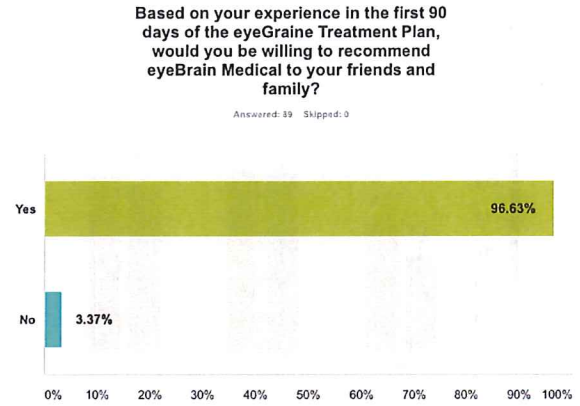
60



Patient-reported symptom reduction with neuroLenses:

- Basically gone
- Decreased substantially
- Decreased slightly
- No change
- Increased

n = 279



n = 89

Punctal Occlusion

- May wait on punctal occlusion if have:
  - Allergies
  - Severe MGD
  - Significant blepharitis
  - Inflammatory dry eye?
- Treat those conditions first then plug
- Ideal FIRST treatment option for:
  - Neurotrophic keratopathy
  - Post-LASIK dry eye
  - Lagophthalmos

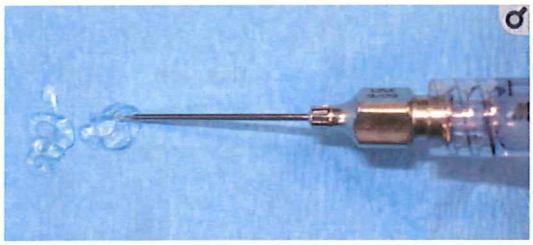
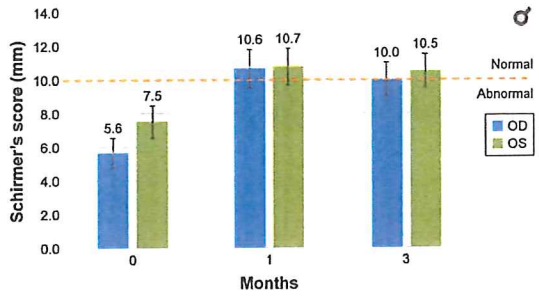
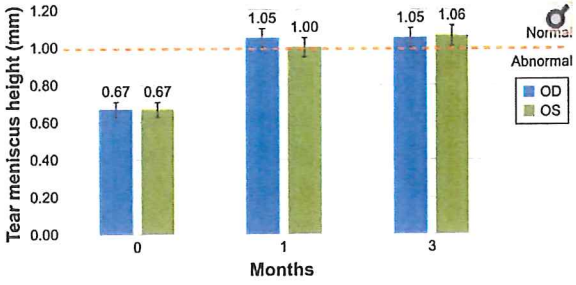


Figure 4

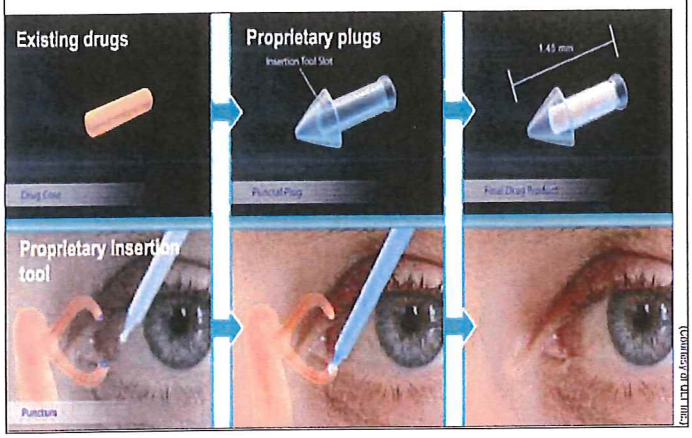


67



68

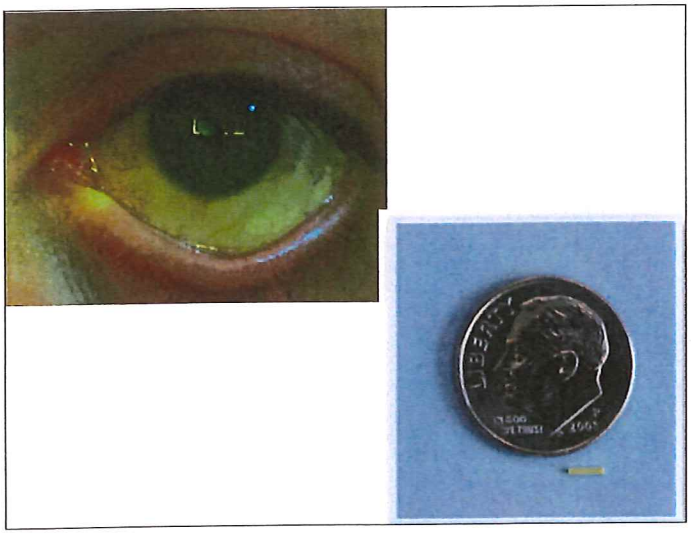
Drug Delivery Advances

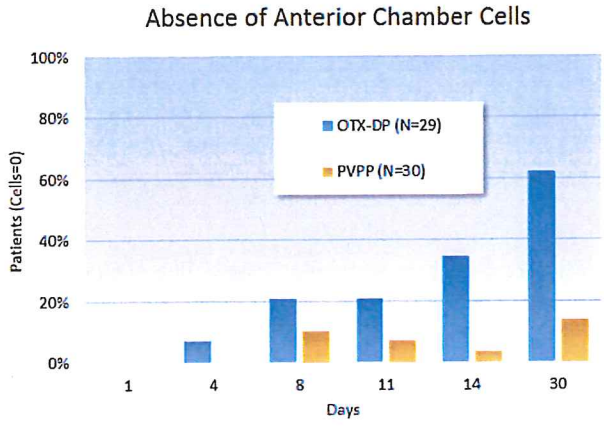


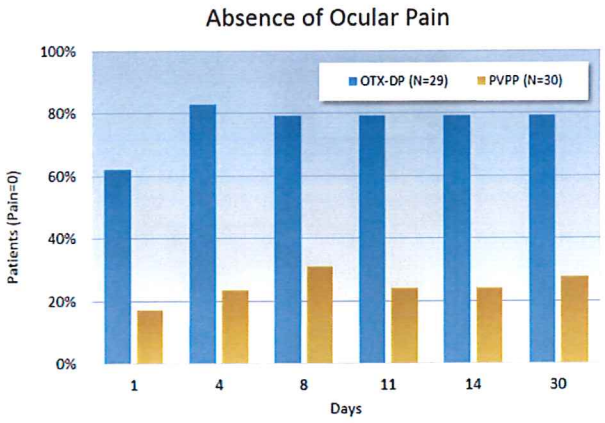
Punctal Plug Drug Deliver

- Dextenza post cataract
- Dextenza for allergic conjunctivitis
- Sustained release Travoprost
- Dry eye therapy via a punctal plug

70





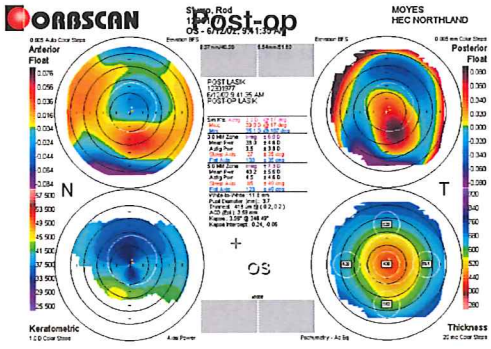


Phase III Punctal Plug Drug Deliver

- Evolute
- 94% retention rates in clinical study
- Statistical improvement in inflammation and pain following cataract surgery with only an NSAID within the plug

Collagen Cross Linking (CXL)

Ectasia Diagnosis and Management



Corneal Cross-Linking

- First introduced by Theo Seiler MD
- Involves saturating the cornea with riboflavin (Vit B2)
- Expose cornea to UV light (370 nm) for 30 minutes
- Riboflavin absorbs UV light and produces singlet oxygen
- Causes cross-linking of collagen fibers and extracellular matrix proteins
- To protect the endothelium:
  - Soak cornea for 30 minutes prior
  - Originally required debridement of corneal epithelium
  - Ensure riboflavin has penetrated to the AC

Corneal Cross-Linking

- Riboflavin prevents penetration of uv light
- Older corneas vs. younger corneas and progression of keratoconus
- CXL appears to be the first technology than can halt the progression of ectasia

Corneal Cross-Linking

79

36

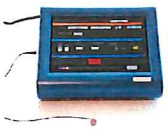
Other potential applications

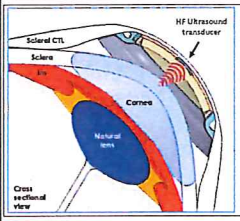
- Physician sponsored IND for infectious keratitis treatment
  - Ulcers limited to 250 microns
  - May also help with infectious load
- Treatment of corneal edema
  - Cross linking reduces imbibition pressure
  - Internationally it appears to work for 3 mo to 12 mo duration
- Treatment for fluctuating vision post RK

On-Eye Crosslinking: Comfort and Control

Scleral CTL with fiber optic UV delivery

- Eyes open/closed for comfort
- Eliminates motion challenges
- Customized treatment
- Small touchscreen control





Closed-loop ultrasound elastography feedback control

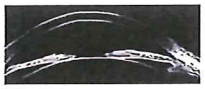
- Accurately measure pre-treatment corneal biomechanics
- CXL induced tissue changes monitored in real time
- UV transparent fluid interface provides acoustic medium and oxygen supply

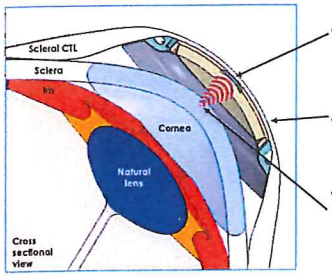
82

Ultrasonic Dosimetry (Patents Pending)

Accurate dosing of the UV requires monitoring corneal changes during the treatment

- The cornea is an ideal tissue to query with ultrasound
- Only CXLens' on-eye delivery of UV enables real time ultrasonic dosimetry





- CXLens® UV delivery system design includes a high frequency (HF) ultrasonic transducer within the optical diffuser
- Positional stability of scleral lens enables precise acoustic measurement of ophthalmic structures
- Doppler capability allows assessment of stiffness of corneal membrane

83

TECLens Approach to Vision Correction

CXLens® - Crosslinking Lens

- CXLens® is single use ultraviolet energy delivery and ultrasound monitoring system built into a scleral contact lens.
- Placed directly on the eye, this next generation CCXL technology enables a multitude of superior capabilities and advantages.

84

CXLens® Non-Surgical Vision Correction

Myopia
- Crosslink the center of the cornea to stiffen (and thus flatten) the central region

Hyperopia
- Create annular crosslinked region to flatten periphery and steepen center

Astigmatism
- Create a custom 'butterfly' pattern to flatten areas that are aspherically too steep

Drug Therapy for keratoconus

- Topical treatment
- Phase IIb trials were positive with >1.8D improvement
- Entering phase III clinical studies
- MOA: Upregulates lysyl oxidase (LOX) and induces corneal crosslinking pharmacologically

DALK-Deep Anterior Lamellar Keratoplasty

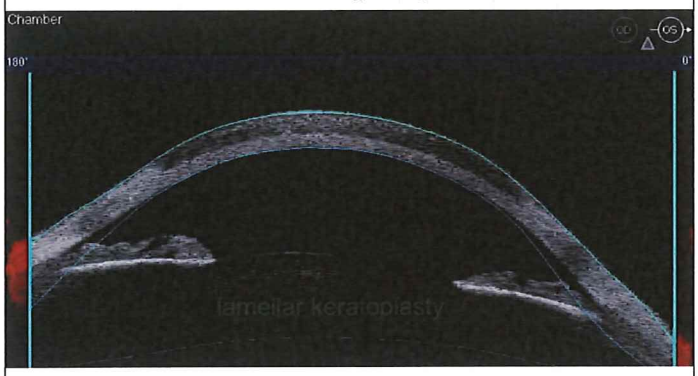


image courtesy of Dr. L. Buratto

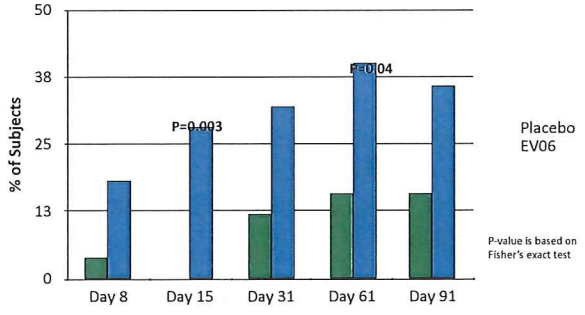
Presbyopia Correction

- Accommodating IOLs
- Multifocal/EDOF/Trifocal IOLs
- Corneal Inlay Technology
- Scleral expansion
- Pharmaceutical agents/eye drops

Topical Treatment for Presbyopia

- Pupil Modulating Therapies
  - Contains miotics but also proprietary components that allow full 12-14 hours of near and far vision
- Lens Softening
  - Contains drops that selectively target and disrupt the disulfide bonds in the lens
  - Total of 3-4 weeks of treatment and permanent results thus far

Percent of Subjects with Gain of ≥10 Letters in DCNVA

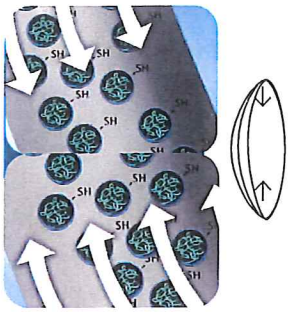


DCNVA=Distance-corrected near visual acuity

Note: Preliminary analysis based on LOCF in study eye only

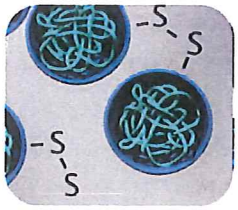
How Is Accommodation Lost?
Why Does Presbyopia Happen?

Young Eye



Cytosol Displacement Centrally = Accommodation

Aging Eye



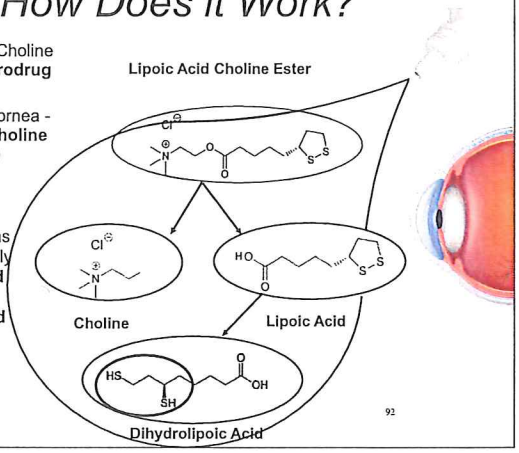
Oxidation induced disulfide bonds form between crystalline proteins - a Leading Potential Cause

Lens Stiffening = Compromised Accommodation

91

What is EV06?
How Does it Work?

- EV06 (Lipoic Acid Choline Ester, 1.5%) is a **prodrug**
- EV06 penetrates cornea - metabolized into **Choline & Lipoic Acid**, two naturally occurring substances
- Enzymes within lens fiber cells chemically reduce **Lipoic Acid** to active form **Dihydrolipoic Acid**

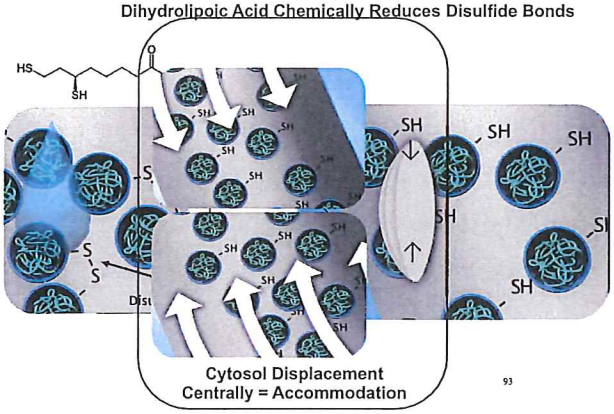


92

LENS ELASTICITY IS REGAINED

Dihydrolipoic Acid

Dihydrolipoic Acid Chemically Reduces Disulfide Bonds



Cytosol Displacement Centrally = Accommodation

93

EV06 Safety & Tolerance Results

- No Subjects Discontinued For Adverse Events, Safety Concerns, or Tolerability
- No Sight Related Adverse Events
- Upon Instillation
  - Mean EV06 Comfort Rating 3.0
  - Mean Placebo Comfort Rating 2.7
    - (Scale 0 – 10; "0" = Very Comfortable)
- No Change In Best Corrected Distance Visual Acuity

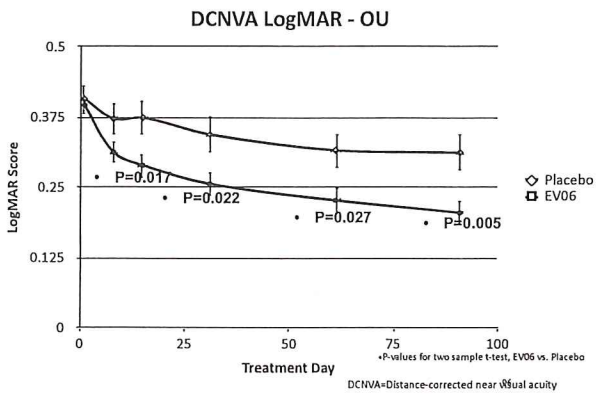
94

EV06 Efficacy Results

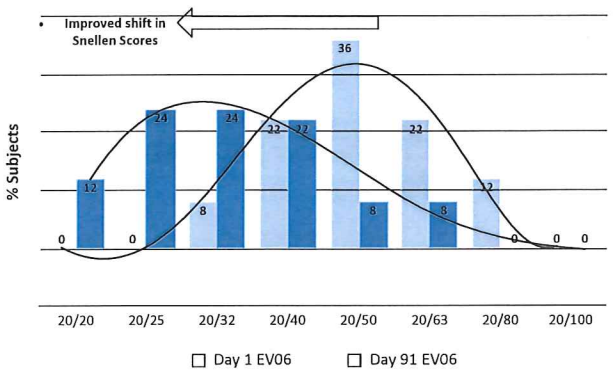
- Achieved both Primary Efficacy Results:
  - Improvement in Distance Corrected Near Vision Acuity (DCNVA) in the Study Eye after treatment, which continued throughout the dosing period
  - Higher proportion of subjects with gain of ≥10 letters in DCNVA in the study eye vs. placebo

95

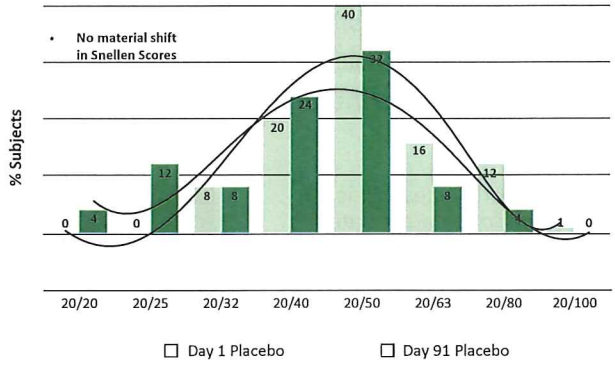
Improvement in Distance Corrected Near Vision Acuity



- **EV06 DCNVA Snellen score - Day 1 & Day 91**



- **Placebo DCNVA Snellen score - Day 1 & Day 91**



Future presbyopia drops: miotics

Orasis Pupil Modulation Eye Drop Solution

Demonstrated Efficacy, Safety and Comfort in Phase 2b Studies

LOW CONCENTRATION PILOCARPINE

+

PROPRIETARY MULTI-FACETED VEHICLE

- ✓Exceptional near visual acuity
- ✓No reduction of distance vision & night vision
- ✓High safety and tolerability profile
- ✓Improved comfort

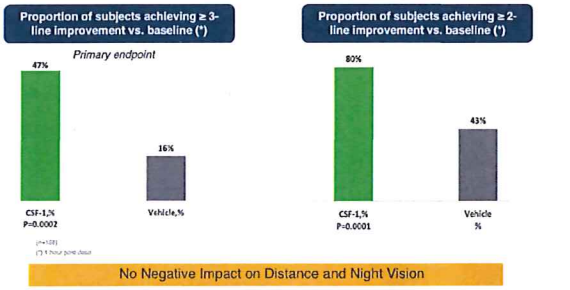
Phase 2b Study Design

- Parallel-group study (active, vehicle)
- Primary endpoint: 3-line improvement in near visual acuity
- Secondary endpoints: 2-line improvement (near); impact on distance and night vision, various safety and tolerability endpoints

166 subjects

- BID Administration
- Duration – 2 weeks
- Assessments – end of week 1 and end of week 2

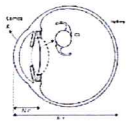
Phase 2b demonstrated Efficacy, Safety & Comfort



Cataract Surgery Outcomes

Challenge to consistently achieve great results

- 2016 toric meta-analysis[1]: ~65% of eyes achieve 20/25 or better
- Limited by ability to predict the post-operative eye



Error Source	Contribution*
Post-op IOL Position	35%
Post-Op Corneal Power	15%
Axial Length	17%

1. Line Kessel, MD, PhD, Et Al. Toric Intraocular Lenses in the Correction of Astigmatism During Cataract Surgery – A Systematic Review and Meta-Analysis Ophthalmology, 2016 Feb;123(2): 275-86

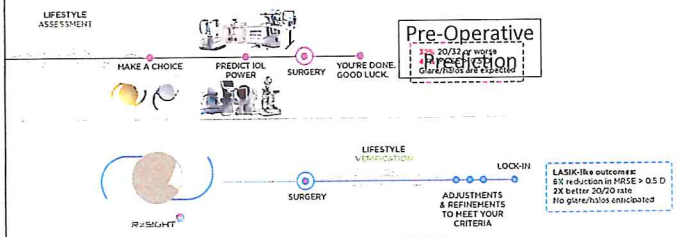
* Norrby, S. Sources of error in intraocular lens power calculation. J Cat Ref Surg 2008: 368-76

Post-Op is the New Pre-Op!

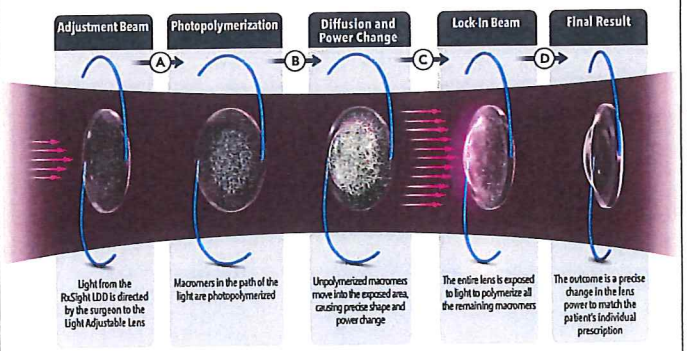
The RxLAL is the world's first adjustable intraocular lens that allows office-based optimization of vision after lens implantation and healing

- Delivers world's best clinical outcomes for cataract patients
- Overcomes limitations of both pre-operative and intra-operative prediction processes
- Premium channel driver
- Private pay

A Better Way to Deliver Premium Cataract Surgery



Post-Operative Adjustment



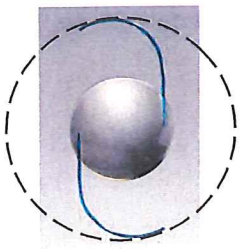
How It Works

Standard Cataract Implant Procedure	~~Residual Refractive Error is~~ Determined Using Standard Phoropter	Refractive Error is Entered into Light Delivery Device
• Low Stress Cataract Surgery • Not dependent on prediction of SIA, ELP, Individual Healing, Surgical Technique, Sophisticated Equipment	• Interactive Post-Op Process • Refraction optimized with patient after healing is complete and ocular media clear	• Office Based Refractive Treatment on IOL • Unparalleled flexibility and accuracy • Bifurcated cataract and refractive procedure

RxLAL

OPTIC BODY

- Photo-reactive UV absorbing Silicone
- Biconvex
- Anterior surface – rounded edge
- Posterior surface – squared edge
- 6mm diameter



HAPTICS

- Blue core polymethylmethacrylate (PMMA) Monofilament
- Modified 'C'
- Haptic angle – 10º
- 13mm - RxLAL Total Diameter

Light Delivery Device (LDD)

The RxSight LDD consists of the following components:

- Anterior segment biomicroscope
- Patient Chin and headrest
- Computer system for planning and performing light treatments
- Ultraviolet (UV) light projection system

UV Protective Glasses

At the end of surgery RxLAL Patients are provided with UV Protective glasses to help protect the RxLAL from sources of UV light

- The patient may discontinue wear of the UV protective glasses 24 hours after the final light treatment has been completed
- Exposure to UV light, such as sunlight, can cause uncontrolled changes to the RxLAL

US FDA Study Results

- RxLAL eyes achieved UCVA of **20/20 or better** at 6 months postoperatively at approximately **2x the rate** of patients receiving a monofocal lens
- **91.8% of RxLAL eyes achieved result within 0.50 D** of target MRSE (similar to LASIK results)
- **Superior Quality of Vision** at all measures compared to control lens:
  - Including BCVA, Vision Rating, Driving Difficulty, Dim Light Conditions, Glare, Halos, and all measures of Contrast Sensitivity

U.S. FDA Clinical Study
Prospective Randomized Study
N=391 (eyes) RxLAL; N=193 (eyes) Control Monofocal
17 U.S. Sites
Phaco and Implantation of RxLAL -Correction of +/- 2 D sphere & 0.75-2.0 D cylinder
6 Month Outcomes

Capsulotomy System Consists of:

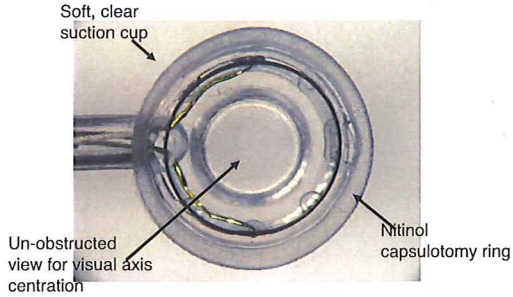
Disposable Handpiece

Capsulotomy Tip

Control Console

111

Capsulotomy Tip



112

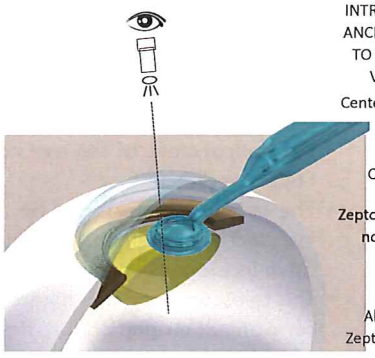
Operating Principles

- Suction pulls capsule against capsulotomy ring
- Electrical energy applied to ring for 4 milliseconds
- Phase transition of water molecules

↓

Precision Pulse Capsulotomy

113



ZEPTO INTRAOPERATIVELY ANCHORS SURGERY TO THE PATIENTS VISUAL AXIS

Center Zepto on P1*

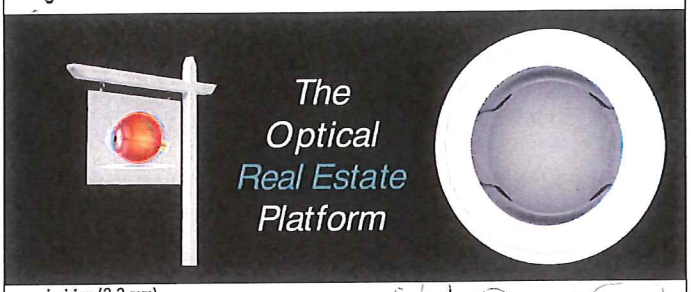
Create capsulotomy

Zepto capsulotomy is now reference marker

Align IOL with Zepto capsulotomy

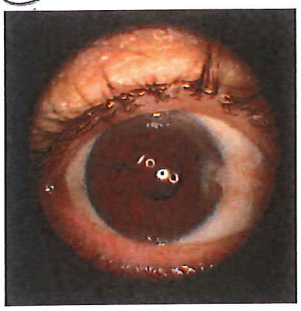
114

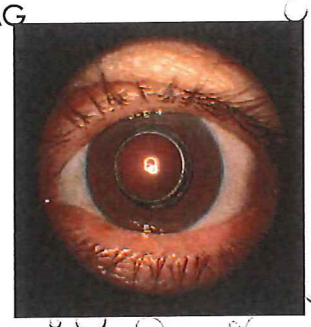
THE BENEFITS OF THE 3D CAPSULE



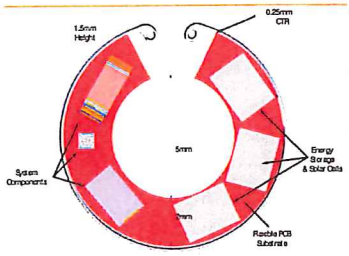
incision (2.2 mm)

18 MONTHS POST IMPLANTATION-NO YAG



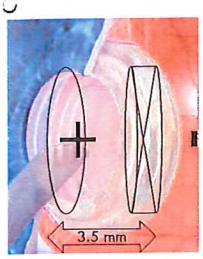


THE WIRELESS PRESSURE SENSOR



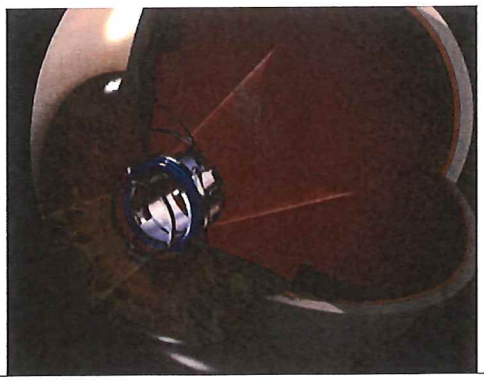
- Designed to fit within the central slot of the prosthetic capsule
- Communicates through tissue up to to a peripheral device
- Measures IOP 4 times/ hour without intervention
- Easily removed if needed
- Central 5mm is an open aperture

LOW VISION INTRAOCULAR TELESCOPE ASSEMBLY

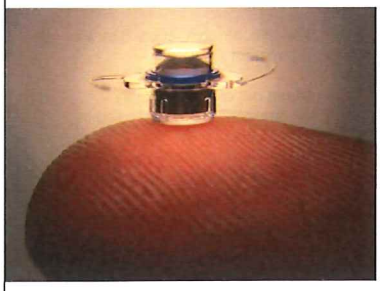


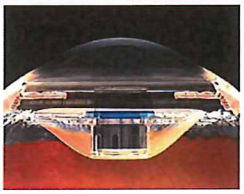
- Not all AMD patients had significant disease at the time of cataract surgery
- A platform for modification of the optical state of the eye has huge benefits
- The assembled parts can be inserted through traditional sub 3mm incisions.
- The telescope can be "tuned" for optimal magnification, field of view and prismatic offset.

Telescopic IOL for Advanced AMD



Telescopic IOL for Advanced AMD





Implantable Miniature Telescopess

- Renders retinal image ~2.7x larger than natural lens
  - Images seen upon viable perimacular tissue
  - Field of view 20-24 degrees
- 67% achieve >/= 3 lines of improved VA (control = 13% - worse seeing eye for treatment eye)*
- Improved ADL's and Vision-Targeted Psychosocial Domains*

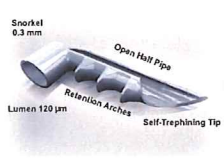
*Hudson H. A team approach helps severely visually impaired AMD patients. Optimal Management. 2012; 52-54.

MIGS

MIGS

MIGS

iStent is the smallest medical device known to be implanted in the human body and weighs just 60 µg



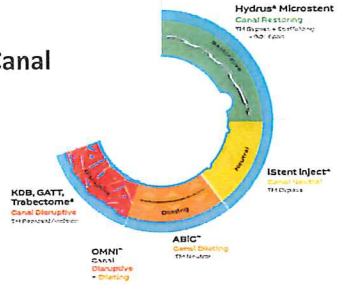
MIGS

***i*Stent® is designed to be used in conjunction with cataract surgery to safely and effectively reduce IOP while facilitating the eye's natural outflow in mild to moderate OAG patients currently on hypotensive medication**

- Lowers IOP and may reduce or eliminate medication burden[1]
- Decrease risk of IOP fluctuations associated with non-adherence to prescription medication regimens
- Avoid serious complications associated with end-stage filtration and shunt procedures
- Spare the conjunctiva and safely preserve future treatment options
- Minimizes risks of hypotony and bleb related complications

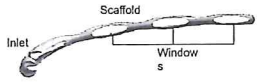
Current MIGS Mechanisms to Enhance Conventional Outflow

From Tissue Disruption to Canal Restoration



The Hydrus Microstent

VIEW FROM ANTERIOR CHAMBER

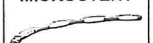


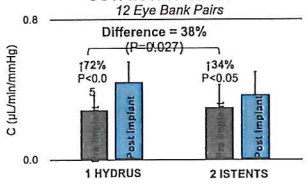
VIEW FROM CANAL

- Flexible, biocompatible 8 mm length microstent
- Made out of nitinol (highly biocompatible material used in cardiovascular stents)
- Contoured to match canal curvature
- Three open windows face anterior chamber
- The canal-facing surface is completely open for unobstructed collector channel access

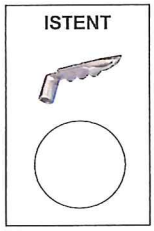
Outflow Comparison: Hydrus and Two iStents

HYDRUS MICROSTENT





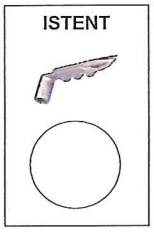
ISTENT

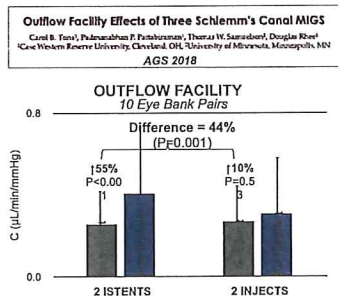


*Hunter et al, Clinical Ophthalmology 2014;8:495-506

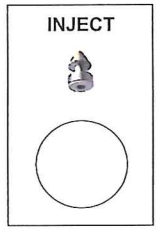
Outflow Comparison: Two iStents and Inject

ISTENT





INJECT



*Hunter et al, Clinical Ophthalmology 2014;8:495-506

HORIZON Clinical Trial

4-Year Results

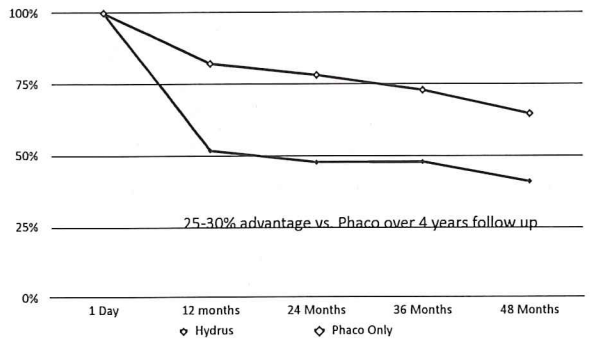
HORIZON 3 – 5 Year Follow up

- HORIZON is unique: only MIGS study with 5 year continuous follow-up
  - 83% follow-up at 4 years
- Primary endpoint assessment was based on washed out IOP… wash out was discontinued after 24 months for practical reasons
- Long term effectiveness based on:
  - Medication free
  - Failure rates (progression to surgery)
  - Safety findings (vision, ECD, and adverse events)

Medication Free

Durable effect through 4 Years

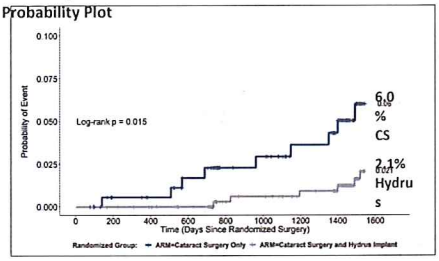
% Patients Remaining Medication Free After Preop Wash Out



133

Key Finding: Reduced Risk of Reoperation

4-Year Kaplan Meier Cumulative Incisional Glaucoma Surgery Probability Plot



Incisional Glaucoma Surgery:

- Trabeculectomy,
- Tube shunt,
- Cilioablative procedure

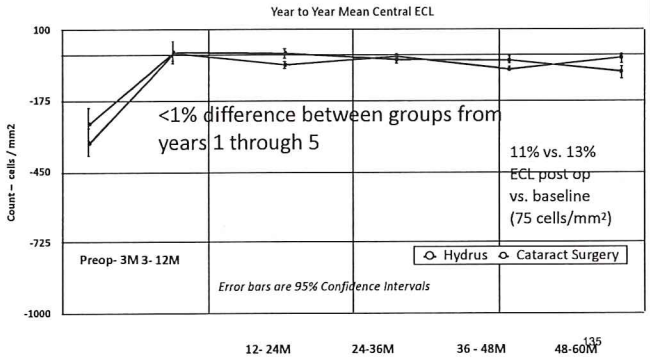
65% reduction in Hydrus arm

Rhee DJ. 4 Year Findings from the HORIZON Trial AGS 2020, Washington DC

134

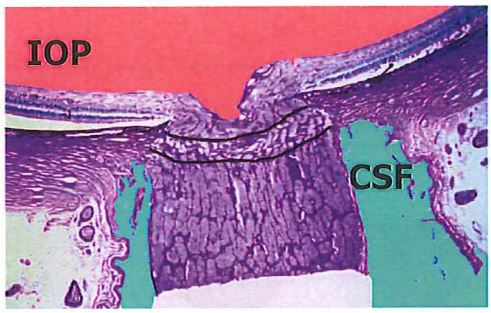
More than half of these patients were mild at baseline (VF MD -4 DB or better)

Corneal Endothelial Cell Counts



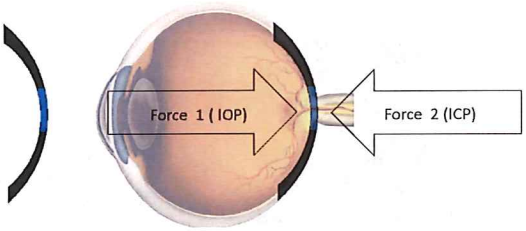
135

Rhee DJ. 4 Year Findings from the HORIZON Trial AGS 2020, Washington DC



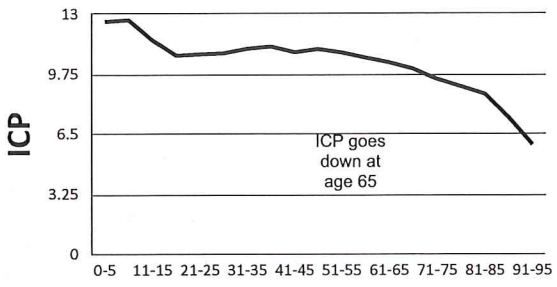
Jonas JB, Berenshtein E, Holbach L.Anatomic relationship between lamina cribrosa, intraocular space, and cerebrospinal fluid space. Invest Ophthalmol Vis Sci. 2003 Dec;44(12):5189-95.

136



137

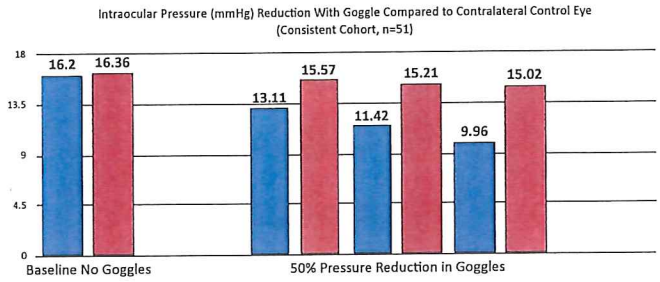
ICP changes with age



138

Solution?

139



140

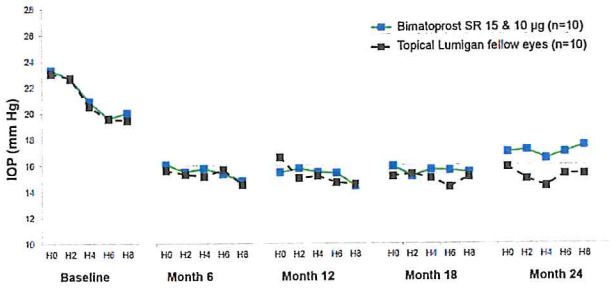
Bimatoprost SR

Bimatoprost SR

- A biodegradable bimatoprost sustained-release implant (Bimatoprost SR) addresses the problem of nonadherence in glaucoma
- The implant is placed intracamerally and was designed to deliver a slow release of bimatoprost for IOP lowering over a period of 4–6 months
- Bimatoprost SR is administered using a prefilled, single-use applicator system

2 Weeks Post-injection

Diurnal IOP after single Bimatoprost SR treatment



142

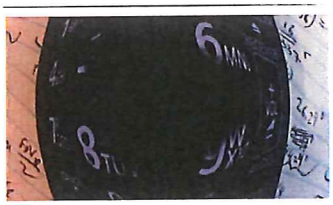
Other options for Augmented Reality

- Surgical Systems
- AMD

Providing the whole picture by both maintaining a Wide Field of View and recovering the Central Field

View with AMD (central scotoma)

View with Magnification (this limits the Field of View)



Eyedaptic effectively recovers the visual field!

144

How it Works:

Open Market AR Hardware + Proprietary Software [1]

Image Capture

Display

Vision w/AMD

Adaptive Systems [1]

Simulated Natural Vision

1. Patents pending & FTO completed

Technology Validation

30 Users to Date
73 – 105 Age Range
20/60 – 20/400 Vision
Mostly Dry AMD

Technology validated

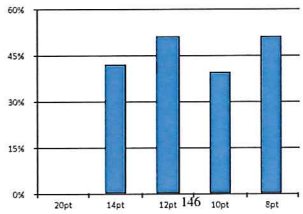
improved reading

&

everyday tasks easier

50% Improvement

% increase in reading speed

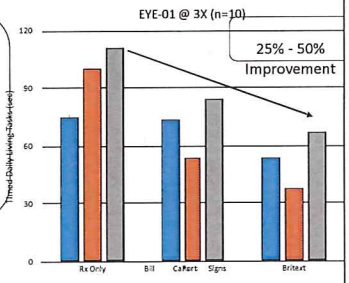


Clinical Trial: Validation of Features

A New Timed Instrumental Activities Of Daily Living (TIADL) Measure For Evaluation Of Rehabilitation Outcomes *(V.L. Gills[1], M.MacKeben[2], D.C. Fletcher[1,2])*

Timed Independent Activities of Daily Living (TIADLs):

- **Reading a bill**
- **Identifying & Reading food cans**
- **Sign spotting & reading**

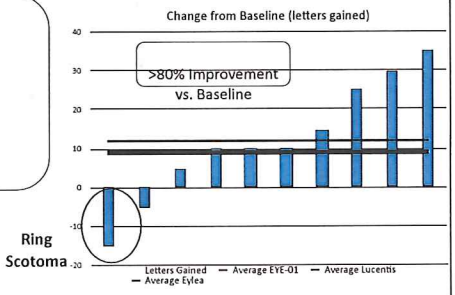


Clinical Trial: Validation of Features

Quantitative Evaluation of reading ability and visual acuity

MNRead Reading Assessment:

- **Critical print size**
- **Reading Acuity**
- **Scotoma pattern dependencies**

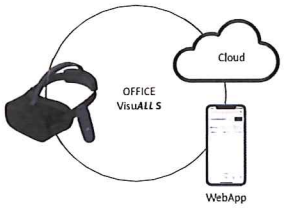


Augmented reality VF

Virtual Reality Platform (VRP) that is cloud enabled to monitor the eye function

- Enhanced version for eyecare professionals
- Simplified model for Home

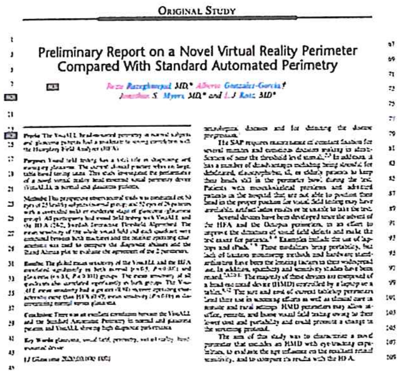
VRP



VisVRP has three main components:

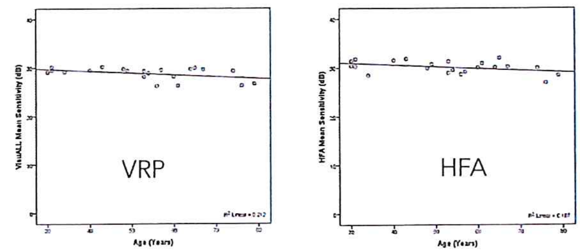
- **Cloud** (*Analytics, Storage, Insights*)
- **WebApp** (For Eyecare Providers: *Data Management, Reporting*)
- **Headset** (For Patients: *Testing, Education*)

Validation Study

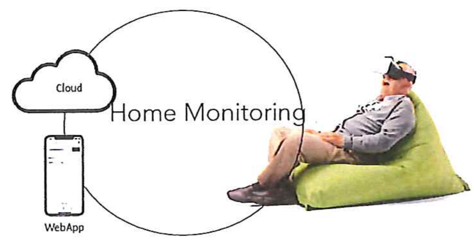

ORIGINAL STUDY

Preliminary Report on a Novel Virtual Reality Perimeter Compared With Standard Automated Perimetry

Scientific Validation



VRP



Gene Therapy & Genomics

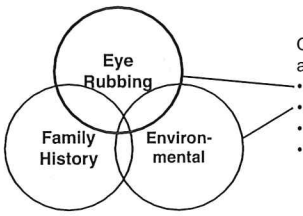
- Generic variants causing most ocular diseases are being discovered
- Examples include glaucoma, dry AMD, Fuchs' and all corneal dystrophies
- Early treatment vs. repair
- Prevention of disease progression (e.g. Avellino Labs)
- Ocular anatomy and architecture are uniquely situated for gene based research

Genetic Testing is here

Why a Genetic Test for Keratoconus?

Don't we already know the etiology?

- Relies on patient memory
- May not be accurate or relevant



Observable and actionable:
- Topography
- Tomography
- Behavior changes
- Medications

There is no one gene responsible for the development of keratoconus but **there is a strong genetic component or link within each group.**[1]

157

1. Gordon-Shaag A, et al. BioMed Res Int. Volume 2015, Article ID 795739, 19 pages.

Global Keratoconus Risk 2019

Millions of patients are at risk based on corneal curvature alone

309,000,000
Patients with >46D corneal curvature or >2D cylinder

90%
Live in Asia-Pacific Countries
60% in India and China

1,700,000
Between ages 15-30 yrs old

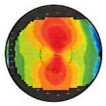
15

158

Identifying At Risk Patients

Patients with higher than normal risk for triggering or natural progression of disease

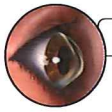
Patients with >47D cc and/or >2D astigmatism



Contact Lens and Ortho-K Candidates

Refractive Surgery Candidates

Family History of Keratoconus



15

159

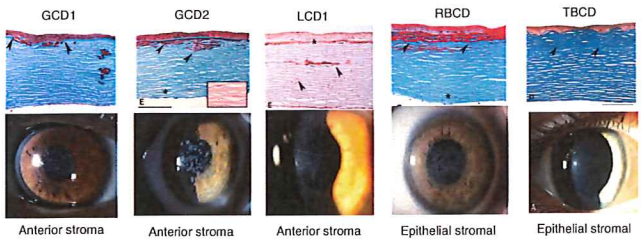
Using Genetic Testing to Identify Patients at Risk

Extraction → Sequencing → Referencing and Variant Risk Scores → Patient Report

160

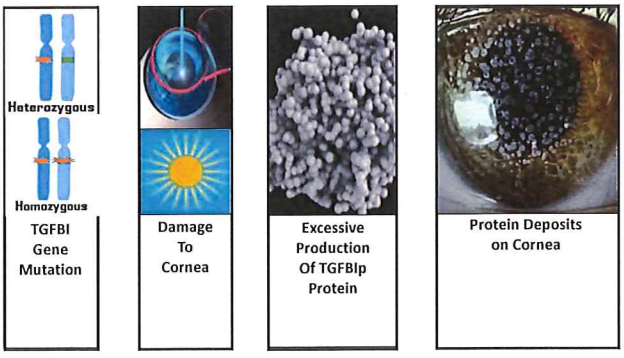
TGFBI Corneal Dystrophies

histologic and clinical appearances



161

Mechanism of *TGFBI* Induced Corneal Dystrophy



Proprietary and Confidential

162

Exacerbation after LASIK is cited in the literature

In 2002, the first case report of exacerbation of GCD2 after LASIK was published in Cornea by E.K. Kim and colleagues

Exacerbation of Avellino Corneal Dystrophy After Laser In Situ Keratomileusis

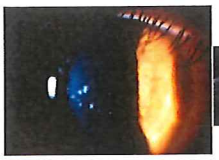
163

Post LASIK Exacerbation

In 2004 , Jun et al published a case in Ophthalmology. A 25 year old female experienced decreased vision five years after LASIK. Genetically confirmed as GCD2

Roo Min Jun, MD, et al.
Opthalmology III.3 (2004):463-468

OD - No Surgery, 5 years later



OCT cross section

OCT cross section

OS – 5 years post LASIK

164

Genetic Capability Pipeline

Continuous addition of detection capabilities will make the genetic eye test.

Front

2008 - 2019

Corneal Dystrophies
Keratoconus

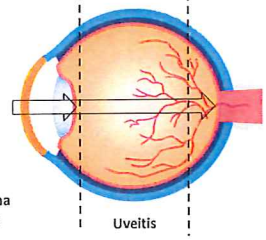
2019 - 2020

Fuchs ECD
EBMD
Fleck CD
Macular CD
Schnyder CD

2021+

Glaucoma
Cataract
Myopia
Hyperopia

Middle



Uveitis

Back

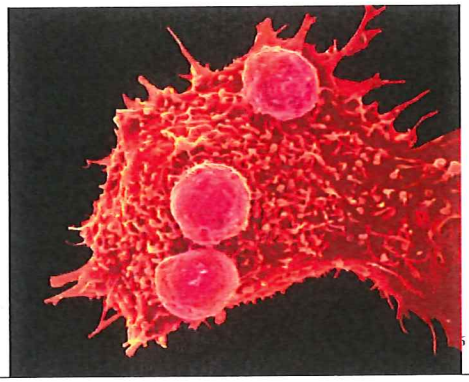
2020+

Retinitis Pigmentosa
AMD
Stargardt's Disease

15

165

CRISPR Gene Editing and an Adenovirus vector



CRISPR can remove the damaged or faulty genes

Modified Adenovirus can present the proper genetic code to the body for integration

Article | OPEN

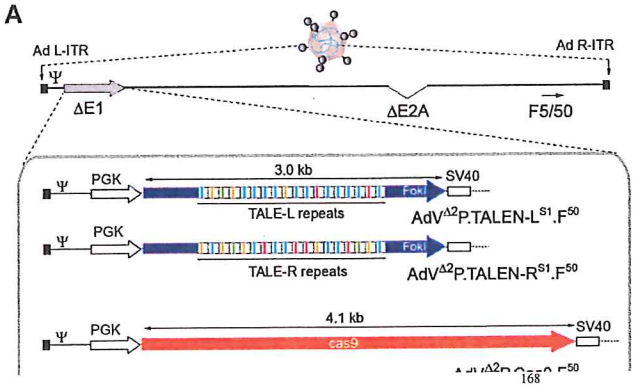
Adenoviral vector delivery of RNA-guided CRISPR/Cas9 nuclease complexes induces targeted mutagenesis in a diverse array of human cells

Ignazio Maggio, Maarten Holkers, Jin Liu, Josephine M. Janssen, Xiaoyu Chen & Manuel A. F. V. Gonçalves

167

From: Adenoviral vector delivery of RNA-guided CRISPR/Cas9 nuclease complexes induces targeted mutagenesis in a diverse array of human cells

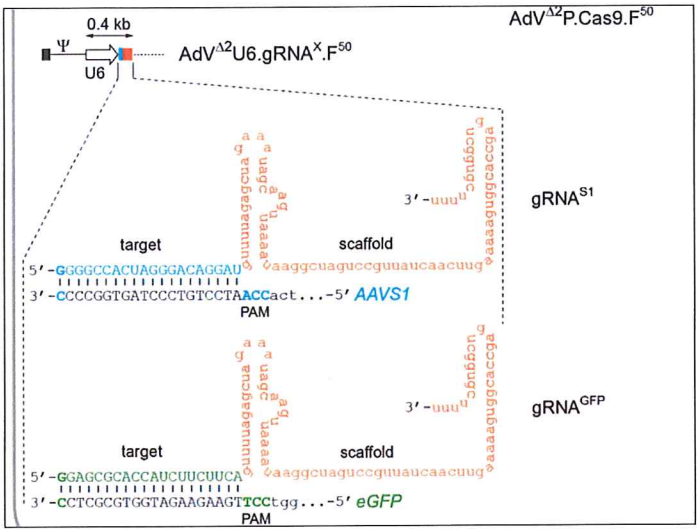
A

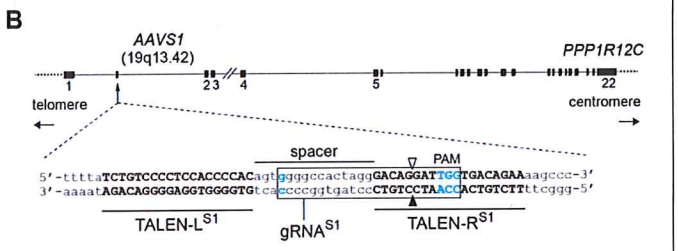


168

LHON Genetic Treatment

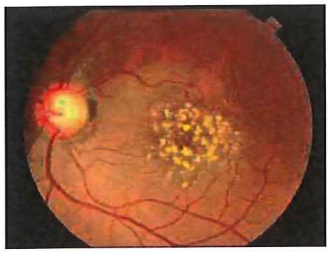
CRISPR followed by injecting the correct code for Leber's Optic Neuropathy





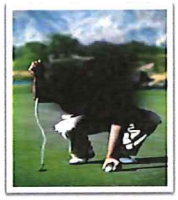
AMD Opportunity

Medical Utility - The AMD Problem

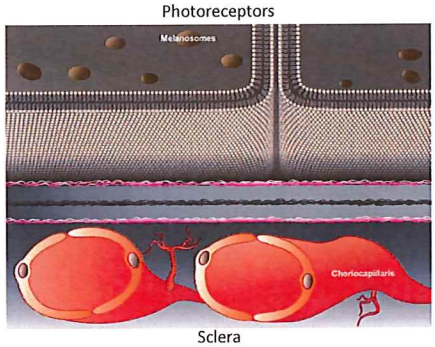


How can the Primary Eye Care Professional identify those at Risk?

Only 15% to 20% of Early / Intermediate AMD will progress to Advanced disease



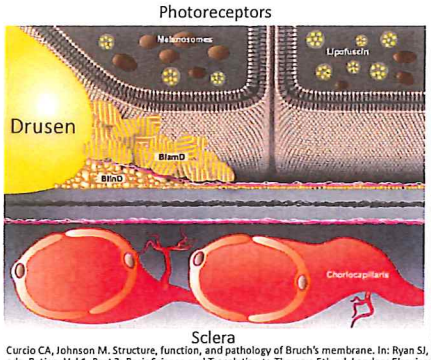
Dark Adaptometry



Curcio CA, Johnson M. Structure, function, and pathology of Bruch's membrane. In: Ryan SJ, et al, eds. *Retina, Vol 1, Part 2: Basic Science and Translation to Therapy*. 5th ed. London: Elsevier; 2013:466–481.

Dark Adaptometry

Photoreceptors



Sclera

Cholesterol accumulation leads to panmacular deposits (BlinD and BlamD)

Peaks in these deposits eventually become clinically visible drusen

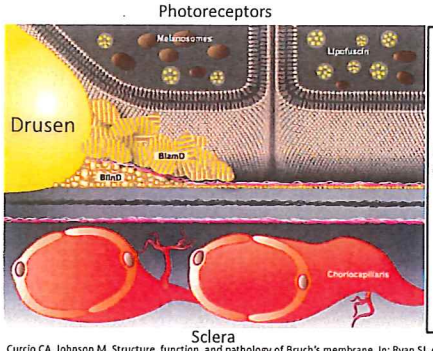
These extracellular cholesterol deposits affect photoreceptor health by impairing transport, causing inflammation, and predisposing to CNV

In addition, they impair normal transport, including that of vitamin A, across Bruch's membrane

Curcio CA, Johnson M. Structure, function, and pathology of Bruch's membrane. In: Ryan SJ, et al, eds. *Retina, Vol 1, Part 2: Basic Science and Translation to Therapy*. 5th ed. London: Elsevier; 2013:466–481.

Dark Adaptometry

Photoreceptors



Sclera

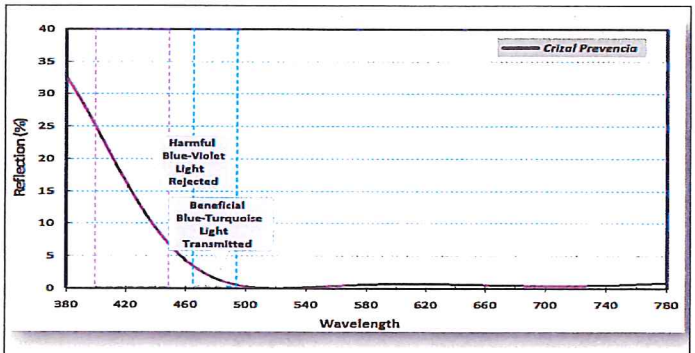
In effect, AMD causes a localized deficiency of vitamin A, and dark adaptation is the best test to measure this change

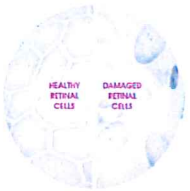
Curcio CA, Johnson M. Structure, function, and pathology of Bruch's membrane. In: Ryan SJ, et al, eds. *Retina, Vol 1, Part 2: Basic Science and Translation to Therapy*. 5th ed. London: Elsevier; 2013:466–481.

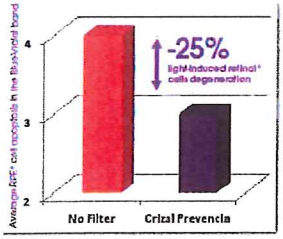
Dark Adaptometry

Dark adaptation is the process of adjusting from day vision to night vision

Easy-to-measure aspect of night vision







A Breakthrough Study in Blue Light Lenses


Medscape

Blue Light-Blocking Glasses May Help, Study Suggests

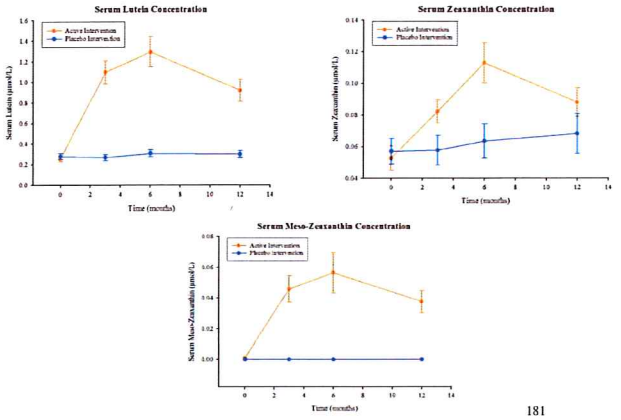
- Nova Southeastern University College of Optometry
- Study Independently conducted
- Randomized Controlled Crossover Trial (The gold standard)
- 24 Subjects wore BluTech after 6:00 PM for 5 days, and then Clear Lenses with Anti-reflective Coating Only* for the following 5 days
- Actigraphy watches noninvasively recorded sleep patterns
- Melatonin samples collected from saliva after day 5
- Mood & neurobehavioral performance assessed with NIH Toolbox Emotion and Cognition Batteries, respectively.

CONCLUSION:
Wearing BluTech Lenses is clinically proven to double your nighttime Melatonin levels, which MAY improve sleep and cognition.

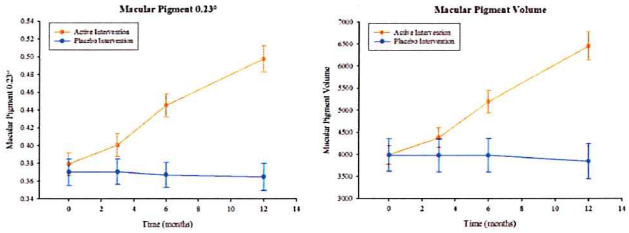
Key Findings:
Wearing BluTech for just 5 days, participants demonstrated:

1. Increase in Melatonin levels by 96% (P=0.036)
2. Less awakening during sleep, reduced sleep onset latency
3. Improved cognition using pattern comparison test (P=0.047)

SERUM CAROTENOID RESPONSE



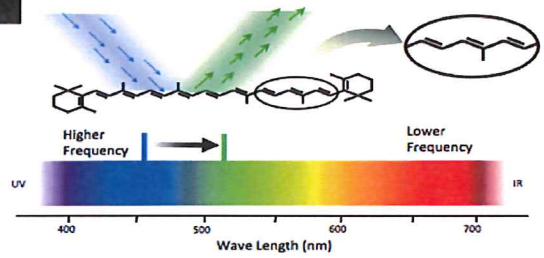
MACULAR PIGMENT RESPONSE



- All subjects in active intervention exhibited augmentation of MP;
- MP Volume mean ± SD = 2436 (± 1451), range 738 to 6464;
- In percentage terms, mean ± SD = 73% (± 62%), range 16% to 337%;

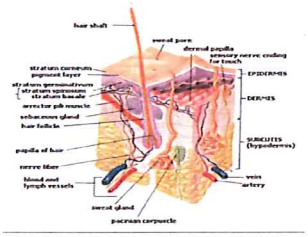
Raman Spectroscopy Sir C. V. Raman, Nobel Prize in Physics, 1930

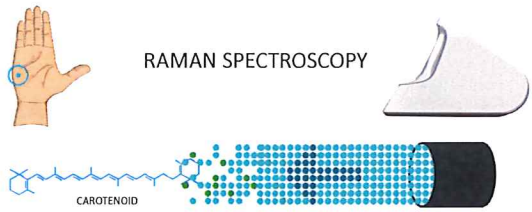
When blue light (at exactly 473 nm) is shined onto carotenoids, the energy of the reflected light is *'shifted'* to green (510 nm) due to a molecular characteristic shared among all carotenoids. This is known as *'Raman shift'*



Skin Carotenoids

- Measured in stratum corneum (0.1 mm) layer of the skin
  - α- and β-Carotenes,
  - Lycopene,
  - Lutein,
  - Zeaxanthin,
  - α-, β-Cryptoxanthin





510 nm PHOTONS

473 nm PHOTONS

Resonance Raman spectroscopic evaluation of skin carotenoids as a biomarker of carotenoid status for human studies

Susan T. Mayne [a,*], Brenda Cartmel [a], Stephanie Scarmo [a,b], Lisa Jahns [c], Igor V. Ermakov [d], Werner Gellermann [d]

[a] Yale School of Public Health and Yale Cancer Center, 60 College St., P.O. Box 208034, New Haven, CT 06520, USA
[b] Center for Science in the Public Interest, 1220 L Street, N.W., Suite 300, Washington, DC 20005, USA
[c] USDA/ARS Grand Forks Human Nutrition Research Center, 2420 2nd Avenue North, Grand Forks, ND 58203, USA
[d] Department of Physics and Astronomy, University of Utah, Salt Lake City, UT 84112, USA

ARTICLE INFO

Article history:
Available online xxxx

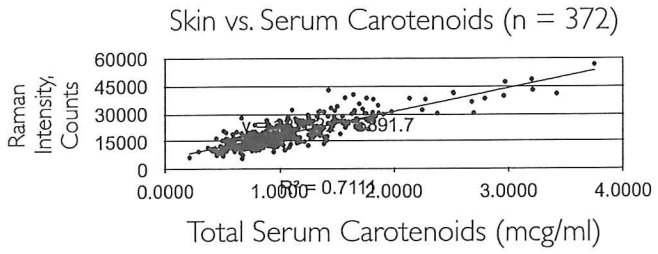
Keywords:
Carotenoids
Skin
Resonance Raman spectroscopy
Beta-carotene
Biomarker

ABSTRACT

Resonance Raman spectroscopy (RRS) is a non-invasive method that has been developed to assess carotenoid status in human tissues including human skin in vivo. Skin carotenoid status has been suggested as a promising biomarker for human studies. This manuscript describes research done relevant to the development of this biomarker, including its reproducibility, validity, feasibility for use in field settings, and factors that affect the biomarker such as diet, smoking, and adiposity. Recent studies have evaluated the response of the biomarker to controlled carotenoid interventions, both supplement-based and dietary [e.g., provision of a high-carotenoid fruit and vegetable (F/V)-enriched diet], demonstrating consistent response to intervention. The totality of evidence supports the use of skin carotenoid status as an objective biomarker of F/V intake, although in the cross-sectional setting, diet explains only some of the variation in this biomarker. However, this limitation is also a strength in that skin carotenoids may effectively serve as an integrated biomarker of health, with higher status reflecting greater F/V intake, lack of smoking, and lack of adiposity. Thus, this biomarker holds promise as both a health biomarker and an objective indicator of F/V intake, supporting its further development and utilization for medical and public health purposes.

*Arch Biochem Biophys. PMC 2014 M

Initial Study: Correlation study of skin carotenoids and serum carotenoid levels ; r = 0.84 (p<0.0001)



ARVO 2016
RESEARCH: A VISION OF HOPE MAY 1 – 5 | SEATTLE

Interrelationships between Macular, Skin, and Serum Carotenoids Tue, May 03

Author Block: *Christopher D. Conrady[1], James E. Bell[1], Brian M. Besch[1], Aruna Gorusupudi[1], Werner Gellermann[1], Kelliann Farnsworth[1], Paul S. Bernstein[1]*
[1] Ophthalmology, University of Utah - Moran Eye Center, Salt Lake City, Utah, United States

Conclusion:

"Skin RRS is a reasonable biomarker of macular carotenoid status that can be readily performed in a wide variety of research, clinical, and non-clinical settings."

Composite skin carotenoid concentration is related to macular pigment volume: The Pharmanex BioPhotonic Scanner

Stephanie Byrne[1], Rachel Moran[1], Rebecca Power[1], John Nolan[1]
[1]Nutrition Research Centre Ireland, School of Health Science, Waterford Institute of Technology, Waterford, Ireland.

Introduction

- Carotenoids are a group of phytonutrients that play an important role in human health via their antioxidant and anti-inflammatory properties.
- Three carotenoids lutein (L), zeaxanthin (Z) and meso-zeaxanthin (MZ) are exclusively found in the central part of the macula where they are commonly referred to as macular pigment (MP) [1]. Recent studies have also shown that L and Z are also present in the brain [2].
- Measurement of these carotenoids in humans is challenging, costly and time consuming.

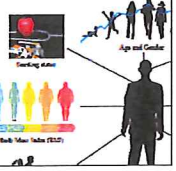
  Invasive measurements include:
  - Obtaining biological samples (blood, skin biopsies) for High Performance Liquid Chromatography (HPLC) analysis.

  Minimally invasive measurements include:
  - MP measurements using dual-wavelength autofluorescence.
- With improvements in technology there is now the potential to non-invasively measure carotenoid status in the skin. Devices such as the Nu Skin Pharmanex S3 scanner measure total

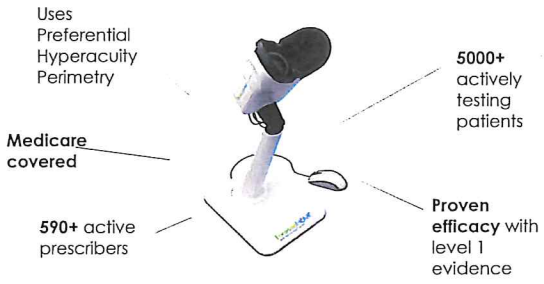


Method

- Demographic, lifestyle and heal subjects recruited at the Nutri Ireland (NRCI) were used for this
- SCS was measured using the Pl Scanner.
- MP was measured using the HRA+OCT Multicolour system.



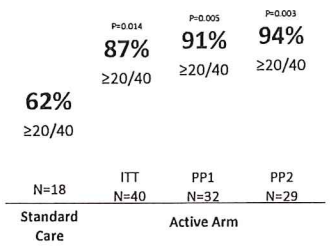
Home monitoring



Reference: Data on File.

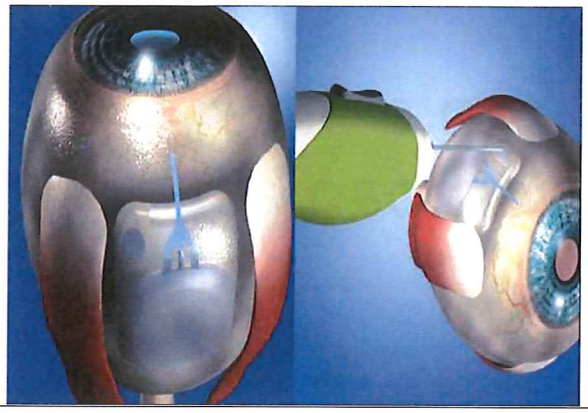
Preferential hyper acuity perimetry delivers accurate, highly sensitive, specific disease detection

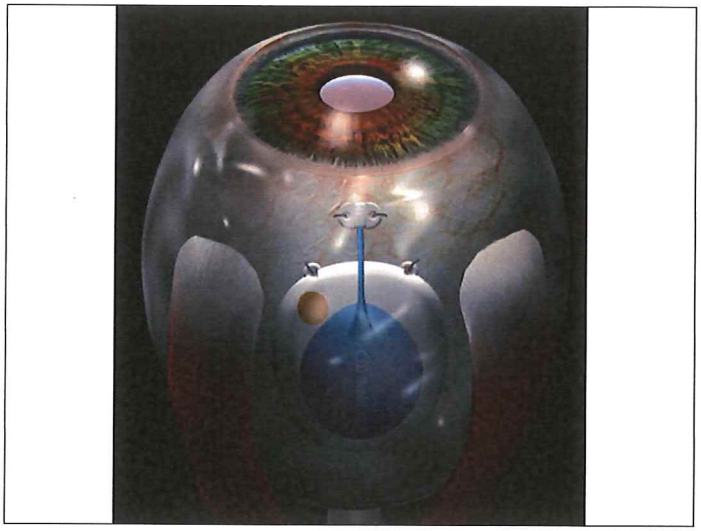
More patients who used it maintained good vision

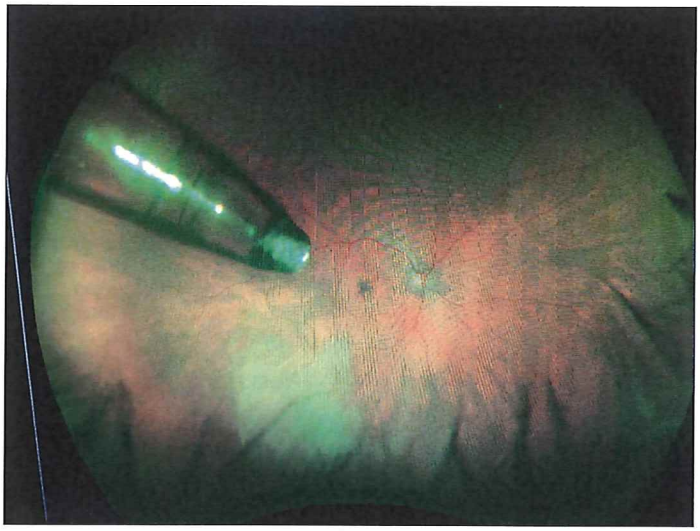


50% INCREASE
in patients in active arm compared to standard care alone

Drug Delivery Advances







Adverum Biotechnologies	**ADVM-022**	wAMD	Gene therapy
Alkahest	**AKST4290**	wAMD	Inhibit the negative biological chronokines that increase with age
AsclepiX Therapeutics	**AXT107**	wAMD	A peptide derived from the non-collagenous domai of collagen IV, which inhibits VEGF and activates Tie2
Graybug Vision	**GB-102**	wAMD	Sunitinib malate aimed at reducing intravitreal injections to 2x per year in patients with wet AMD currently managed with anti-VEGF.
Graybug Vision	**GB-103**	wAMD	Formulated to elute sunitinib over a longer duration that may enable once yearly dosing instead of twic yearly dosing
Ophthotech Corp.	**Zimura**	wAMD	inhibit the complement protein C5 preventing inflammasone formation
Outlook Therapeutics	**ONS-5010**	wAMD	Anti-VEGF
REGENXBIO	**RGX-314**	wAMD	One-time subretinal treatment for wAMD that includes the NAV AAV8 vector containing a gene encoding for a monoclonal antibody fragment. The expressed protein is designed to neutralize VEGF activity.
Replenish	**MicroPump Systems**	wAMD, chronic DME or glaucoma	Small, refillable via injection, implantable ocular dru pump. The pump can be programmed to dispense precise nanoliter-sized doses or medication
Aerie pharmaceuticals	**AR-13503**	wAMD, DME	RhoKinase inhibitor implant

Stealth BioTherapeutics	**elamipretide**	dAMD	A peptide compound that penetrates cell membranes, and targets the inner mitochondrial membrane where it binds reversibly to cardiolipin thus normalizing mitochondrial structure and function
Cell Care Therapeutics		Diabetic retinopathy	using stem cell components to harness the patient's immune system to drive the resolution of the inflammatory process and initiates tissue remodeling leading to the stabilization and recovery of retinal neurovascular tissue
Allegro Pharma	**Risuteganib**	DME	Integrin peptide
AsclepiX Therapeutics	**AXT107**	DME	A peptide derived from the non-collagenous domain of collagen IV, which inhibits VEGF and activates Tie2
Oculis	**OCS-01**	DME	Dexamethasone cyclodextrin nanoparticle drops, Glucocorticoid receptor agonists; Immunosuppressants
Oxurion	**THR-149**	DME	PKal Inhibitor
Outlook Therapeutics	**ONS-5010**	DME & BRVO	Anti-VEGF
Oxurion	**THR-687**	DR	Pan RGD integrin antagonist
Oxurion (Thrombogenics)	**THR-317**	DR, DME, MacTel	anti-PIGF

Geographic Atrophy

Allergan/AbbVie	**Brim DS device**	Dry AMD/ Geographic Atrophy	Briminodine alpha adrenergic for neuroprotection
Apellis Pharmaceuticals	**APL-2**	Dry AMD/ Geographic Atrophy	First-in-class treatment targeting C3 (Compliment system)
Galderma	**Oracea**	Geographic Atrophy in AMD	Doxycycline to inhibit MMP
Janssen	**CNTO-2476**	Geographic Atrophy in AMD	AMD cell therapy
Iveric	**Zimura**	Geographic Atrophy in AMD	inhibit the complement protein C5 preventing inflammasone formation

Complement 3 & 5 Directed Pharmaceuticals

- New drug in phase III FDA trials for geographic atrophy
- Moderate to early stage disease showing the potential for reversal

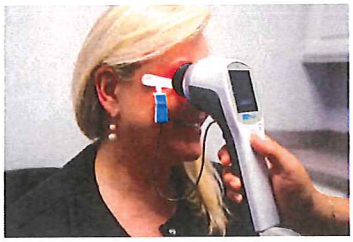
199

Apple-like companies

Hand-held Portable non-mydriatic Full-Field ERG + VEP

1. Soft eye cup for patient comfort
2. IR camera to view eye during testing
3. Immediate test results right on the device
4. Simple joystick control
5. Ergonomic to fit comfortably in hand
6. Small charging base
7. Lithium Ion battery for up to 8 hours* of use
8. Docking station offers USB connectivity

*Approximately 70 patients before recharging, depending on protocol used.



Hand-Held, Full-Field ERG

Quick Facts

- **The first, and only FDA cleared, hand-held, mobile, non-mydriatic Full-Field ERG device**
- Affordable ERG testing in the palm of your hand
- Easily integrates into your current practice flow
- No dedicated test room or additional staff required
- OF RETEVAL IN USE

202

Hand-Held, Full-Field ERG

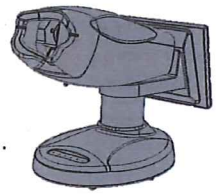
Quick Facts

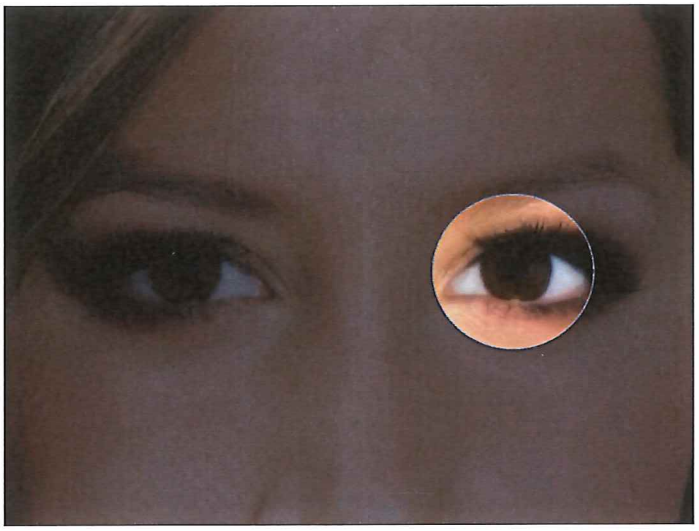
- Complementary to other tests of *function* like visual fields and *cone-isolation contrast sensitivity (ColorDx)*
- Largely unaffected by cataracts
- May be useful for following progression of disease (e.g. diabetes)
- Normative database for easy, color coded interpretation of most protocols

203

Pupillometry

Pupil diagnostics have just been transformed from the dark ages to the 21st Century





What is it…

- EyeKinetix is an *objective* machine vision alternative to the SFM for assessing APDs
- *Objectively* assess pupils in less than 1 minute; an order of magnitude more detailed than the finest human observer
- It includes a scotopic / photopic pupil measurement + PD
- Fast color vision screener in the works

Pupil reflex / SFM facts

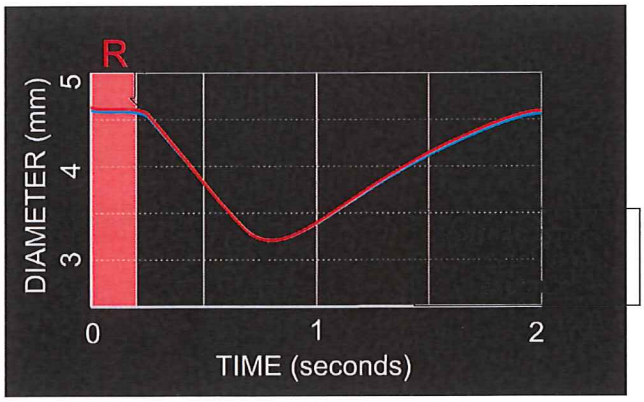
- The only reasonably accurate method of quantifying an APD requires neutral density filters (0.3, 0.6, 0.9, 1.2, 1.8)
- 0.3 is when we become suspect
- Glaucoma (asymmetric) is the most common cause of APDs
- At least 50% of open angle glaucoma is normal tension
- Most clinicians would agree that an APD of 0.6 or less would be extremely difficult if not impossible to see without magnification (MA-SFM)
- In one paper, only 2 healthy controls had an APD >0.3
- IMO the most important misconception is that clinically significant APDs are big enough to be seen with the SFM

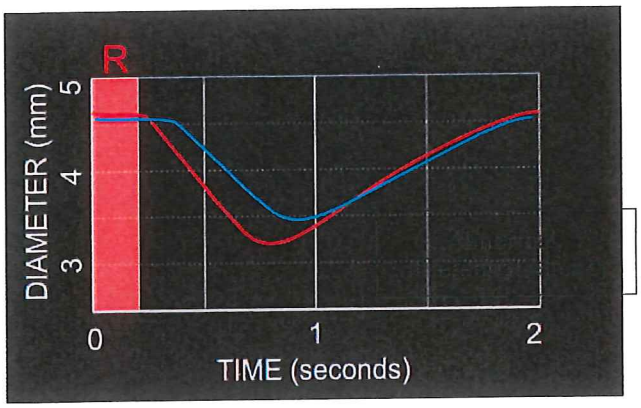
208

Test: Full Field Stimuli

Analog of
Swinging Flashlight

Expanded Stimuli





Key Clinical Papers

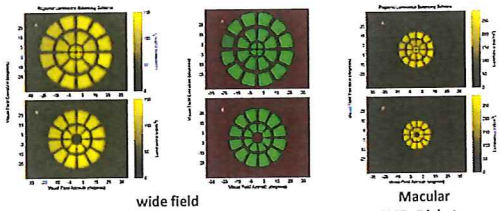
- There is evidence that very subtle APDs (above 0.3) are present in the vast majority of glaucoma subjects [1]
- Studies have shown that automated *objective* pupillography identified more than twice as many RAPDs than the SFM[2]
- Clinically detected asymmetry in disc damage was missed 49% of the time with the SFM compared to 21% with automated *objective* pupillography[2]
- When using automated *objective* pupillography, the pupillary light reflex is strongly correlated with VF functional testing and measurements of RNFL thickness[3]

1. Tatham, A.J., Meira-Freitas, D., Weinreb, R.N., Marvasti, A.H., Zangwill, L.M. and Medeiros, F.A., 2014. Estimation of retinal ganglion cell loss in glaucomatous eyes with a relative afferent pupillary defect. *Investigative ophthalmology & visual science*, *55*(1), pp.513-522.
2. Ali, M., Lu, L., Martinez, P., Faria, B., Gupta, L., Zhang, A., Hwang, E., Moster, M. and Spaeth, G., 2013. Pupil-based detection of asymmetric glaucomatous damage-comparison of the Konan RAPDx pupillograph, swinging flashlight method, and magnifier-assisted swinging flashlight method. *Investigative Ophthalmology & Visual Science*, *54*(15), pp.4811-4811.

Objective VF Analyser

Three Stimulus Methods

- Normative database for each protocol from 179 persons, each tested twice

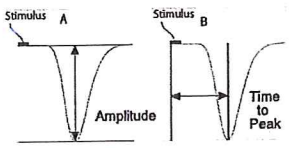


wide field
Glaucoma, Neurological

Macular
AMD, Diabetes

Data obtained

- Pupil responses, down = contraction
- Pupil constriction amplitude = sensitivity; also get response delay (time to peak)

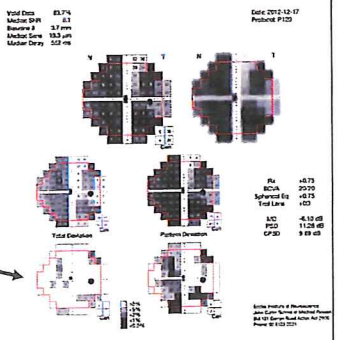


- These two measures are relatively independent and combining them into a composite report can improve the capacity to detect functional abnormalities.
- Analysis are tolerant of up to 15% loss of data due to blinks or loss of fixation.

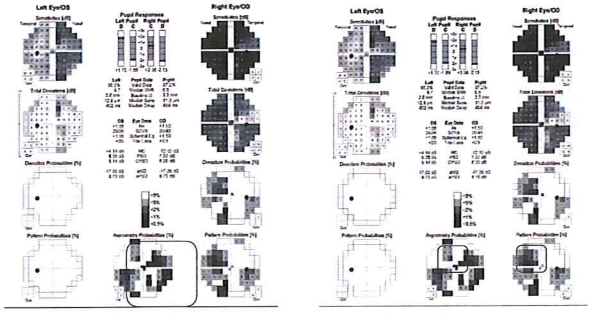
- so 176 sensitivities and 176 delays, and SE for each

30-2+ Report

- Emulates SAP report
- True 30-2 pattern
- Plus 4 extra central regions
- Red border shows 24-2 pattern



Binocular Report

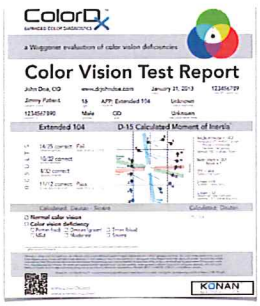


Asymmetry Report

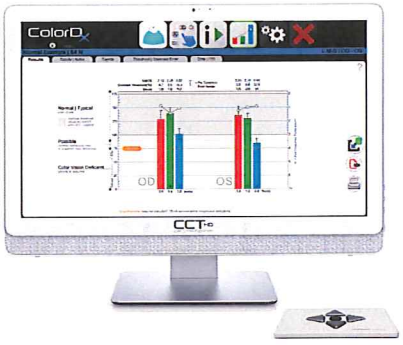
Asymmetry Report

ColorDx™

EXPANDED COLOR VISION DIAGNOSTICS



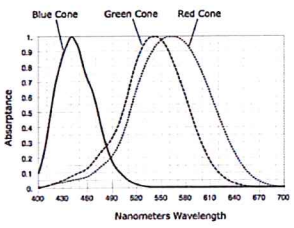
The Device

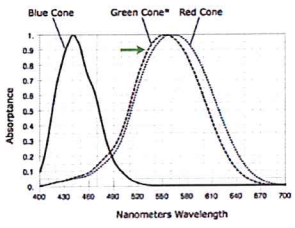


Color Deficiency

- Affects 1 in 200 females
- Affects 1 in 8 males
- 30 Million Americans have some level of color deficiency
- Deuteranopia being most common
- Protanopia occurs more often with acquired disease
- Ishihara misses 100% of protanopia

Color Deficiency

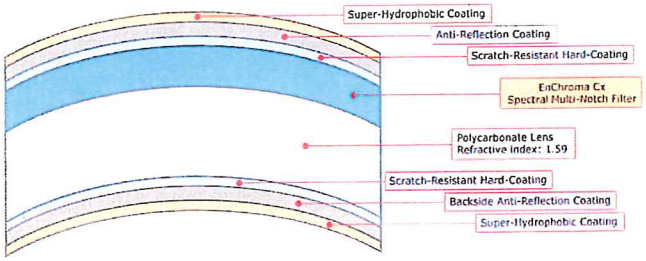


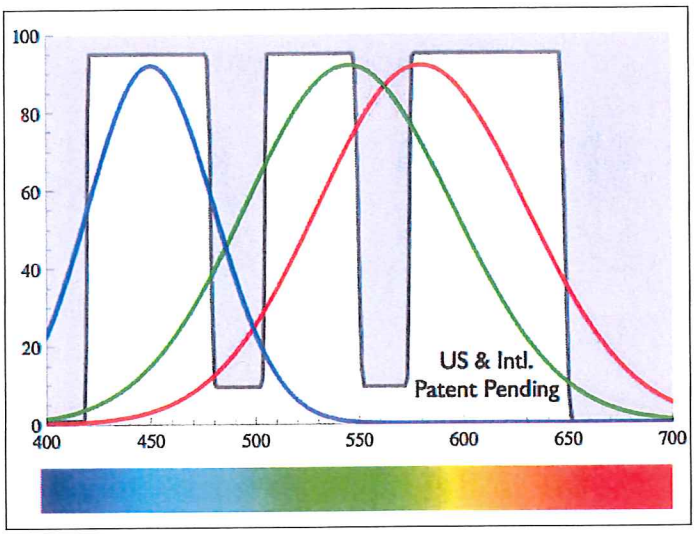


Artificial Intelligence for Color Enhancement

- Clear lenses
- AI helps ensure 'actual' color potential
- Indoor and outdoor lens

Wavelength Blocking Lenses





Wavelength Blocking Lenses

225

THANK YOU!

Karpecki@Karpecki.com