# Disruptive Technology

Dr James Thimons, Founding Partner, OCC

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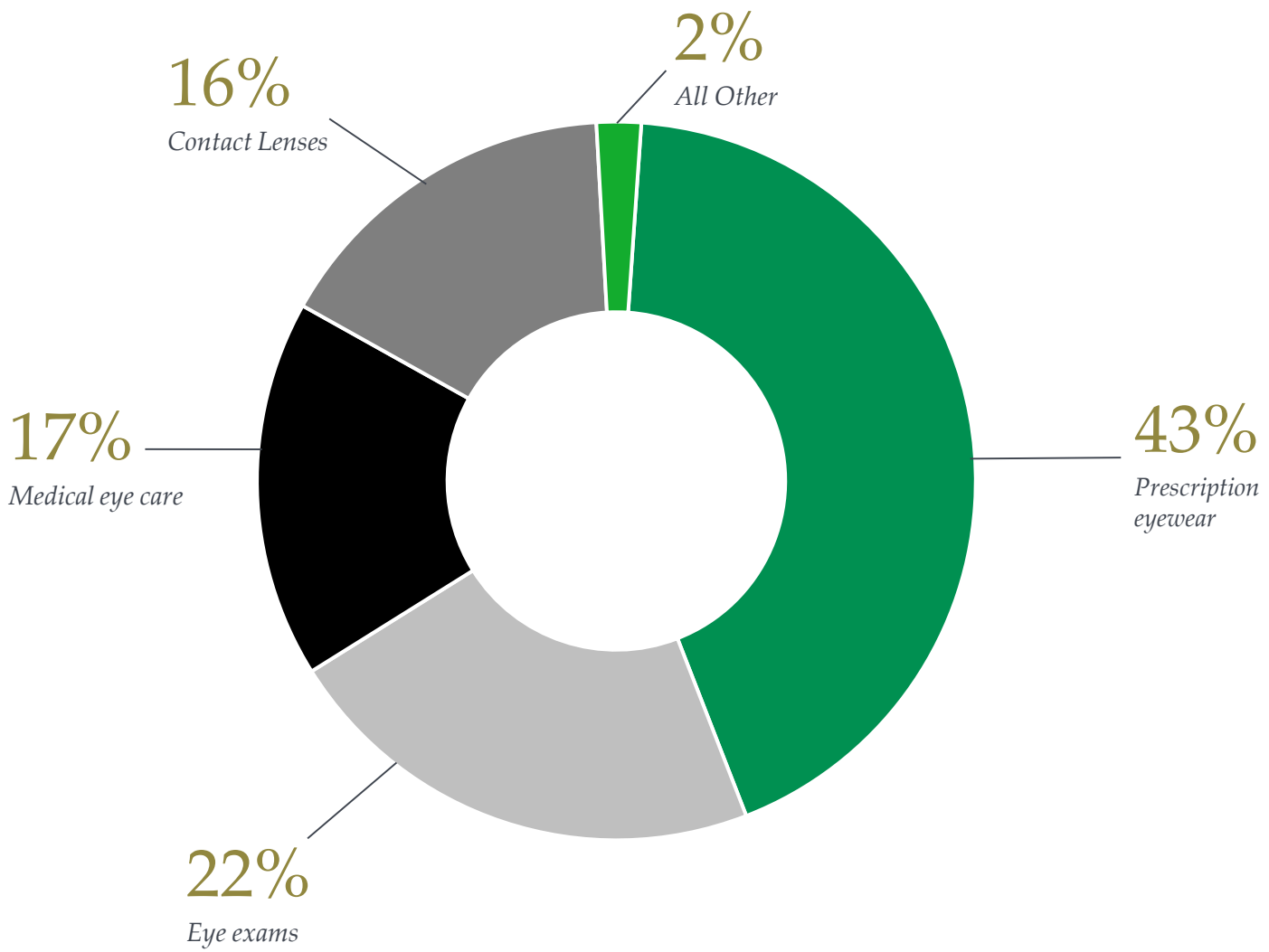
# Disclosures

- Speaker
  - Alcon
  - Allergan
  - PRN
  - Tear Lab
  - Shire
  - Zeiss
  - B&L
  - Diopsys
  - Reichart
  - Glaukos
  - InFocus
  - Aerie

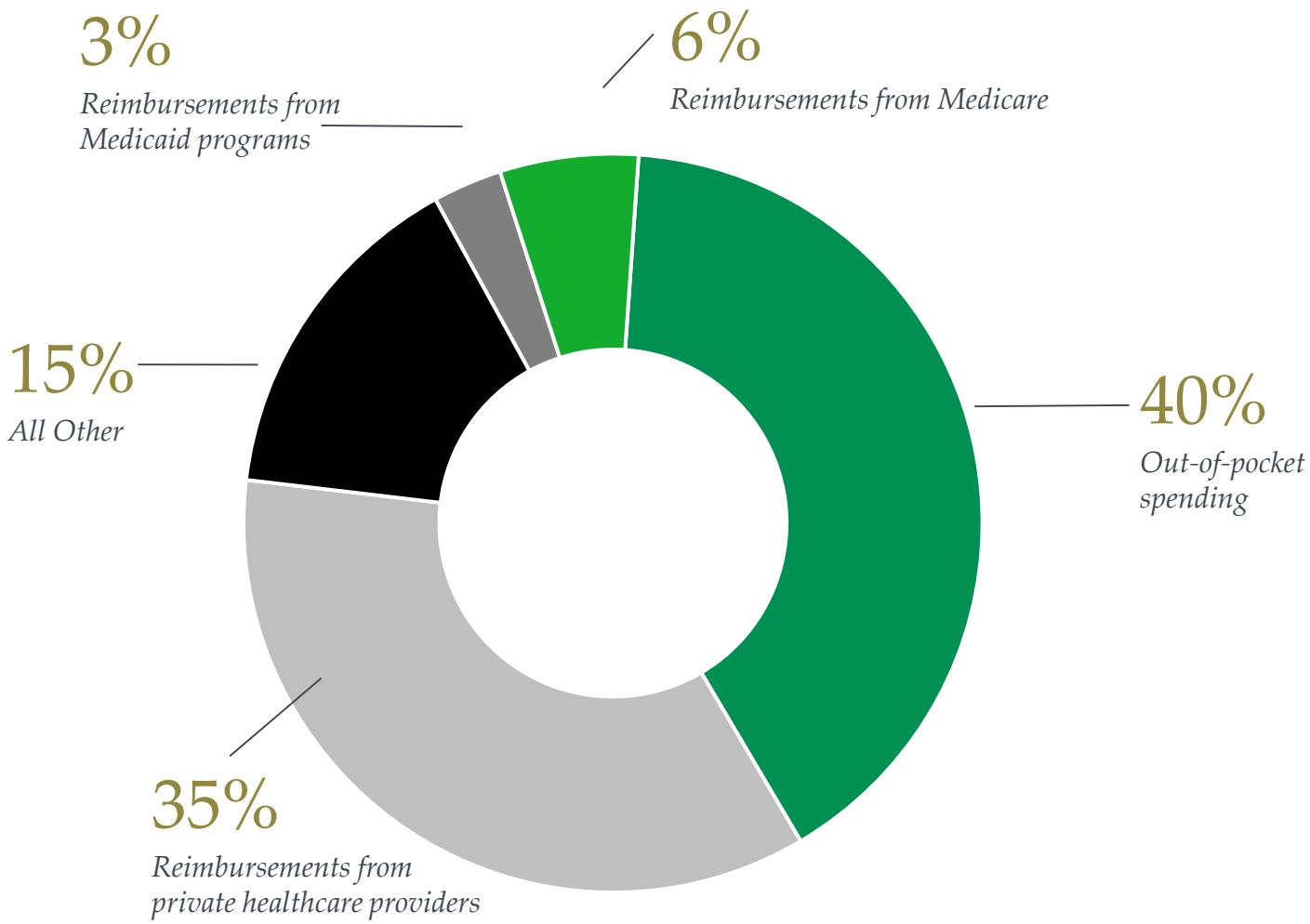
# INDUSTRY AT A GLANCE

| | | |
|---|---|---|
| #1 | 2019 Revenue | $17.4 billion |
| #2 | Annual Growth '14-19 | The annual growth rate was 2.4% over this 5 year period. Forecasted revenue over the next five years is expected to remain flat 2.4% |
| #3 | Business Volume | According to the most recent IBIS World data, there are 32,981 active businesses in the United States |
| #4 | Wages | $6.1 billion |

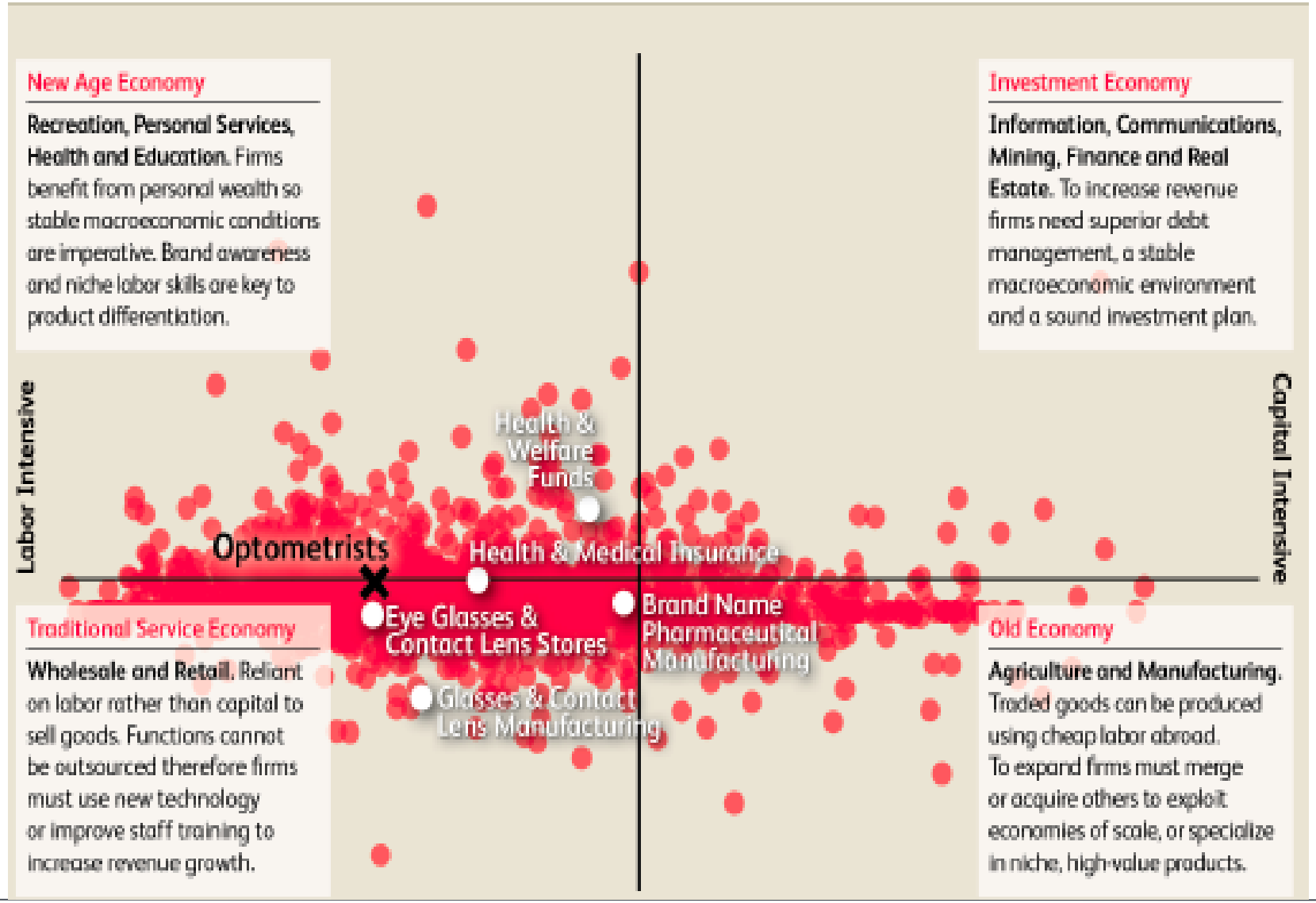
# SEGMENTATION



# MAJOR MARKET SEGMENTATION



# GROWTH STRATEGIES FOR SUCCESS



# WORKPLACE DEMOGRAPHICS

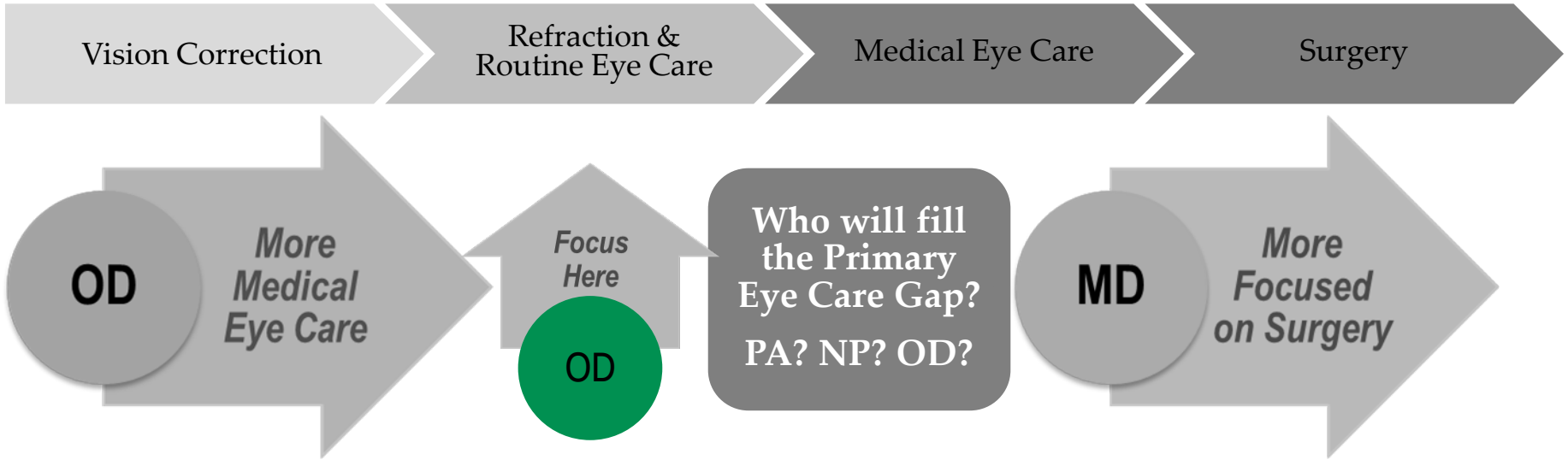
- *Female Workforce (2015-2025)*
  - *New Optometrists: 65% - 67%*
  - *New Ophthalmologists: 39%*
- *Female practitioners*
  - *Optometry: 42% - 50%*
  - *Ophthalmology: 23% – 27%*
- *Note: Exiting male and female rates estimated at 2.5% per annum*

- *Total New Optometrists (2017-2025)*
  - *2017: 42,903*
  - *2025: 48,191*
  - *Percent Change: 12.3%*
- *Total FTE Optometrists (2017-2025)*
  - *2017: 41,179*
  - *2025: 45,983*
  - *Percent Change: 11.7%*
- *Total Ophthalmologists (2017-2025)*
  - *2017: 16,671*
  - *2025: 17,023*
  - *Percent Change: 2.1%*
- *Total FTE Ophthalmologists (2017-2025)*
  - *2017: 15,945*
  - *2025: 16,190*
  - *Percent Change: 1.5%*

Source: Company proxy statements, investor filings, and Capital IQ.
(1) As of April 2017 10-Q filing.

# GROWING DEMAND MUST BE MET BY OD'S

*The Eyecare Spectrum*




***OPPORTUNITY TO:***
- ✓ *Meet consumer demand*
- ✓ *Diversify revenue stream*
- ✓ *Enhance margins*
- ✓ *Transform the practice of Optometry*

# The Evolution Of Optometry

- 1901 – First state Law regulating the profession.
- 1910- First courses at Columbia
- 1915- First regulation passed to remove Optometry from the control of the Board of Medicine
- 1923- PCO awards the first Doctor of Optometry
- 1952- The first soft contact lens
- 1971- Rhode Island became the first state to authorize DPA use
- 1976- West Virginia passes first therapeutic drug law
- 1986- Medicare Parity passed
- 1998- Oklahoma passes first surgical law ( lasers)
- 2000- All states achieve therapeutic laws
- 2019- Still waiting on Massachusetts/ New York to obtain oral legislation

# Advances in Drug Therapy

**New Horizons in Corneal Therapy**

**1. Oxervate**

**2. Regenerize**

**Presbyopia Therapy: The “Holy Grail”**

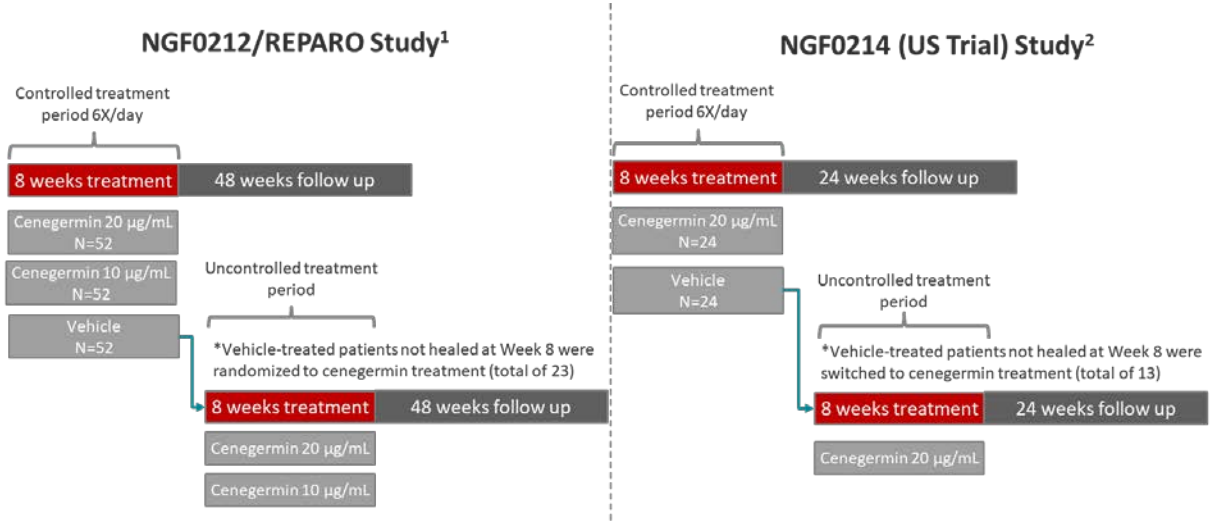
**1. Visus**

**2. Eyenovia**

# Oxervate (cenegermin-bkbj 20mcg/ml)

- Dompe
- The first Biologic for the Anterior Segment

# OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% Pivotal Trials Study Design

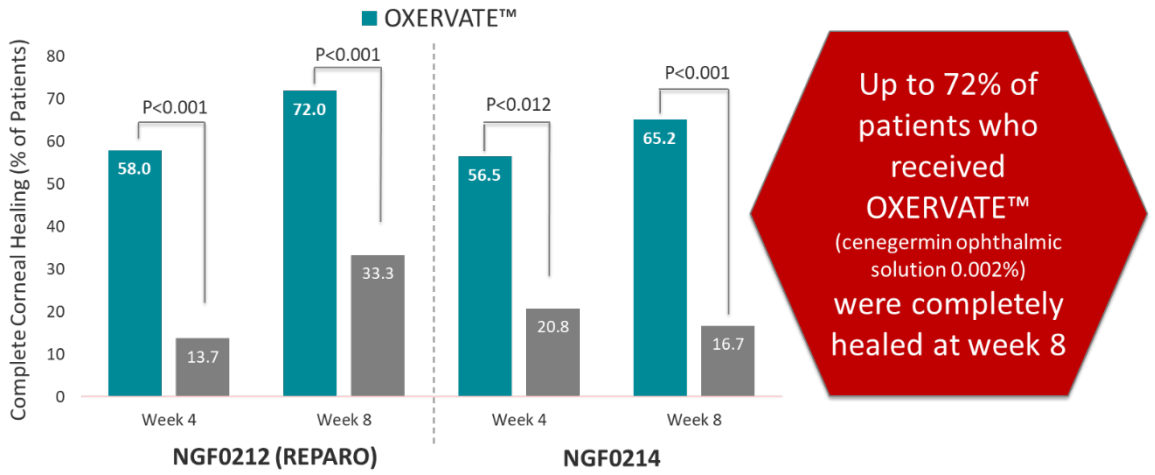



The primary efficacy endpoint, which was determined by a central reading center, was "complete corneal healing" defined as 0 mm staining in the lesion area and no persistent staining in the rest of the cornea


1. Bonini S, Lambiase A, Rama P *et al.* Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis. *Ophthalmology* 2018;125:1332-1343.
2. Chao W, J. BDC, R. D *et al.* Data on file. Healing of persistent epithelial defects or corneal ulcers by recombinant human nerve growth factor eye drops in patients with stage 2 or 3 neurotrophic keratitis. Presented at: Congress of the European Society of Ophthalmology (SOE) 10–13 June, 2017, Barcelona, Spain. 2017.

# Efficacy established as early as week 4

Endpoint of complete corneal healing: **0 mm staining in the lesion area and no persistent staining in the rest of the cornea** (last post-baseline observation carried forward; chi-squared test).





1. Bonini S, Lambiase A, Rama P *et al. Ophthalmology* 2018;125:1332-1343.
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# Study Conclusions

*Up to 72% of patients achieved complete corneal healing;*

*80% of healed patients were recurrence free after 1 year**

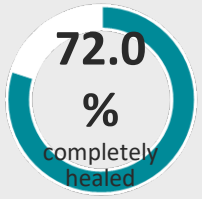
## After 8 weeks of treatment, 6 times daily

In the majority of patients across two clinical studies OXERVATE™ (cenegermin ophthalmic solution 0.002%) was well tolerated and more effective than vehicle in promoting complete corneal healing of moderate or severe NK.

**50**
**clinical trial sites in Europe and the U.S.**

**Study NGF0212 (REPARO) (N=52 per group)**
European patients with NK in one eye

*NCT01756456*

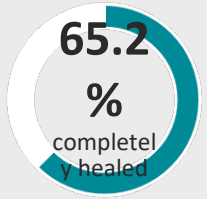



Vehicle response rate 33.3%

**Study NGF0214 (N=24 per group)**

U.S patients with NK in one or both eyes

*NCT02227147*




Vehicle response rate 16.7%

Of patients who healed after one 8-week course of treatment…

**80%**

Remained healed for one year*

*Based on REPARO, the study with longer follow-up


1. Bonini S, Lambiase A, Rama P *et al. Ophthalmology* 2018;125:1332-1343.
2. Chao W, J. BDC, R. D *et al.* Data on file. Healing of persistent epithelial defects or corneal ulcers by recombinant human nerve growth factor eye drops in patients with stage 2 or 3 neurotrophic keratitis. Presented at: Congress of the European Society of Ophthalmology (SOE) 10–13 June, 2017, Barcelona, Spain. 2017.

# Oxervate is neither systemically absorbed, nor immunogenic

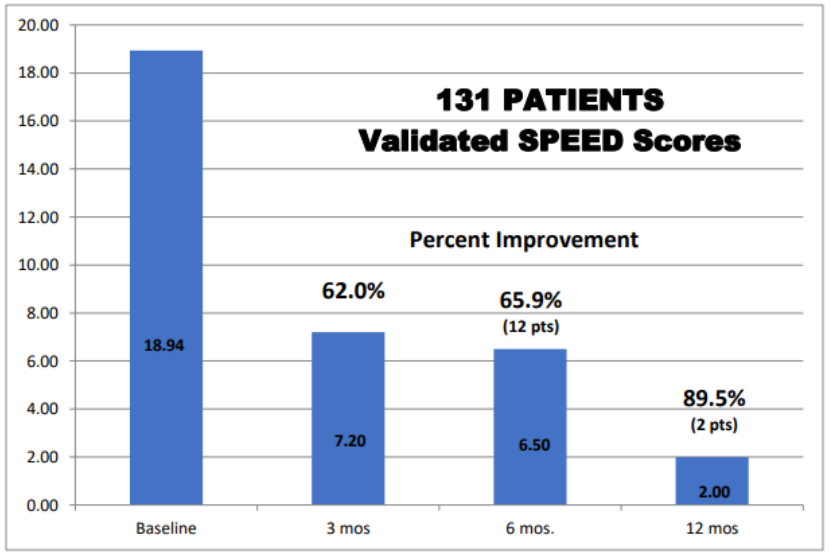
- In Phase I (NGF0112) in healthy patients at doses up to 180 µg/ml , serum concentrations of NGF did not differ from basal levels.
- In Phase I/II (NGF0212/REPARO) in NK patients, NGF serum levels were below the lower level of quantification in almost all patients (detectable serum NGF levels likely reflected known inter- and intra-individual fluctuations independent of study treatment).
- No systemic immunogenicity was detected in any clinical studies. With no (or negligible) systemic exposure, off-target pharmacological activity or toxicity are unlikely.
- The hydrophilic rhNGF solution has a very low residence time in the eye (quickly removed with the tear flow).


1. Bonini S, Lambiase A, Rama P et al. Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis. Ophthalmology. 2018;125:1332-1343
2. Mauro P. Ferrari et al. Safety and Pharmacokinetics of Escalating Doses of Human Recombinant Nerve Growth Factor Eye Drops in a Double-Masked, Randomized Clinical Trial. BioDrugs (2014) 28:275–283

# Regener-Eyes® - Clinical Information

## Regener-Eyes® 12-month Patient Outcome Data

SPEED™ Questionnaire is a validated survey rating frequency and severity of symptoms such as dryness, grittiness, scratchiness, soreness, irritation, burning, watering and eye fatigue. Scores range from 0 to 28, with 28 being the most severe (the lower the score the better).



# Visus

- *First Patients Dosed in 30-Day Efficacy and Safety Trial Evaluating Presbyopia-Correcting Eye Drop*

Visus Therapeutics Inc., a clinical-stage pharmaceutical company in pursuit of developing the world's first presbyopia-correcting eye drop with the potential to last a minimum of eight hours, today announced the commencement of its Phase 2 clinical trial of BRIMOCHOL™ topical ophthalmic solution under investigation for the treatment of presbyopia.

Presbyopia is the loss of near vision associated with aging, making it difficult to perform certain tasks like reading fine print. It typically begins when adults are in their 40s, and becomes almost universal by age 50,[1] impacting approximately 123 million adults in the U.S. alone.[2]

# Visus

- BRIMOCHOL is a proprietary pupil-modulating eye drop that combines two well-studied, FDA-approved pharmaceuticals: carbachol (a cholinergic agent) and brimonidine tartrate (an alpha-2 agonist).
- Together, they produce a “pinhole effect”, which reduces the size of the pupil so that only centrally focused light rays are able to enter the eye, thereby sharpening distant and near images while minimizing side effects.
- The result is clarity of vision for near tasks like reading or using a smartphone.

# Visus

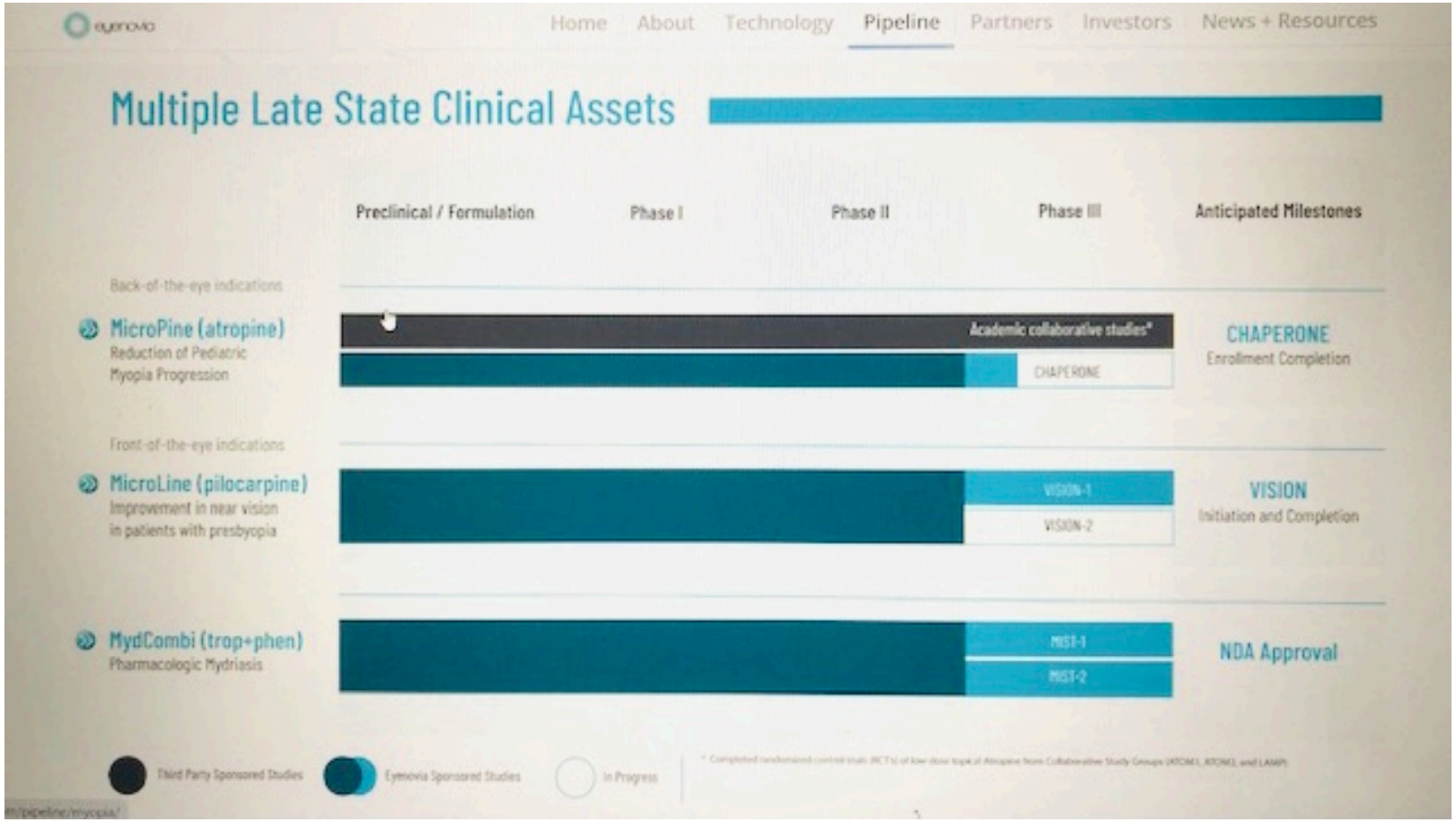
- Brimochol has entered a Phase II clinical trial, expected to enroll 40 patients with emmetropic phakic and pseudophakic presbyopia, to evaluate the safety and efficacy of two proprietary formulations of Brimochol. The primary endpoint is the percentage of patients gaining 3 lines or more in near visual acuity without losing distance vision.
- “We expect to have top-line results from the Phase II at the end of Q2, and two Phase III studies enrolling over 500 patients will commence in Q3 of this year,” Bergo said.
- “Based on that data, we expect to file the NDA [new drug application] in Q3 of 2022, putting us on course for an approval in Q3 of 2023.”

# Eyenovia Announces Positive Topline Results from VISION-1 Phase 3 Clinical Study of MicroLine for the Treatment of Presbyopia

# Eyenovia

- Eyenovia, Inc. (NASDAQ: EYEN), a clinical stage ophthalmic biopharmaceutical company developing a pipeline of MAP™ therapeutics, today announced that its VISION-1 study evaluating the company's proprietary pilocarpine formulation, MicroLine, for the temporary improvement of near vision in adults with presbyopia, achieved its primary endpoint.
- Preparations are underway for a second Phase 3 registration study, VISION-2. These studies are required for FDA approval and will serve as the basis for a planned New Drug Application (NDA) submission to FDA. VISION-1 results will be presented at a future ophthalmic-focused medical meeting.

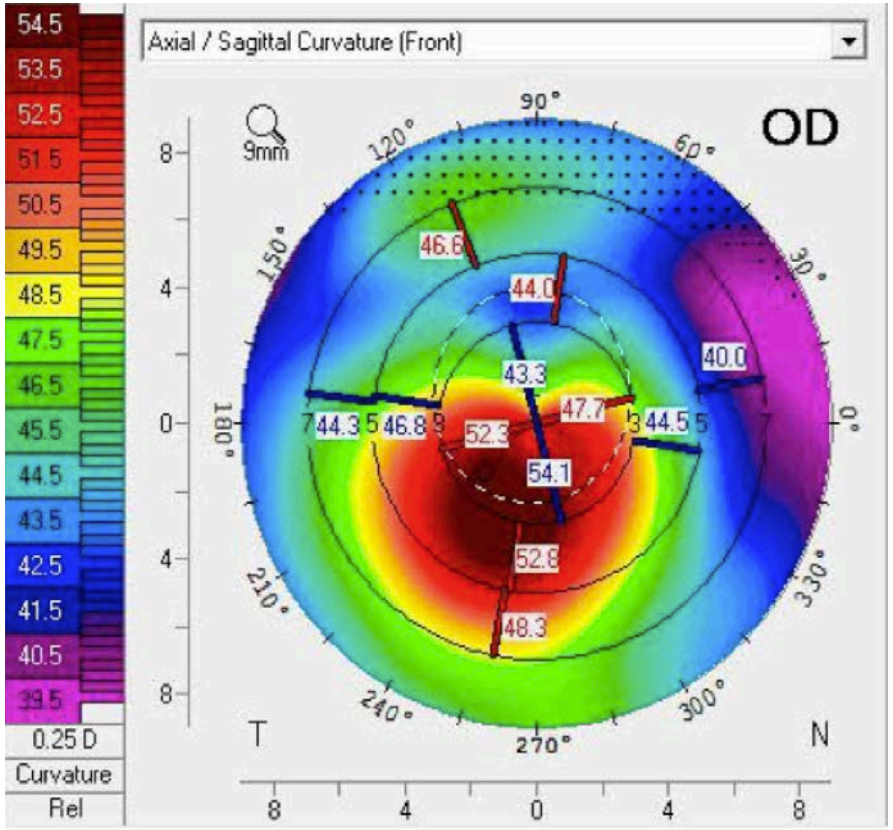
# Eyenovia


eyenovia
Home
About
Technology
Pipeline
Partners
Investors
News + Resources
Multiple Late State Clinical Assets
Preclinical / Formulation
Phase I
Phase II
Phase III
Anticipated Milestones
Back-of-the-eye indications
MicroPine (atropine)
Reduction of Pediatric Myopia Progression
Academic collaborative studies*
CHAPERONE
CHAPERONE
Enrollment Completion
Front-of-the-eye indications
MicroLine (pilocarpine)
Improvement in near vision in patients with presbyopia
VISION-1
VISION-2
VISION
Initiation and Completion
MydCombi (trop+phen)
Pharmacologic Mydriasis
MIST-1
MIST-2
NDA Approval
Third Party Sponsored Studies
Eyenovia Sponsored Studies
In Progress

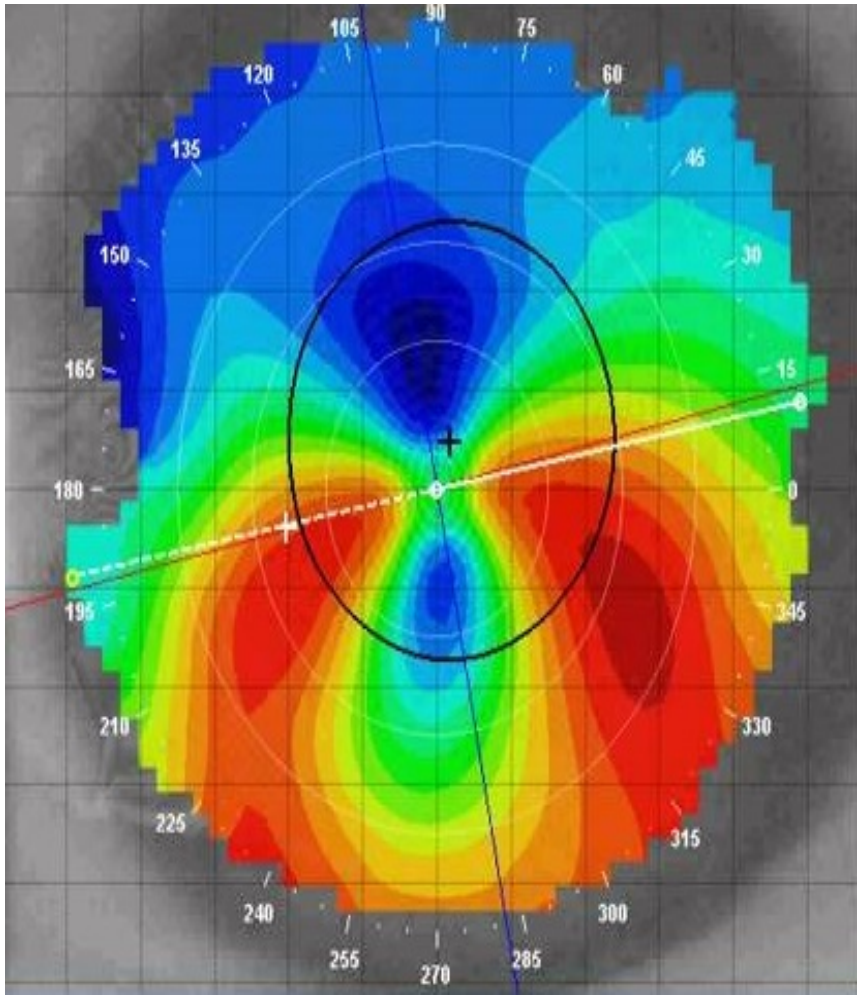
# Refractive/Corneal Surgery is no Longer Just Cosmetic

- CXL
- CXL/ Topoguided PRK
- CXL / Topo/ CEX

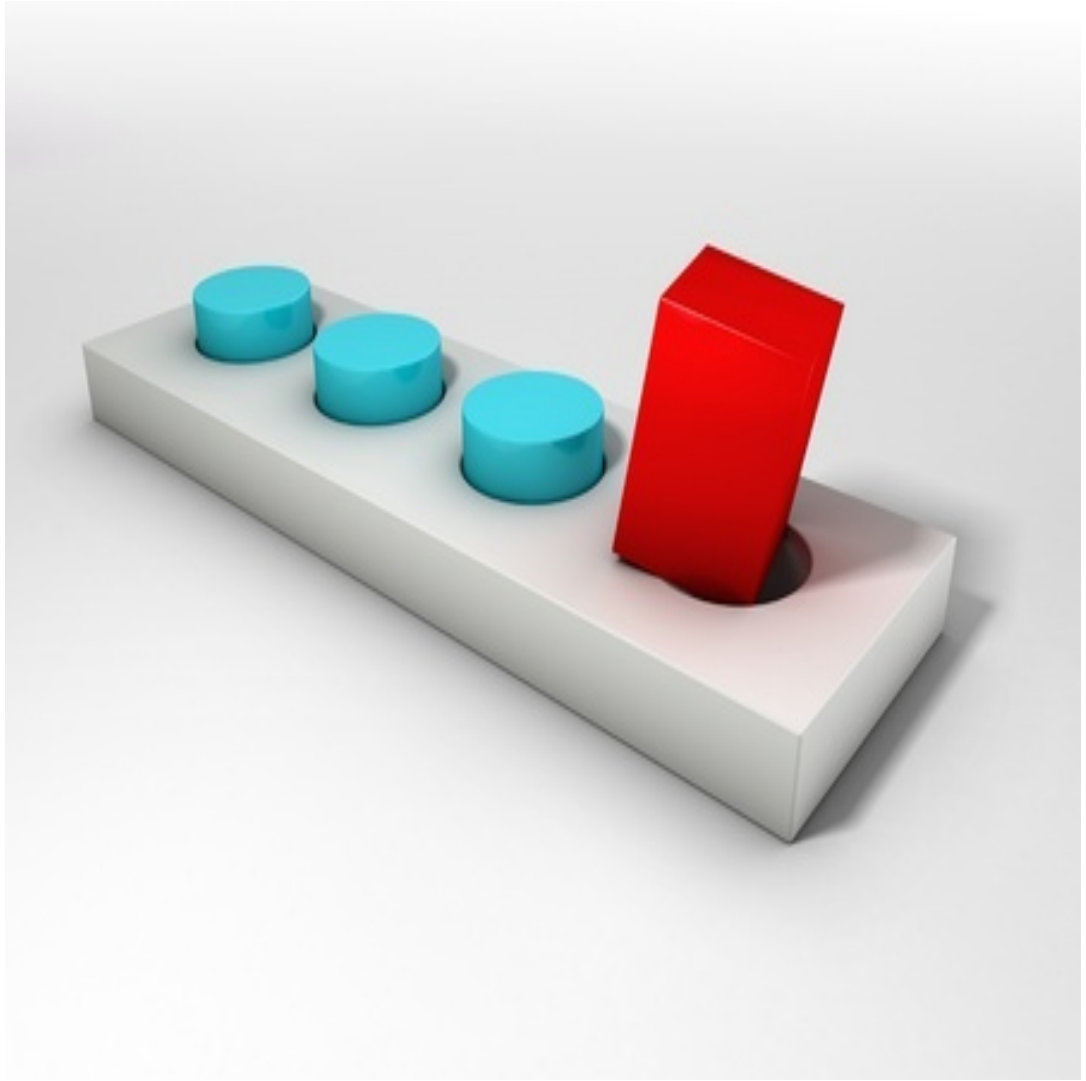
# Refractive Cornea Surgery for the 21 Century



# Where Do You Place a Toric IOL in This Case ?



# Placing a Toric IOL in a Keratoconus Case

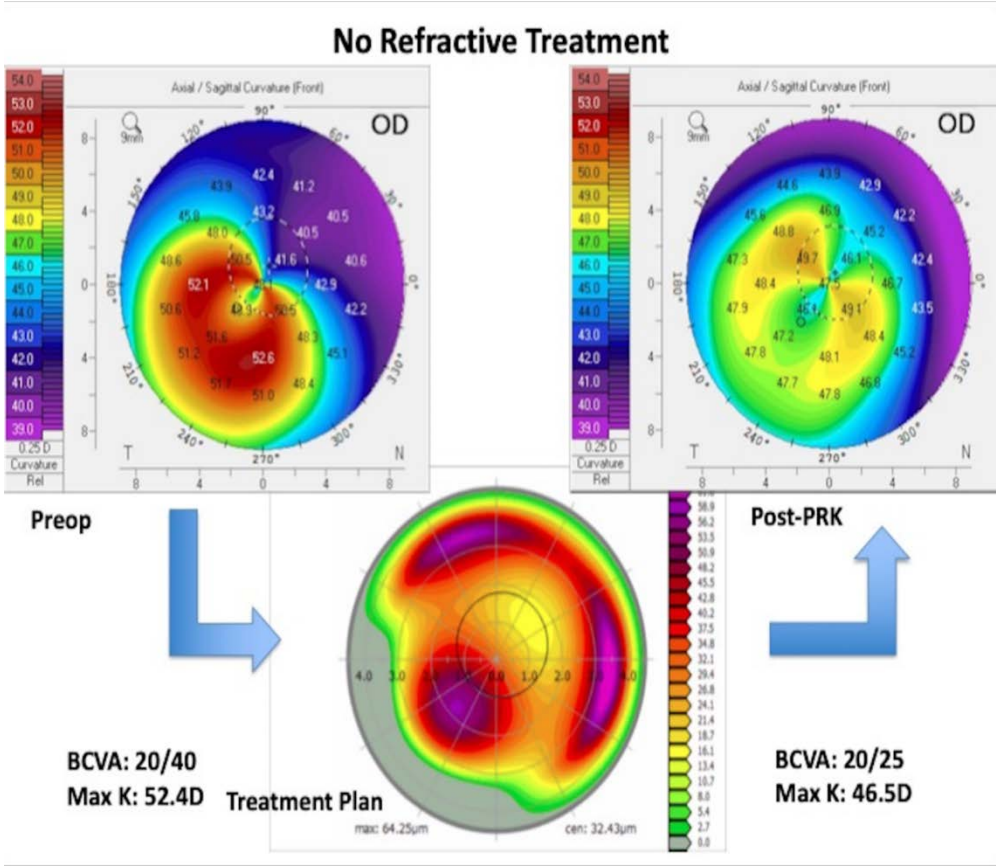


# Crosslinking, Topography-Guided PRK, Followed by Cataract Surgery

## The Triple Lindy of Refractive corneal surgery

- Cornea- Cross link and improve the corneal stability/ wait 3 months minimum
- Refractive- Topographic ablation/ wait 3 months minimum
- Cataract- Cataract surgery often with a toric IOL

# Topographic Ablation Without Refractive Treatment

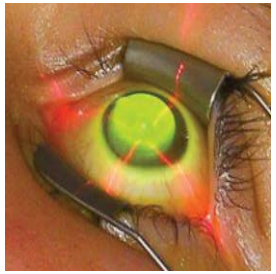


# Non-invasively Stabilizing and Reshaping the Cornea

## *Corneal Remodeling Technology*

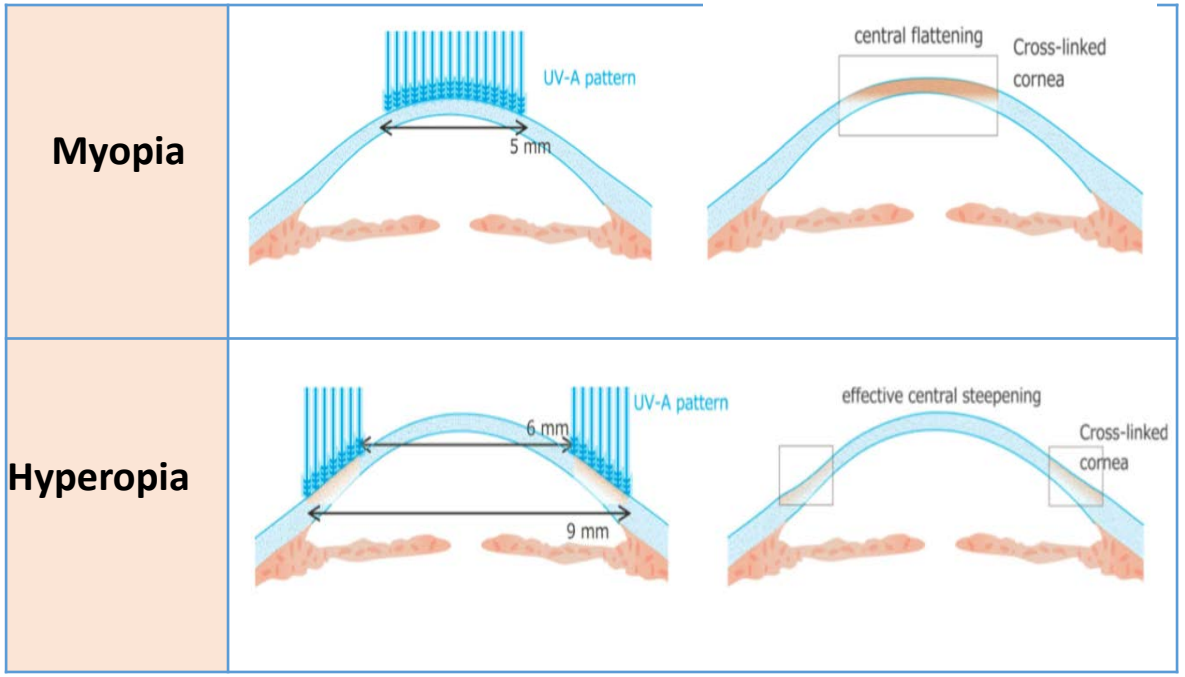
Pharmaceutical Application

Uniform Activation to **Stabilize**



# PiXL: Corneal Remodeling for Refractive Error

## Non-invasive refractive correction treatment concept




**Selective activation** of riboflavin with specific UVA pattern to induce targeted stiffening → corneal remodeling

"Bulging" of the cornea in untreated regions targets **central flattening** for reduction of myopia or **central steepening** for presbyopia

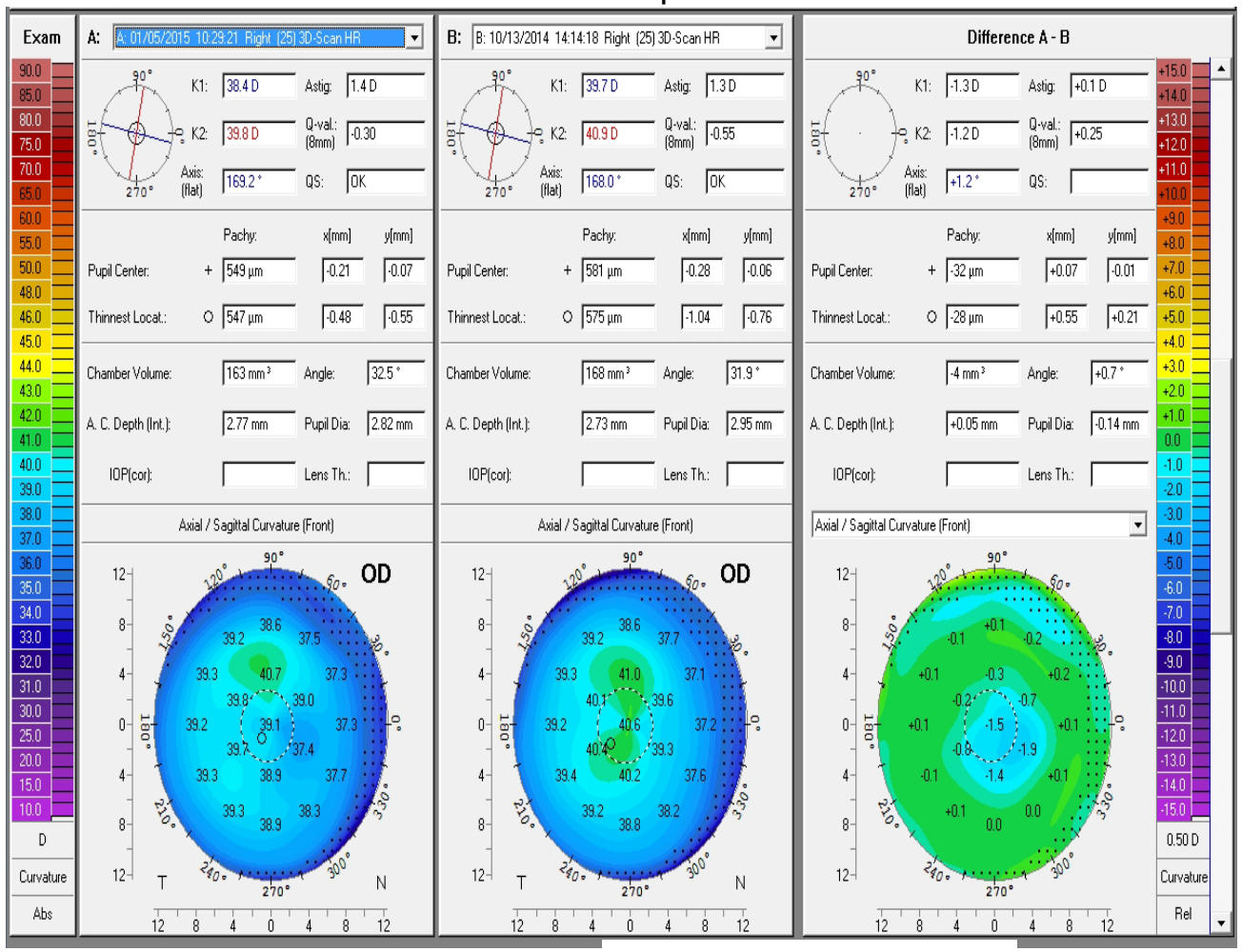
# PiXL Case Example– 38 Year Old Myopic Female

**Pre-OP:**
-1.75-0.75x175
UCVA: 20/50
BCVA: 20/20

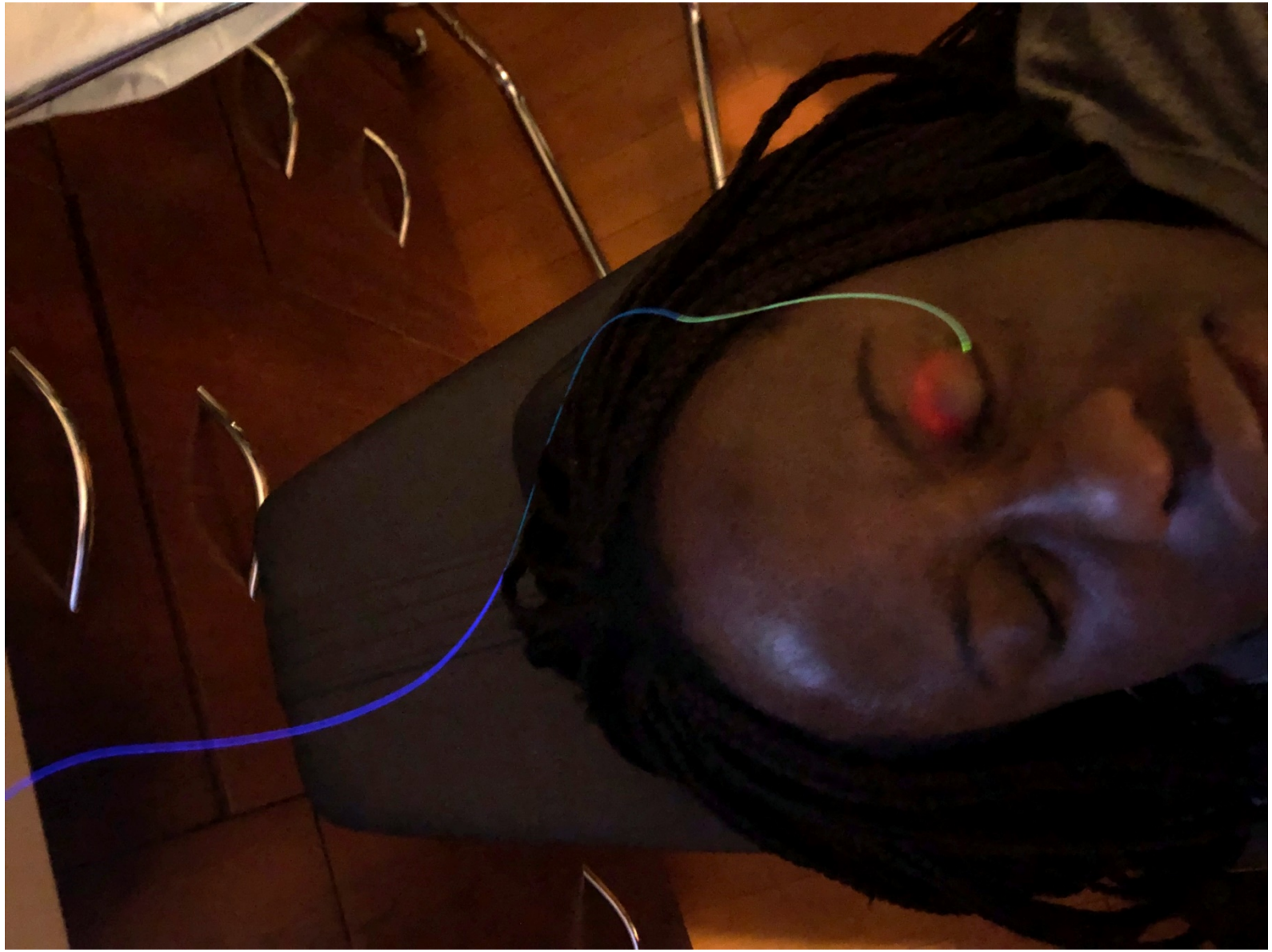
**1 Month Post-Op:**
-0.00-1.00x156
UCVA: 20/25
BCVA: 20/20

**6 Months Post-OP:**
-0.25-0.50x160
UCVA: 20/25
BCVA: 20/20

**12 Months Post-OP:**
-0.25 -0.50x180
UCVA: 20/20
BCVA: 20/20



# Fiberoptic Refractive Crosslinking



# Sustained Release Therapies: The future of drug treatment

Durysta

Dextenza

Dexycu

# Durysta™ (Bimatoprost Implant) for Intracameral Administration

# Proprietary Drug Delivery System

**Sustained-release, Biodegradable Implant**

- Solid polymer matrix[1]
- Biodegrades to water and carbon dioxide[1]
- Single-use applicator[1]
- May be administered as a sterile in-office procedure[2]

**Actual Size**


1. Haghjou N et al. *J Ophthalmic Vis Res*. 2011; 6(4):317-329. 2. Mehta H et al. *Ther Adv Chronic Dis.* 2015; 6(5):234-245.

# Bimatoprost Implant

- Bimatoprost is a prostamide that has been shown to reduce IOP when administered topically
- A biodegradable implant has been developed
- The implant is designed to be placed intracamerally in the eye and provide slow release of bimatoprost over time


Gonioscopic photographs of bimatoprost sustained-release implant 10 µg in the anterior chamber of an eye of a representative patient diagnosed with open-angle glaucoma

IOP = intraocular pressure

Lewis R, et al. *Am J Ophthalmol* 2017;175:137-147.

# Drug Delivery Technology Modifications for Glaucoma

- The drug delivery system can be modified to provide different release profiles[1]
- For glaucoma treatment, the drug delivery system used with the bimatoprost implant has been modified to provide a steady state release of medication[1*]

Bimatoprost implant applicator system

*While the rate at which the body eliminates most drugs is proportional to the concentration administered, known as **first order kinetics**, drugs that work by zero order kinetics work at a predictable, constant rate.[2]

1. Lewis R, et al. *Am J Ophthalmol* 2017;175:137-147. 2. Study.com Zero Order Kinetics. Website: https://study.com/academy/lesson/zero-order-kinetics-definition-pharmacology-examples.html Accessed 9/24/2018.

# Study Background

***ARTEMIS***

| | |
|---|---|
| **Design** | Two multicenter, randomized, parallel-group, patient and efficacy evaluator masked active controlled 20- month studies including eight month follow-up conducted in patients with OAG or OHT |
| **Treatments** | Twice daily topical timolol 0.5% or bimatoprost implant |
| **Outcomes** | **Co- Primary Endpoint:**<br>• Mean IOP by Treatment Group<br>• Treatment Difference in Mean IOP |

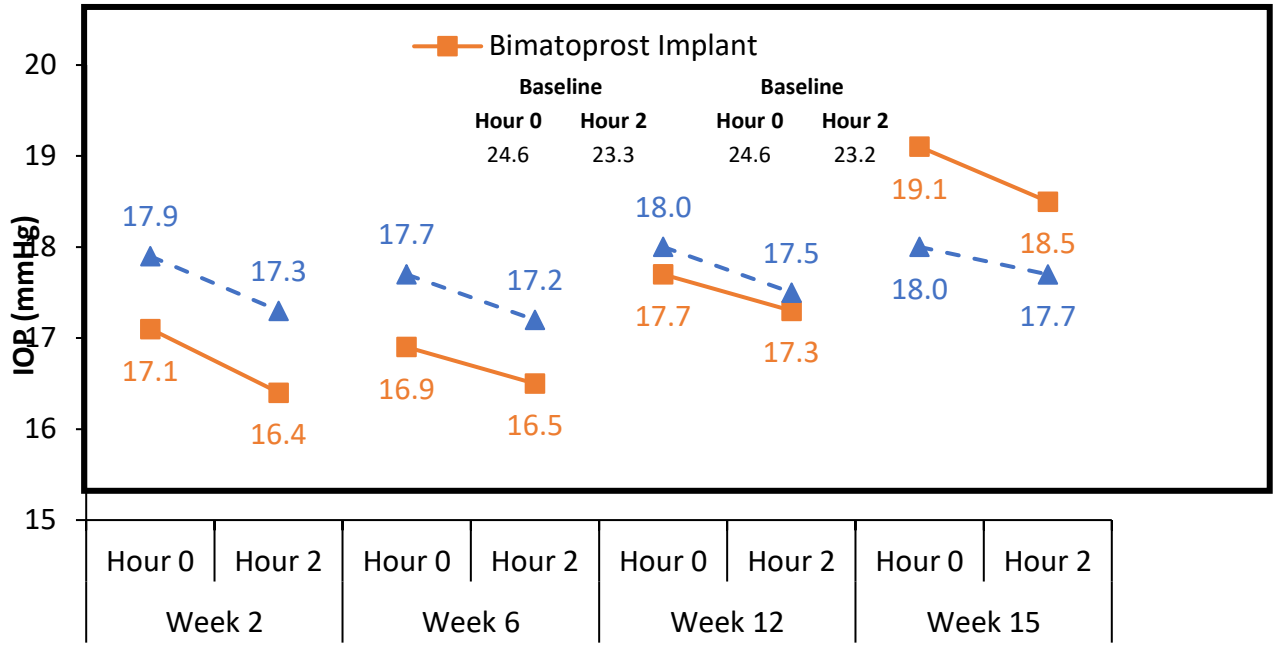
IOP = intraocular pressure; OAG = open angle glaucoma; OHT = ocular hypertension

1. DURYSTA™ [package insert]. Irvine, CA: Allergan USA, Inc., March 2020. 2. . U.S. National Library of Medicine ClinicalTrials.gov. Retrieved from website: www.ClinicalTrials.gov. ClinicalTrials.gov Identifiers: NCT02247804, NCT02250651 Accessed 11/1/20

# Mean IOP by Treatment Group and Treatment Difference in Mean IOP

Primary Endpoint

***ARTEMIS Study 1***

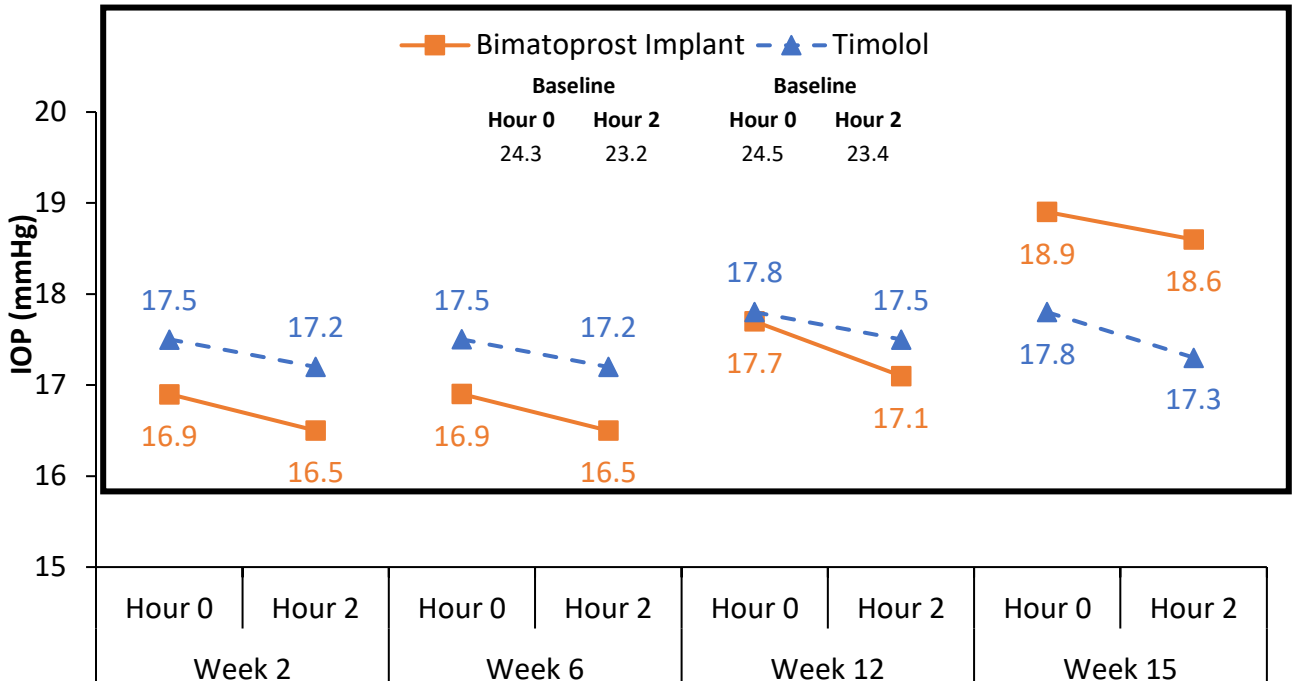



1. DURYSTA™ [package insert]. Irvine, CA: Allergan USA, Inc., March 2020.

# Primary Endpoint

***ARTEMIS Study 2***

## Mean IOP by Treatment Group and Treatment Difference in Mean IOP




1. DURYSTA™ [package insert]. Irvine, CA: Allergan USA, Inc., March 2020.

# Diopter Corporation

- Contact Lens Delivery System for Glaucoma

# Diopter

## The Platform

Patented advanced drug-eluting contact lens
for multiple eye disease indications

Approved
Contact Lens

+

Approved
Drugs

=

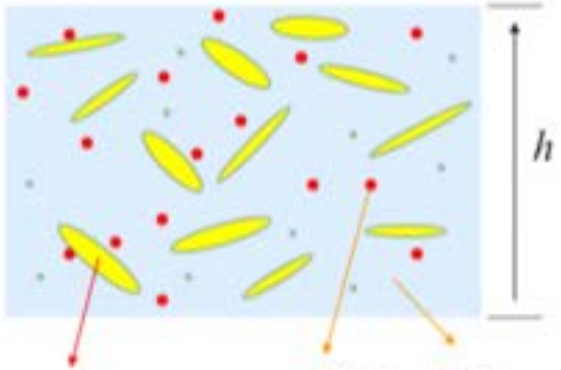
**Products:**
Glaucoma
Infection
Allergy
Rare Diseases

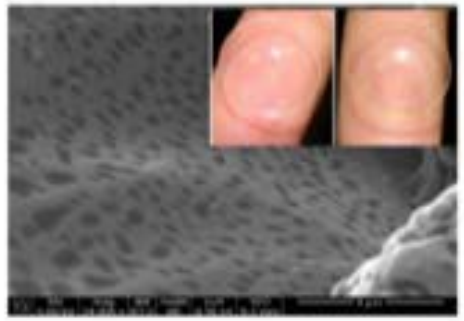
**$B Markets**

# Diopter

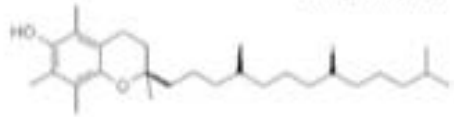
## Novel Diopter Technology

Diffusion Barriers Loaded Lenses



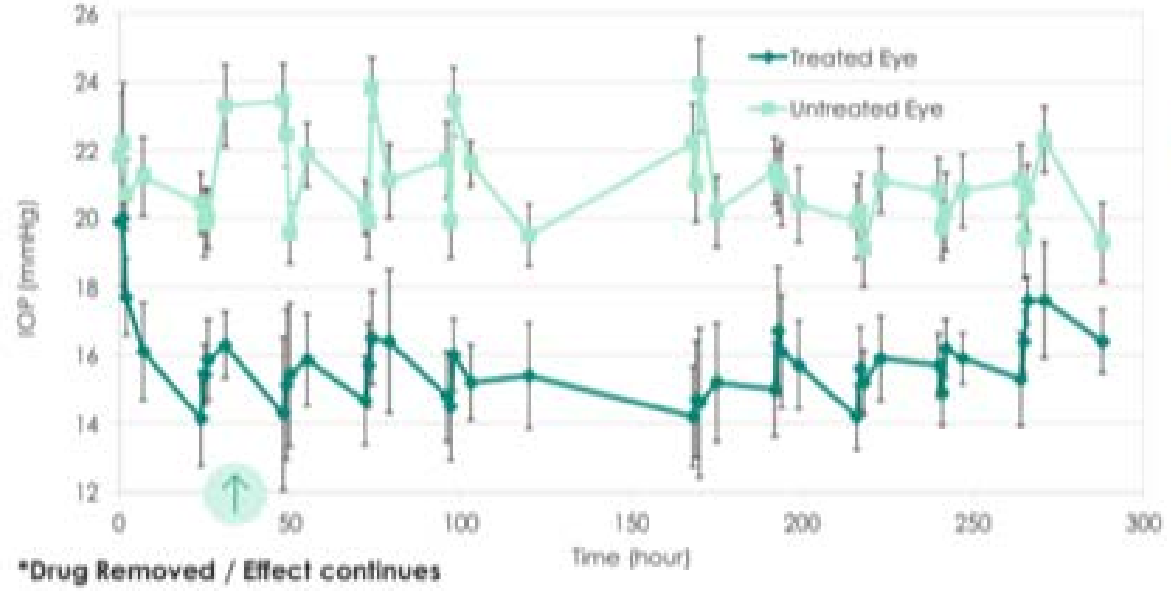
Vitamin E



# Diopter

## Glaucoma Drug Lens

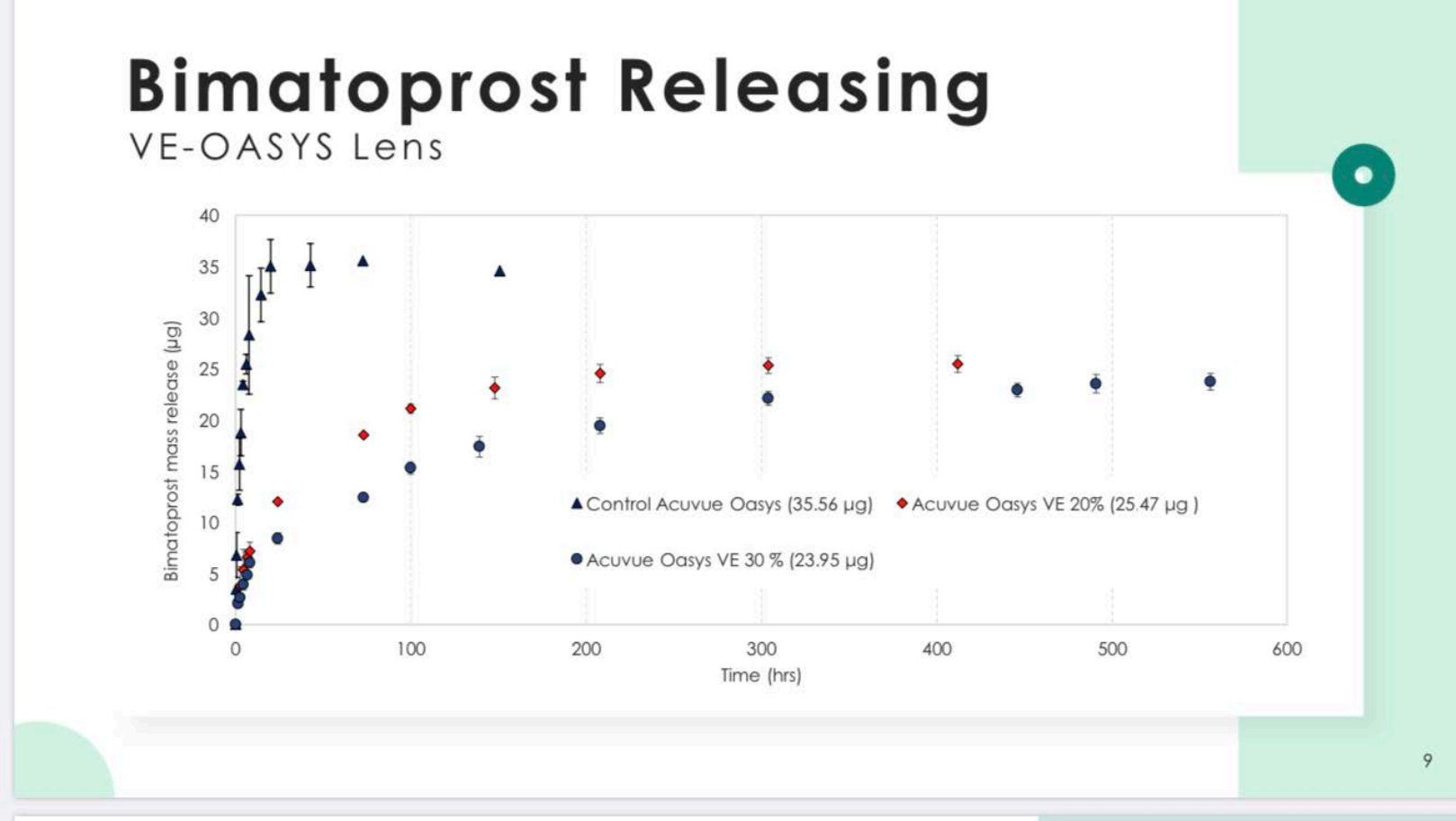
Lowers IOP by 20% in Animal Model




***Drug Removed / Effect continues**

*Timolol & Dorzolamide (Cosopt)

# Diopter


Bimatoprost Releasing
VE-OASYS Lens
Bimatoprost mass release (µg)
0
5
10
15
20
25
30
35
40
0
100
200
300
400
500
600
Time (hrs)
Control Acuvue Oasys (35.56 µg)
Acuvue Oasys VE 20% (25.47 µg )
Acuvue Oasys VE 30 % (23.95 µg)
9

# Innovative Therapy for the Anterior Segment

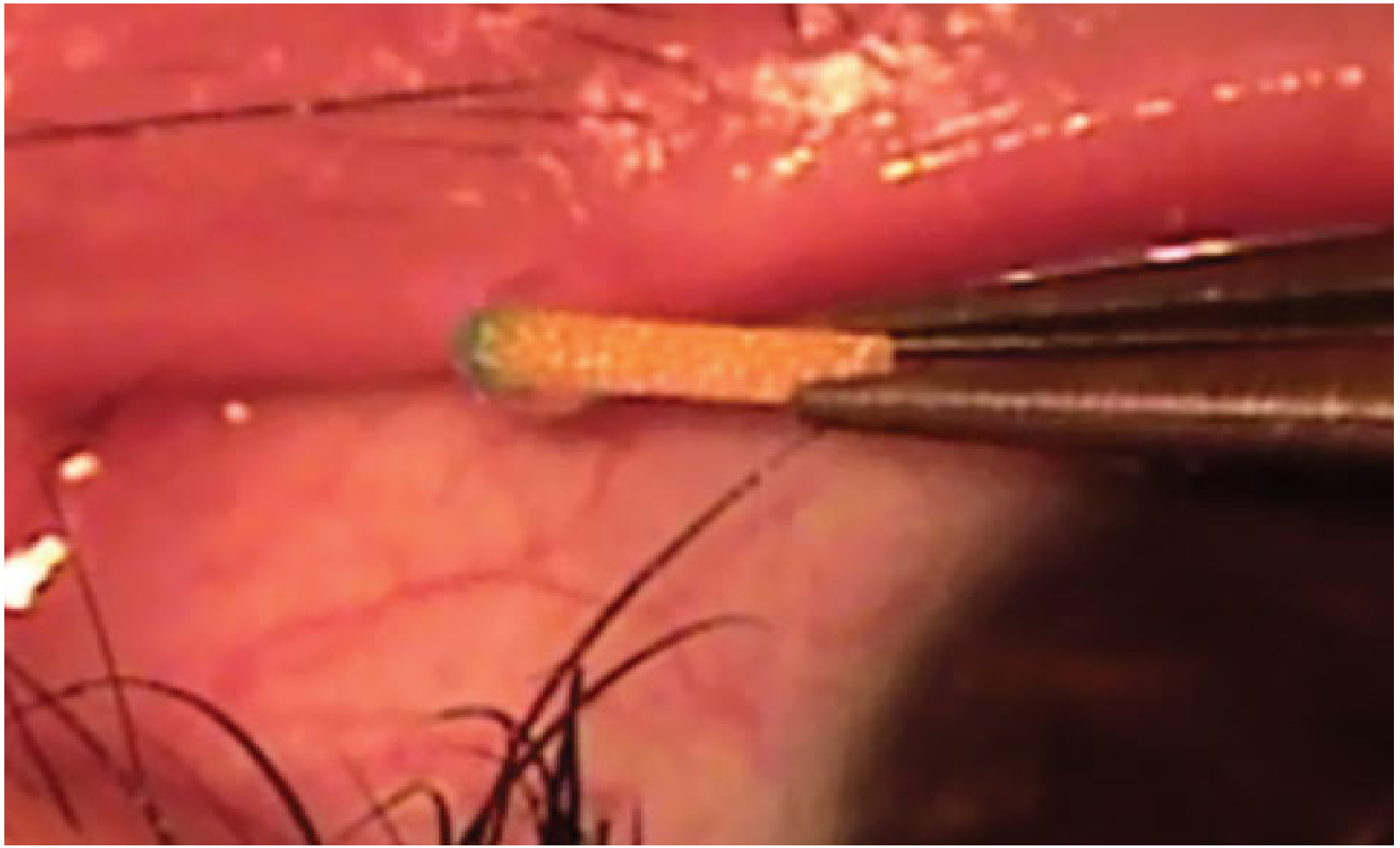
- BAK Filtration Bottle (TearClear Technologies)
- Dexycu Intraocular Sustained Release
- Dexamethasone Punctal Plug (Ocular Therapeutix)

# Sustained Release Dexamethasone - Ocular Therapeutix

- Bioabsorbable intracanalicular hydrogel plug
- Drug . month

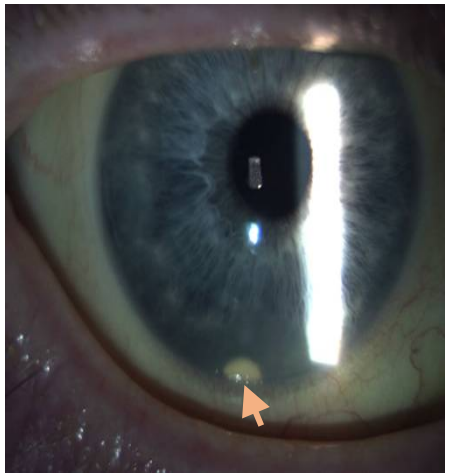

Intracanalicular Depot

# Ocular Therapeutix

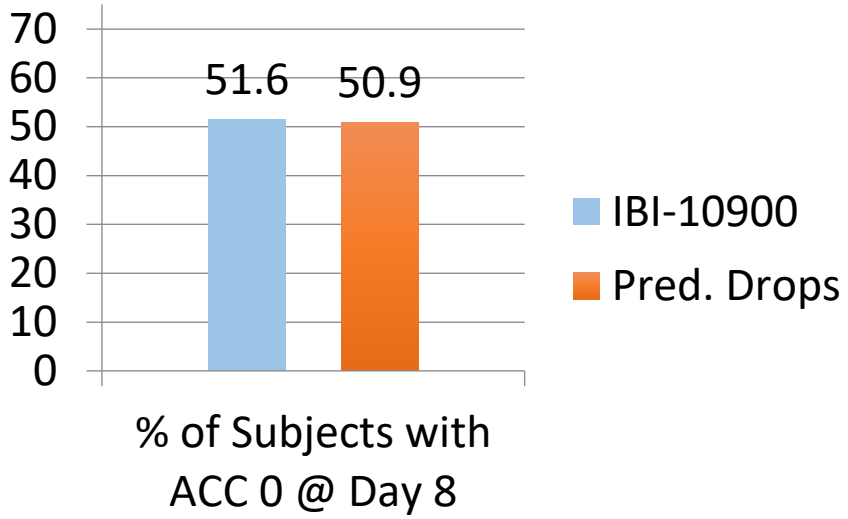


# Dexycu Dexamethasone Suspension for Intraocular Administration

- A bioabsorbable drug delivery product for anterior chamber intracameral placement of dexamethasone
- Therapeutic levels are maintained for up to 21 days with a single administration[a]

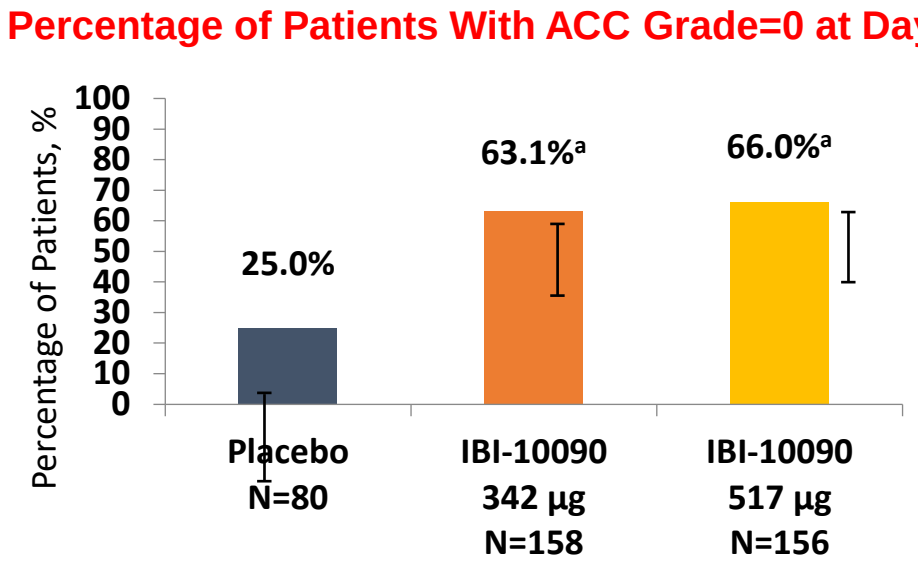


## Percentage of Patients With ACC Grade=0 (Yes/No) at Day 8
## Dexycu vs Prednisolone Acetate 1%




Donnenfeld E; A Prospective, Randomized, Study to Evaluate the Efficacy and Safety of IBI-10090 for the Treatment of Inflammation after Cataract Surgery; ASCRS 2017

# Intracameral Sustained Release Dexamethasone




Donnenfeld, E. The Safety and Efficacy of a Novel Intracameral Dexamethasone Drug Delivery Suspension for Treating Inflammation Associated With Cataract Surgery. *ASCRS* 2015.

# A Prospective Phase 2 FDA Study of Nepafenac Punctal Plug Delivery System Verses Placebo in Controlling Post Cataract Pain and Inflammation

**Eric Donnenfeld, MD**
Clinical Professor of Ophthalmology, New York University
Trustee Dartmouth Medical School

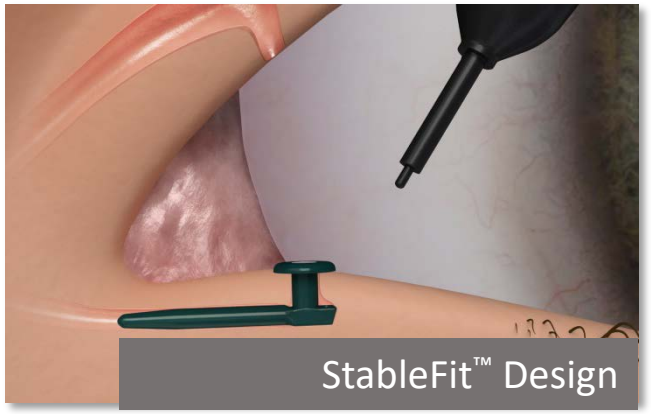
**Edward Holland, MD**
Professor of Ophthalmology, University of Cincinnati

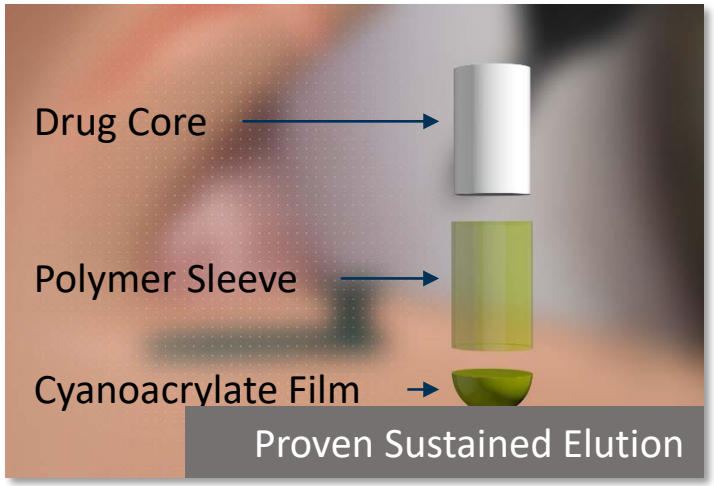
Donnenfeld, Holland JCRS 2020

# Evolute® Punctal Plug Delivery System

## Successful By Design

1. Easy to place and remove
2. Cosmetically invisible – easy to identify
3. Tolerable
4. Consistent, sustained efficacy
5. Use in multiple disease states




# L-PPDS – Target Dosing

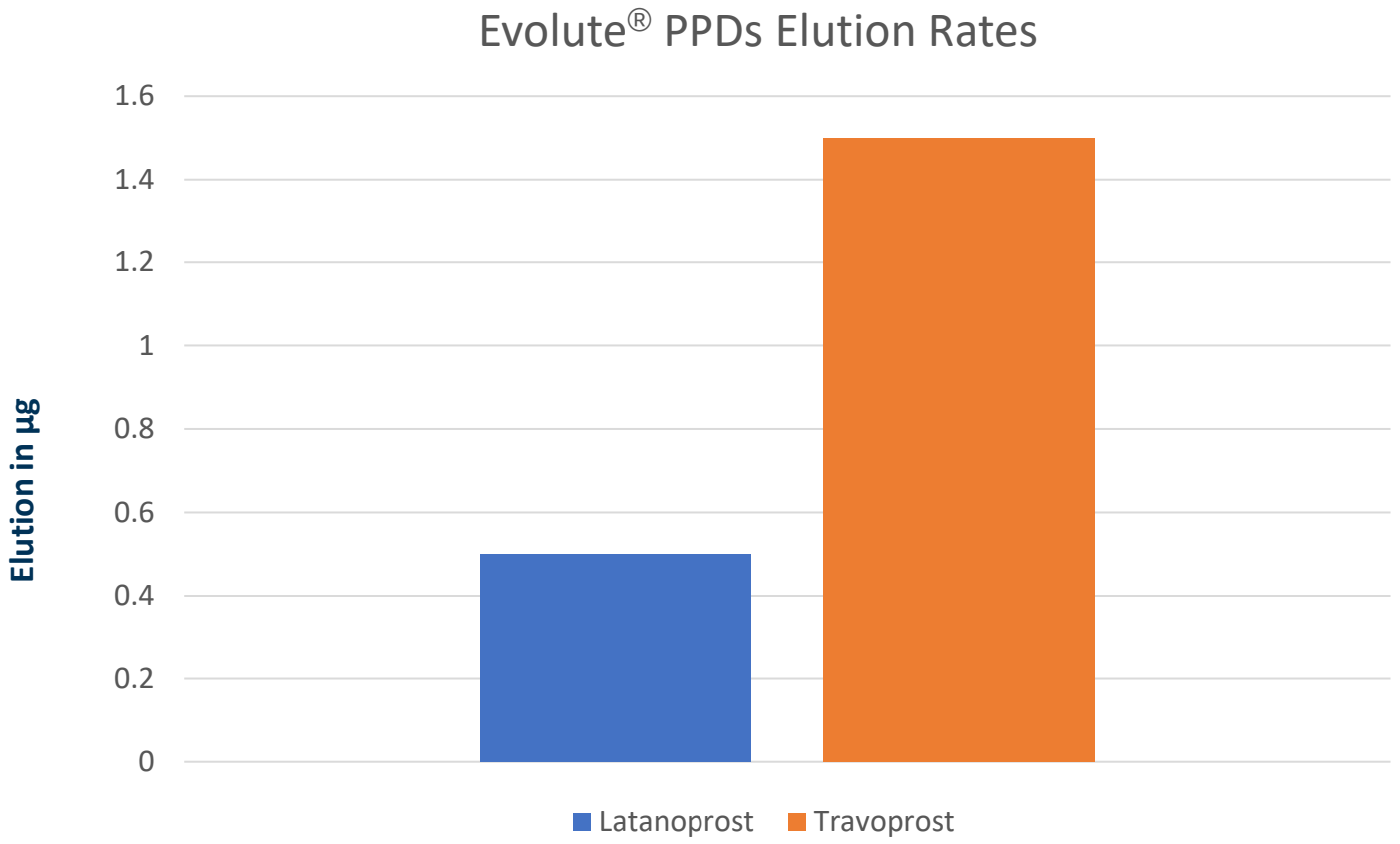
- Commercial latanoprost – Xalatan :
  - Concentration : 0.005% latanoprost
  - Dosing : Once a day

- Assumptions :
  - Drop volume = 25µL to 35µL
  - Delivery efficiency = 10%

- Estimated concentration the surface of the eye receives from a drop:
  - 15µg to 25µg per day of active therapeutic

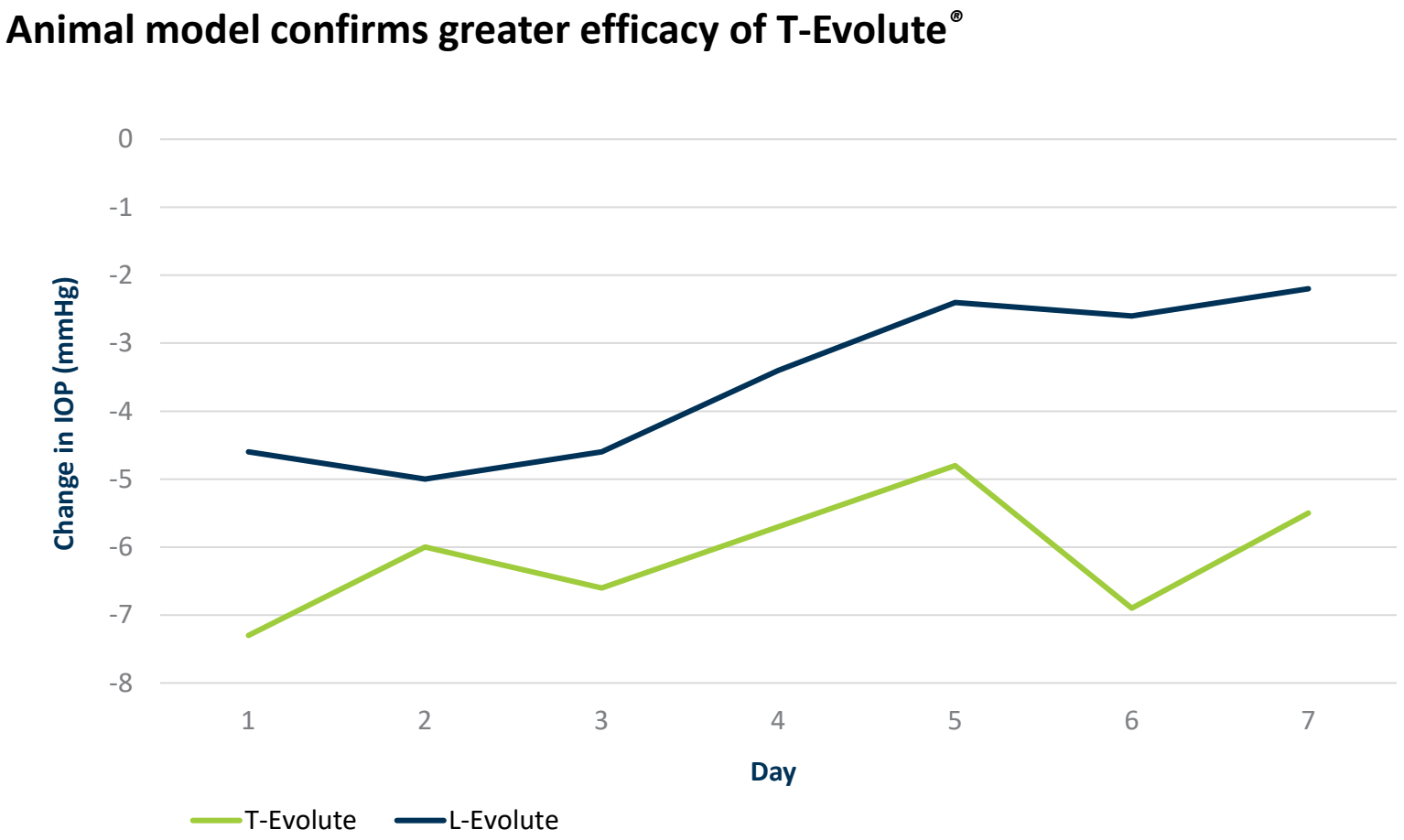
- Amount of latanoprost delivered per day by Evolute® Punctal Plug
  - 0.5µg to 0.7µg per day of active therapeutic without any preservatives

# Travoprost - Accelerated Screening Model for Elution Rates




The Travoprost-Evolute® PPDs is a more potent active and will elute two to three times the concentration of the Latanoprost-Evolute® PPDs

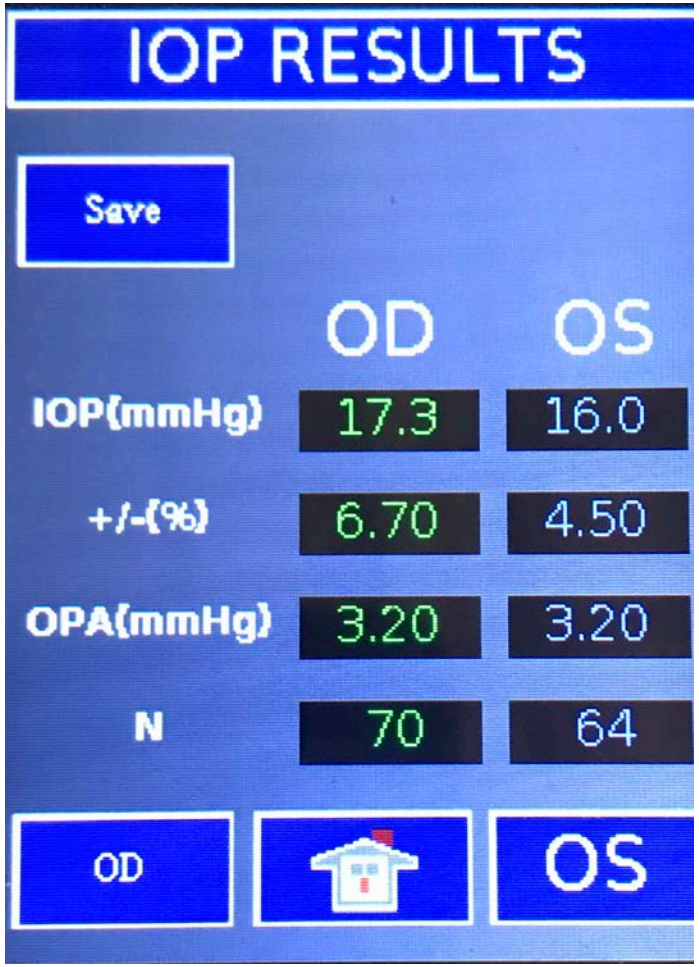
# Animal IOP Model (Mean Time Points) -Travoprost



# Falck Multisystem

# Intraocular Pressure

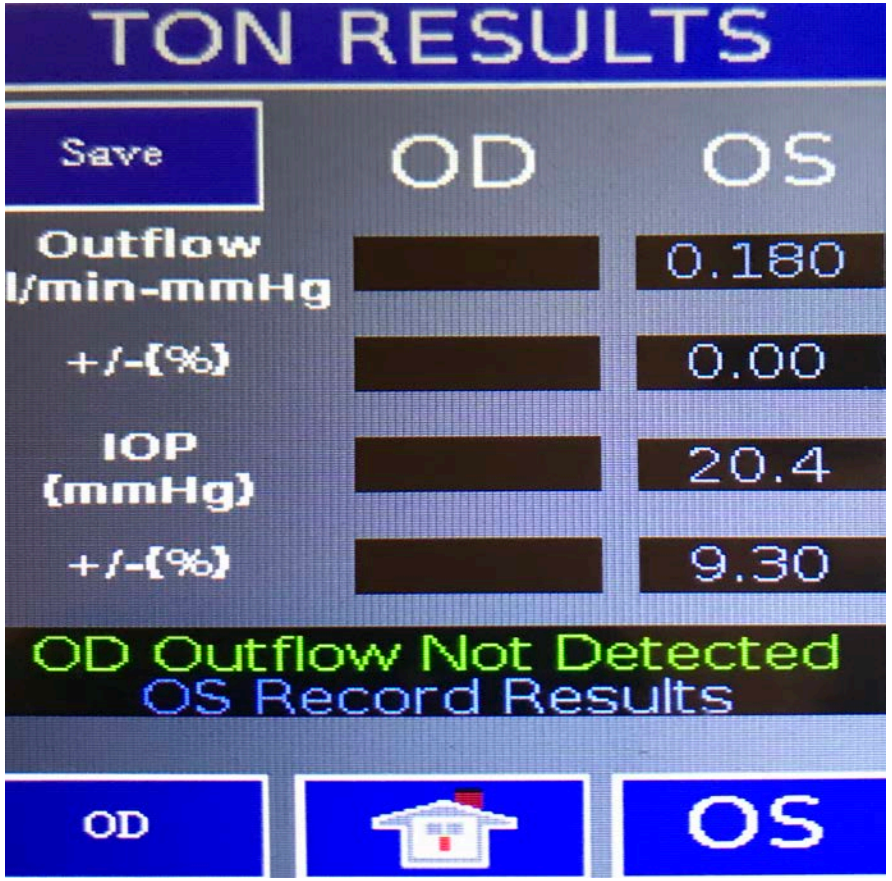
- ✓ Optical  Applanation Measurement
- ✓ Compensates for Corneal Biomechanics
- ✓ Multiple Serial IOP Measurements – N Value
- ✓ Systolic and Diastolic IOP
- ✓ Average IOP Displayed
- ✓ IOP Variation with Cardiac Cycle - OPA
- ✓ Precision Displayed



# TONOGRAPHY

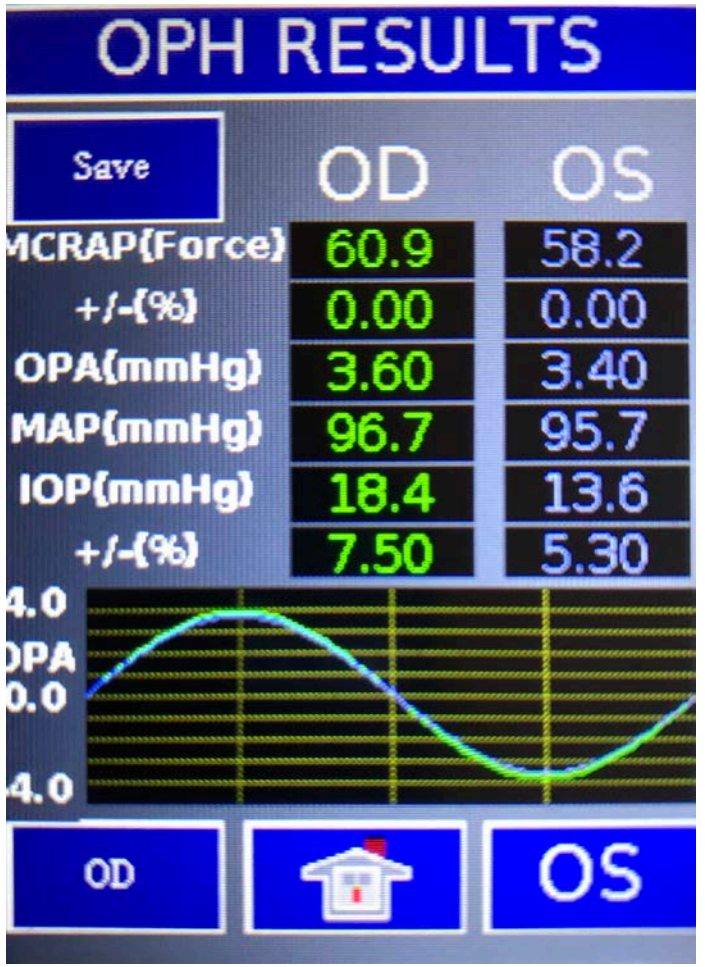
- ✓ Optical Aqueous Humor Outflow Measurement.
- ✓ Aqueous Outflow Decreased in Glaucoma.
- ✓ Decreased Outflow = Increased TM Resistance.
- ✓ Decreased Outflow = Increased IOP Fluctuation.
- ✓ Document Therapeutic Efficacy of Outflow Interventions.
- ✓ Document Need for Additional Intervention.
- ✓ Glaucoma risk assessment.

✓CPT: 92499



# OPHTHALMODYNAMOMETRY

- ✓ Mean Central Artery Pressure (MCRAP) measurement.
- ✓ Data Captured During Multiple Cardiac Cycles.
- ✓ Mean Arterial BP Displayed.
- ✓ MCRAP – IOP = True Ocular Perfusion Pressure (OPP).
- ✓ Reduced OPP is a risk factor for glaucoma progression.
- ✓ Abnormal OPH - Increased Risk of Stroke



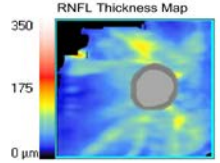
# The Case of the Asymmetric ONH

- 63 y/o white male presented for consultation for glaucoma evaluation
- VA: 20/20 OU
- Peak IOP: 26/23
- Ta: 21/19 mmHg
- Tonography: 0.18 OD / 0.24 OS
- Pach: 560/558
- CH: 8.9/9.1

| | | | | |
|---|---|---|---|---|
| DOB: | 5/7/1957 | Exam Time: | 2:26 PM | 2:27 PM |
| Gender: | Unknown | Serial Number: | 5000-20205 | 5000-20205 |
| Technician: | Stein, Jonathan | Signal Strength: | 6/10 | 9/10 |

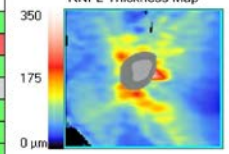
## ONH and RNFL OU Analysis:Optic Disc Cube 200x200 OD ● | ● OS

RNFL Thickness Map

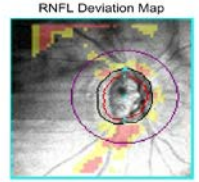



| | OD | OS |
|---|---|---|
| Average RNFL Thickness | 77 µm | 86 µm |
| RNFL Symmetry | 17% | |
| Rim Area | 1.12 mm² | 1.27 mm² |
| Disc Area | 3.00 mm² | 1.87 mm² |
| Average C/D Ratio | 0.78 | 0.56 |
| Vertical C/D Ratio | 0.77 | 0.55 |
| Cup Volume | 0.722 mm³ | 0.149 mm³ |

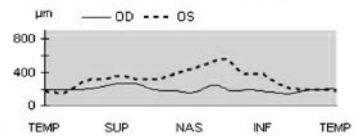
RNFL Thickness Map



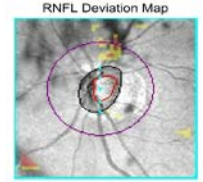

RNFL Deviation Map



Neuro-retinal Rim Thickness

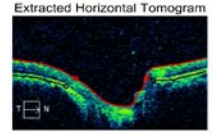



RNFL Deviation Map

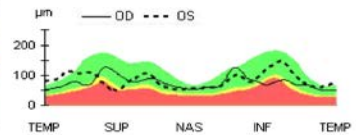


Disc Center(0.72,0.09)mm

Extracted Horizontal Tomogram

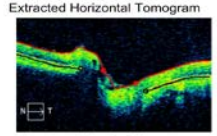


RNFL Thickness

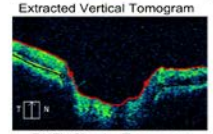


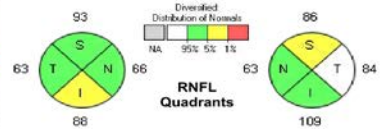

Disc Center(-0.21,0.39)mm

Extracted Horizontal Tomogram

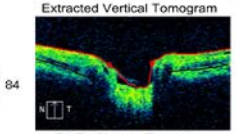


Extracted Vertical Tomogram

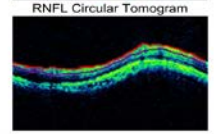


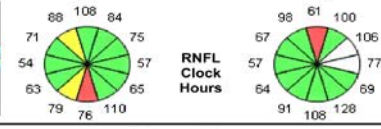



Extracted Vertical Tomogram

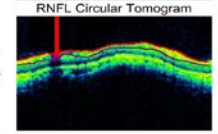


RNFL Circular Tomogram






RNFL Circular Tomogram



Comments

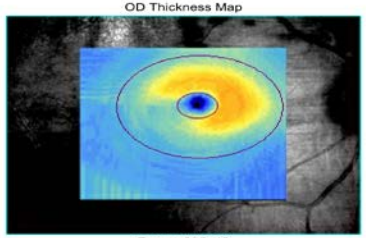
Doctor's Signature

| | | | OD | OS | |
|---|---|---|---|---|---|
| Name: | [redacted] | | | | |
| ID: | CZMI124726[redacted] | Exam Date: | 9/19/2019 | 9/19/2019 | O.C.C. |
| DOB: | [redacted] | Exam Time: | 2:23 PM | 2:27 PM | |
| Gender: | Unknown | Serial Number: | 5000-20205 | 5000-20205 | |
| Technician: | Stein, Jonathan | Signal Strength: | 10/10 | 10/10 | |

## Ganglion Cell OU Analysis: Macular Cube 512x128

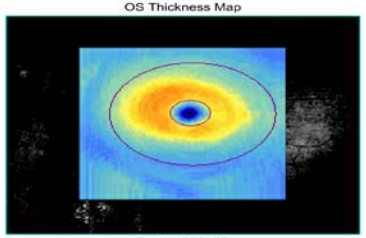
OD ● ● OS

OD Thickness Map



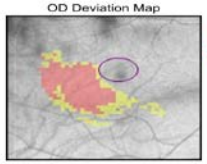

Fovea: 295, 49

OS Thickness Map



Fovea: 279, 55

OD Deviation Map

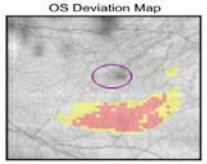


OD Sectors


Diversified Distribution of Normals
95%
5%
1%

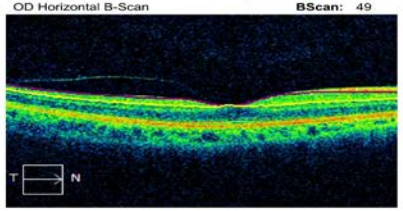
OS Sectors


OS Deviation Map

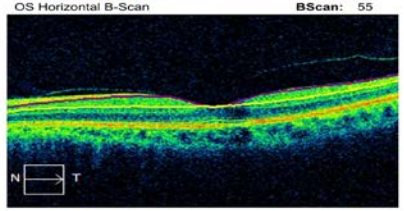


| | OD µm | OS µm |
|---|---|---|
| Average GCL + IPL Thickness | 74 | 77 |
| Minimum GCL + IPL Thickness | 59 | 70 |

OD Horizontal B-Scan **BScan:** 49




OS Horizontal B-Scan **BScan:** 55




Comments

Doctor's Signature

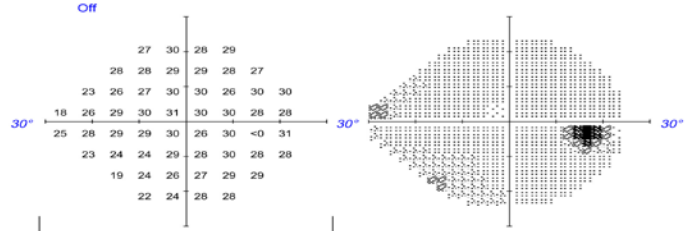
Patient: [redacted]
Date of Birth: [redacted]
Gender: Female
Patient ID: 05071957

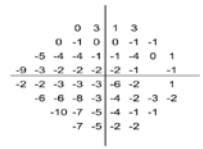
ZEISS

Ophthalmic Consultants of Connecticut
1375 Kings Highway, Ste 301
(203) 366-8000

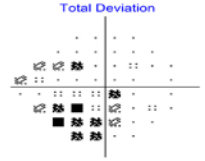
## OD Single Field Analysis — Central 24-2 Threshold Test

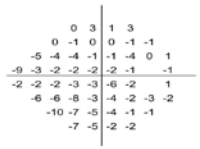
| | | | | | |
|---|---|---|---|---|---|
| Fixation Monitor: | Gaze Monitor | Stimulus: | III, White | Date: | Oct 10, 2019 |
| Fixation Target: | Central | Background: | 31.5 asb | Time: | 11:14 AM |
| Fixation Losses: | 0/0 | Strategy: | SITA Faster | Age: | 62 |
| False POS Errors: | 6% | Pupil Diameter: | 5.1 mm * | | |
| False NEG Errors: | Off | Visual Acuity: | | | |
| Test Duration: | 02:46 | Rx: | +3.25 DS | | |
| Fovea: | Off | | | | |



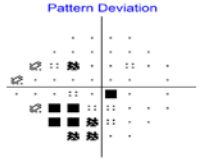




Total Deviation






Pattern Deviation



| | |
|---|---|
| GHT: | Outside Normal Limits |
| VFI: | 94% |
| MD24-2: | -2.85 dB P < 1% |
| PSD24-2: | 2.75 dB P < 2% |

:: P < 5%
P < 2%
P < 1%
P < 0.5%

Comments

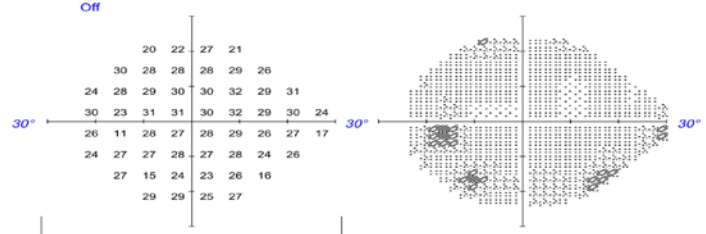
ZEISS

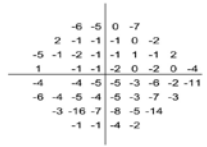
Patient: [redacted]th
Date of Birth: [redacted]7
Gender: **Female**
Patient ID: **05071957**


Ophthalmic Consultants of Connecticut
1375 Kings Highway, Ste 301
(203) 366-8000

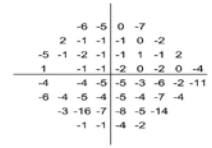

## OS Single Field Analysis — Central 24-2 Threshold Test

| | | | | | |
|---|---|---|---|---|---|
| Fixation Monitor: | Gaze Monitor | Stimulus: | III, White | Date: | Oct 10, 2019 |
| Fixation Target: | Central | Background: | 31.5 asb | Time: | 11:18 AM |
| Fixation Losses: | 0/0 | Strategy: | SITA Faster | Age: | 62 |
| False POS Errors: | 20% XX | Pupil Diameter: | 3.2 mm * | | |
| False NEG Errors: | Off | Visual Acuity: | | | |
| Test Duration: | 03:04 | Rx: | +3.25 DS | | |
| Fovea: | Off | | | | |

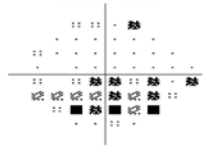


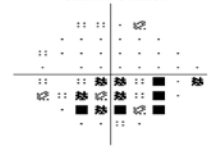



Total Deviation



Pattern Deviation





GHT: Outside Normal Limits

VFI: 91%
MD24-2: -3.26 dB P < 1%
PSD24-2: 3.62 dB P < 1%

*** Excessive High False Positives ***

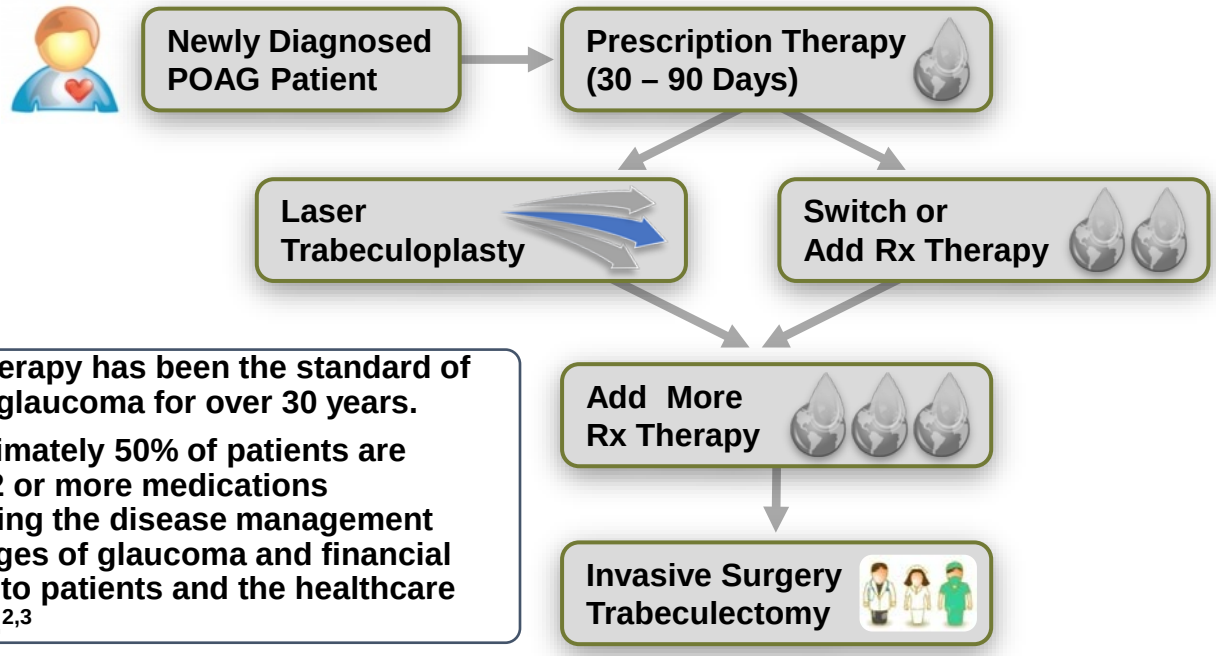
:: P < 5%
P < 2%
P < 1%
■ P < 0.5%

Comments

# The Case of the Asymmetric ONH

- Tx: Vyzulta 1 gtt qhs OU
- Follow up: 3 weeks
- IOP post Tx:
  - OD 17
  - OS 15
  - Tonography: OD 0.25 / OS 0.29
- Next step?

# Current OAG Treatment Algorithm[1]




**Drug therapy has been the standard of care in glaucoma for over 30 years.**

**Approximately 50% of patients are taking 2 or more medications increasing the disease management challenges of glaucoma and financial burden to patients and the healthcare system.[2,3]**

[1]AAO Preferred Practice Pattern; Primary Open Angle Glaucoma. AAO committee 2003.
[2]Stein J, Newman-Casey P, Niziol L, et. al. Association between the use of glaucoma medications and mortality. *Arch Ophthalmol. 2010;*128(2):235-245.
[3]Market Scope Quarterly Glaucoma Report, 4th quarter 2013.

# THE LANCET
## THE “LIGHT” STUDY

VOLUME 393, ISSUE 10180, P1505-1516, APRIL 13, 2019

- **Selective laser trabeculoplasty versus eye drops for first-line treatment of ocular hypertension and glaucoma (LiGHT): a multicentre randomised controlled trial**
- Gus Gazzard, FRCOphth
- Evgenia Konstantakopoulou, PhD
- Prof David Garway-Heath, MD
- Anurag Garg, FRCOphth
- Victoria Vickerstaff, MSc
- Rachael Hunter, MSc
- et al.

# LIGHT Study

- Standardization of laser delivery was achieved by protocol-defined settings and clinical endpoints.[14]
- Selective laser trabeculoplasty was delivered to 360° of the trabecular meshwork. 100 non-overlapping shots (25 per quadrant) were used, with the laser energy varied from 0·3 to 1·4 mJ by the clinician, using an appropriate laser gonioscopy lens.
- One re-treatment with selective laser trabeculoplasty was allowed, provided there had been a reduction in intraocular pressure after the initial treatment; the next escalation was medical therapy.
- Significant complications of selective laser trabeculoplasty (eg, a spike in intraocular pressure) precluded repetition of selective laser trabeculoplasty.

# LIGHT Study

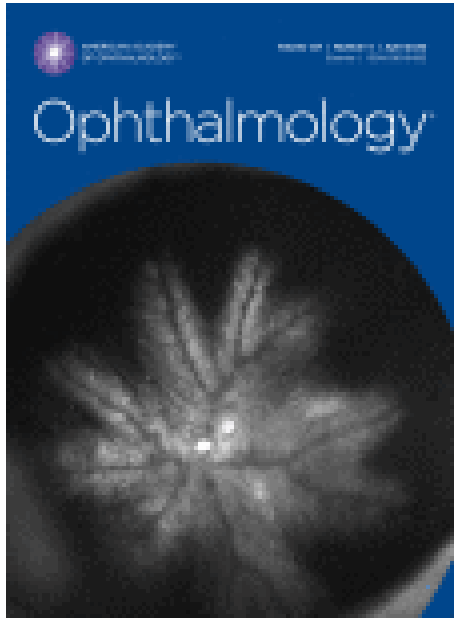
- Drug classes for first, second, or third line treatment were defined by NICE[15] and European Glaucoma Society[19] guidance
- First line was prostaglandin analogues, second line was β blockers, third or fourth line was topical carbonic anhydrase inhibitors or α agonists. Fixed combination drops were allowed.
- Systemic carbonic anhydrase inhibitors were only permitted while awaiting surgery. Maximum tolerated medical therapy was defined by the treating clinician as the most intensive combination of drops an individual could reasonably, reliably, and safely use and thus varied between patients.
- A need for treatment escalation beyond maximum tolerated medical therapy triggered an offer of surgery.

# The Light study

- **Methods**
- **In this observer-masked, randomized controlled trial treatment-naive patients with open angle glaucoma or ocular hypertension and no ocular comorbidities were recruited between 2012 and 2014 at six UK hospitals.**
- **They were randomly allocated (web-based randomization) to initial selective laser trabeculoplasty or to eye drops.**
- **An objective target intraocular pressure was set according to glaucoma severity.**
- **The primary outcome was health-related quality of life (HRQoL) at 3 years (assessed by EQ-5D). Secondary outcomes were cost and cost-effectiveness, disease-specific HRQoL, clinical effectiveness, and safety.**
- **Analysis was by intention to treat. This study is registered at controlled-trials.com (ISRCTN32038223).**

# The Light study

- **Findings**
- **Of 718 patients enrolled, 356 were randomised to the selective laser trabeculoplasty and 362 to the eye drops group. 652 (91%) returned the primary outcome questionnaire at 36 months.**
- **Average EQ-5D score was 0·89 (SD 0·18) in the selective laser trabeculoplasty group versus 0·90 (SD 0·16) in the eye drops group, with no significant difference (difference 0·01, 95% CI –0·01 to 0·03; p=0·23).**
- **At 36 months, 74·2% (95% CI 69·3–78·6) of patients in the selective laser trabeculoplasty group required no drops to maintain intraocular pressure at target.**
- **Eyes of patients in the selective laser trabeculoplasty group were within target intracoluar pressure at more visits (93·0%) than in the eye drops group (91·3%), with glaucoma surgery to lower intraocular pressure required in none versus 11 patients.**
- **Over 36 months, from an ophthalmology cost perspective, there was a 97% probability of selective laser trabeculoplasty as first treatment being more cost-effective than eye drops first at a willingness to pay of £20 000 per quality-adjusted life-year gained.**




# Efficacy of Repeat Selective Laser Trabeculoplasty in Medication-Naive Open-Angle Glaucoma and Ocular Hypertension during the LiGHT Trial

AnuragGargFRCOphth;[1] VictoriaVickerstaffMSc[2,3] NeilNathwaniBSc[1] DavidGarway-HeathMD[1] EvgeniaKonstantakopoulouPhD[1] GarethAmblerPhD[4] CateyBunceDSc[1,5,6] RichardWormaldFRCOphth[1,6] KeithBartonFRCS[1] GusGazzardMD[1] Laser

# Repeat SLT

- Participants
- Treatment-naive OAG or OHT requiring repeat 360-degree SLT within 18 months. Retreatment was triggered by predefined IOP and disease-progression criteria (using objective individualized target IOPs).
- Methods
- After SLT at baseline, patients were followed for a minimum of 18 months after second (repeat) SLT. A mixed-model analysis was performed with the eye as the unit of analysis, with crossed random effects to adjust for correlation between fellow eyes and repeated measures within eyes. Kaplan–Meier curves plot the duration of effect.
- Main Outcome Measures
- Initial (early) IOP lowering at 2 months and duration of effect after initial and repeat SLT.
- Results
- A total of 115 eyes of 90 patients received repeat SLT during the first 18 months of the trial. Pretreatment IOP before initial SLT was significantly higher than before retreatment IOP of repeat SLT (mean difference, 3.4 mmHg; 95% confidence interval [CI], 2.6–4.3 mmHg; $P < 0.001$). Absolute IOP reduction at 2 months was greater after initial SLT compared with repeat SLT (mean difference, 1.0 mmHg; 95% CI, 0.2–1.8 mmHg; $P = 0.02$). Adjusted absolute IOP reduction at 2 months (adjusting for IOP before initial or repeat laser) was greater after repeat SLT (adjusted mean difference, −1.1 mmHg, 95% CI, −1.7 to −0.5 mmHg; $P = 0.001$). A total of 34 eyes were early failures (retreatment 2 months after initial SLT) versus 81 later failures (retreatment >2 months after initial SLT). No significant difference in early absolute IOP reduction at 2 months after repeat SLT was noted between early and later failures (mean difference, 0.3 mmHg; 95% CI, −1.1 to 1.8 mmHg; $P = 0.655$). Repeat SLT maintained drop-free IOP control in 67% of 115 eyes at 18 months, with no clinically relevant adverse events.
- Conclusions
- These exploratory analyses demonstrate that repeat SLT can maintain IOP at or below target IOP in medication-naive OAG and OHT eyes requiring retreatment with at least an equivalent duration of effect to initial laser.

# Repeat SLT

- Results
- A total of 115 eyes of 90 patients received repeat SLT during the first 18 months of the trial. Pretreatment IOP before initial SLT was significantly higher than before retreatment IOP of repeat SLT (mean difference, 3.4 mmHg; 95% confidence interval [CI], 2.6–4.3 mmHg; $P < 0.001$).
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- Repeat SLT maintained drop-free IOP control in 67% of 115 eyes at 18 months, with no clinically relevant adverse events.

# The AI revolution: Rise of the machines

# A Comparison of Perimetric Results from a Tablet Perimeter and Humphrey Field Analyzer in Glaucoma Patients


- Y. Kong, M. He, J Crowston, A Vingrys


- Transl Vis Sci Technol. 2016 Nov; 5(6):2


- University of Melbourne College of Optometry

# **Melbourne Rapid Fields**
## Automated threshold perimeter


Australian Government
Department of Health
Therapeutic Goods Administration

**Australian Register of Therapeutic Goods Certificate**

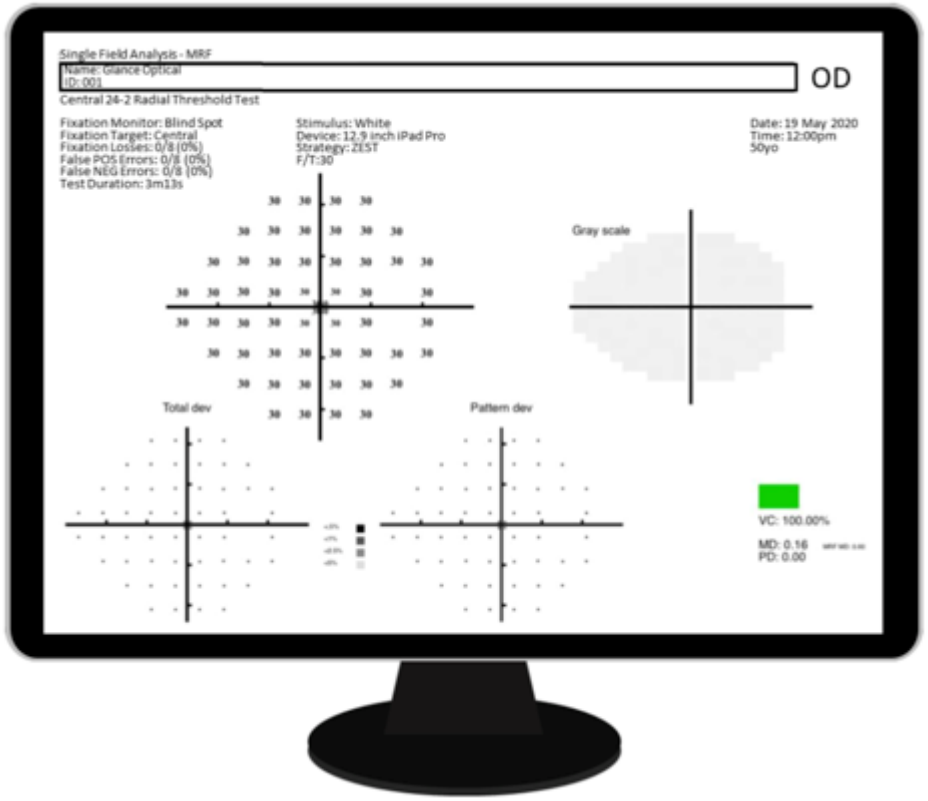
Issued to

**Glance Optical Pty Ltd**

for approval to supply

**Glance Optical Pty Ltd - Visual field plotter**

| | |
|---|---|
| **ARTG Identifier** | 282166 |
| **ARTG Start date** | 7/11/2016 |
| **Product Category** | Medical Device Included Class 1 |
| **GMDN** | 14380 |
| **GMDN Term** | Visual field plotter |

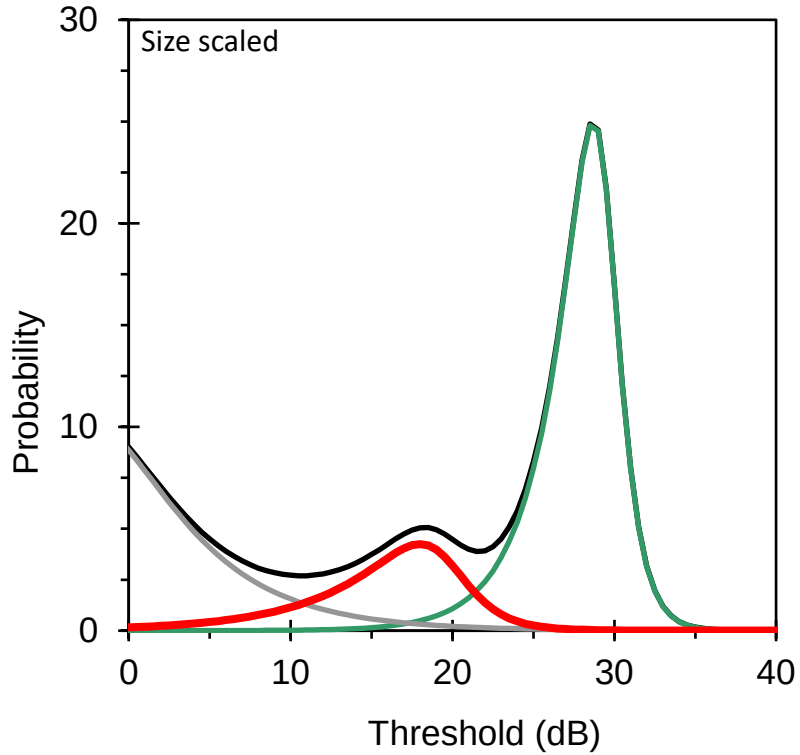


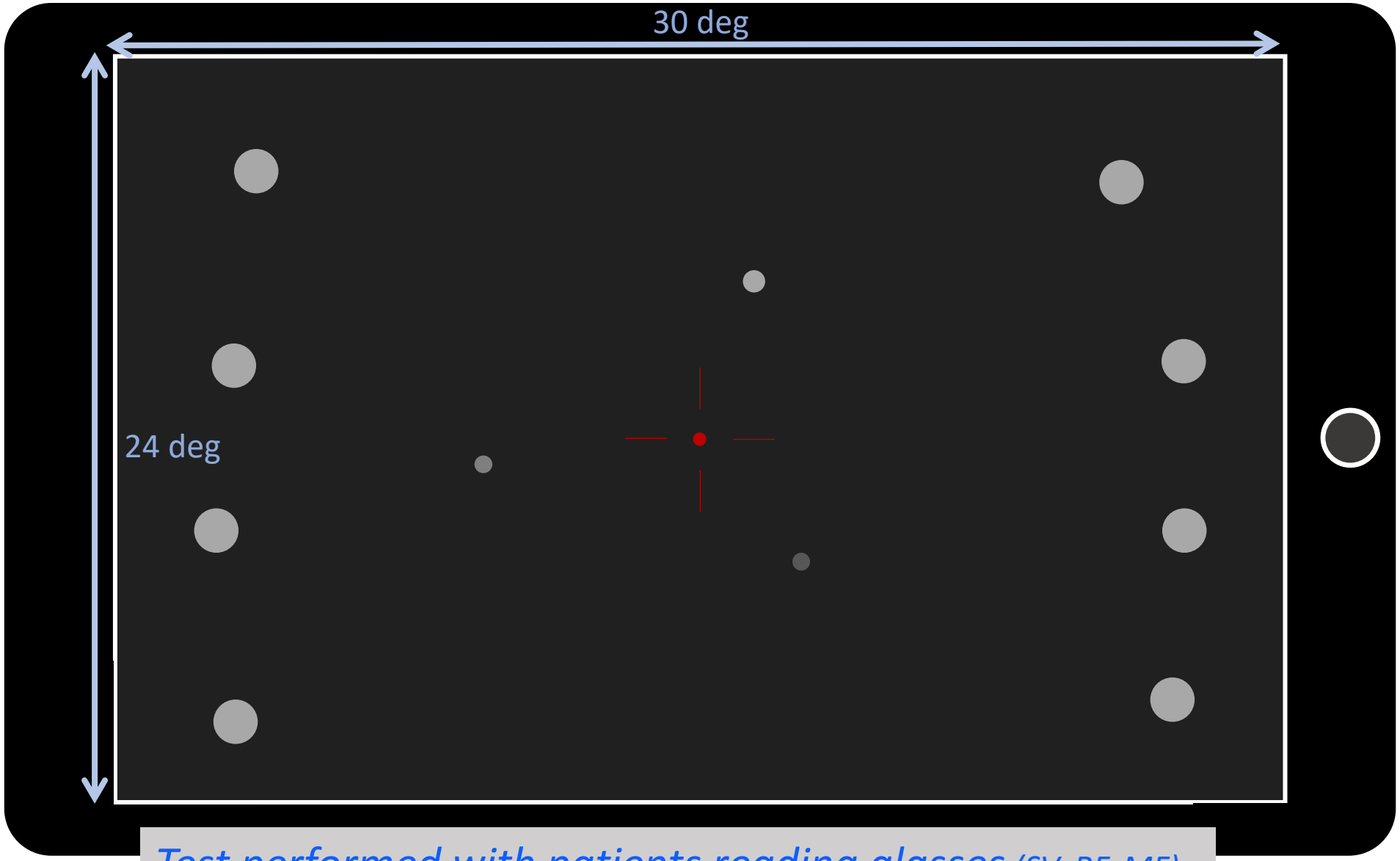

- MRF registered as Medical Device with TGA (Australia) and MedSafe (NZ)
- Complies with MBS 10940, 10941 11221, 11224 definition

# Threshold Strategy — Bayes prediction

- Bayes prediction with neighborhood logic
  - Based on population PDF (probability density function)
  - Similar to SITA, Medmont and FDT

- MRF PDF derived from 587 people (size scaled)
  - 307 normal age 6-95 (mean 54 ± 18)
  - 280 definite disease (Glauc 92, AMD 68, Diabetes 74, Neuro 46)






*Test performed with patients reading glasses (SV, BF, MF)*

# Increasing spot size improves threshold estimate

tvst 2016

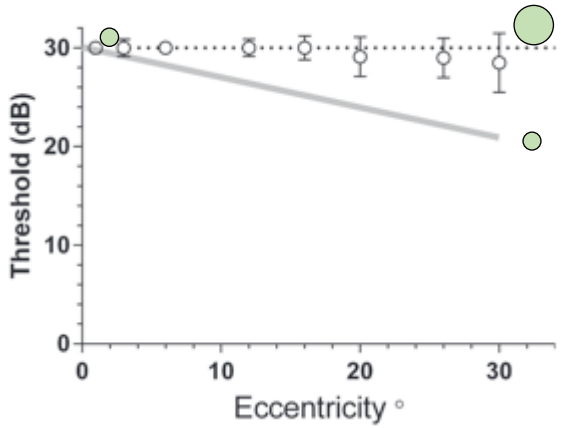
DOI: 10.1167/tvst.5.4.3

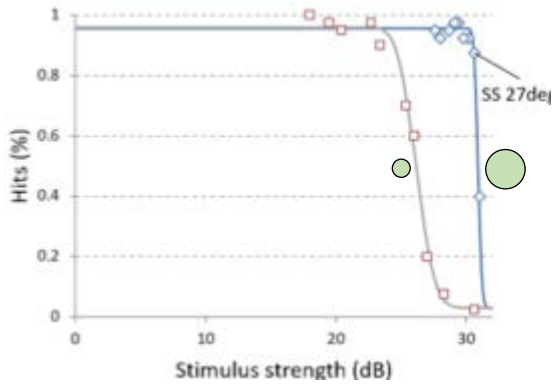
New Developments in Vision Research

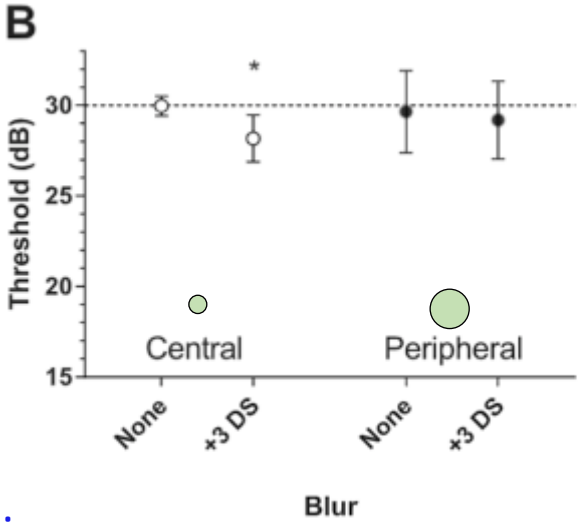
## Validation of a Tablet as a Tangent Perimeter

Algis J. Vingrys[1], Jessica K. Healey[1], Sheryl Liew[1], Veera Saharinen[1], Michael Tran[1], William Wu[1], and George Y. X. Kong[2]

[1] Department of Optometry & Vision Sciences, Melbourne School of Health Sciences, University of Melbourne, 3010, Victoria, Australia
[2] Centre of Eye Research Australia, 32 Gisborne St East Melbourne, Victoria, Australia



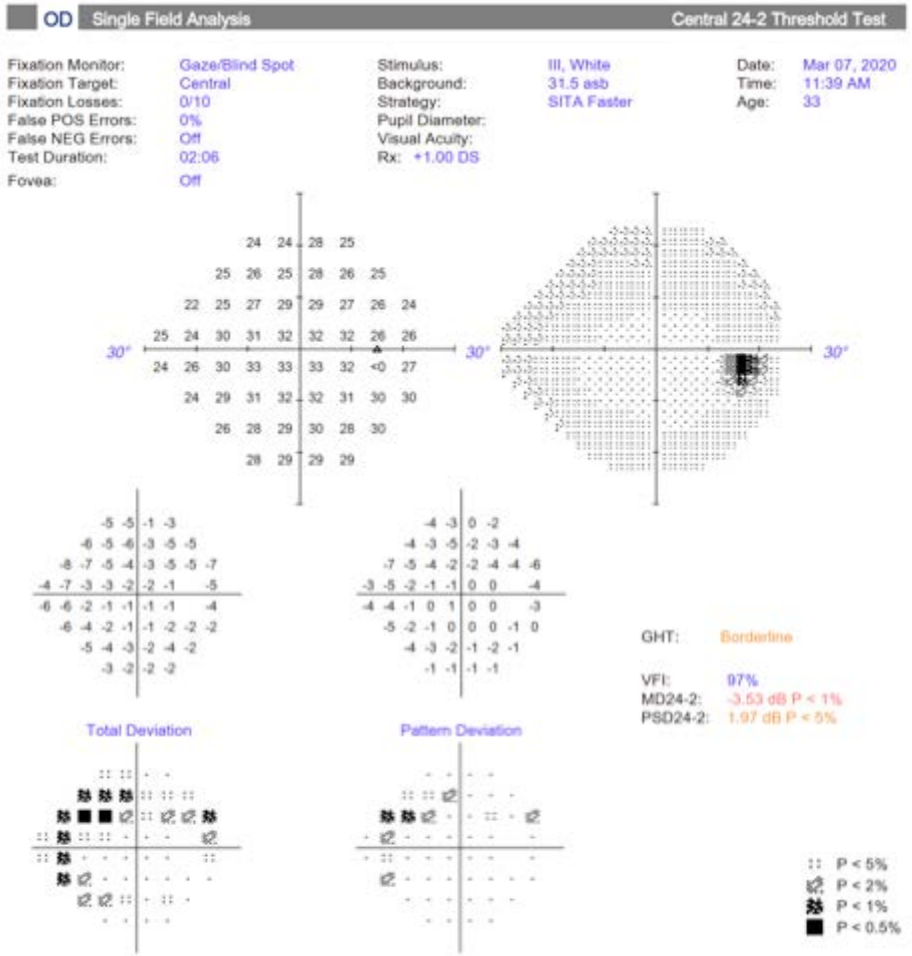

Spot size increases in peripheral locations:

- large spots are easier to see & robust to blur
- return a fixed threshold with eccentricity
- reduce variability

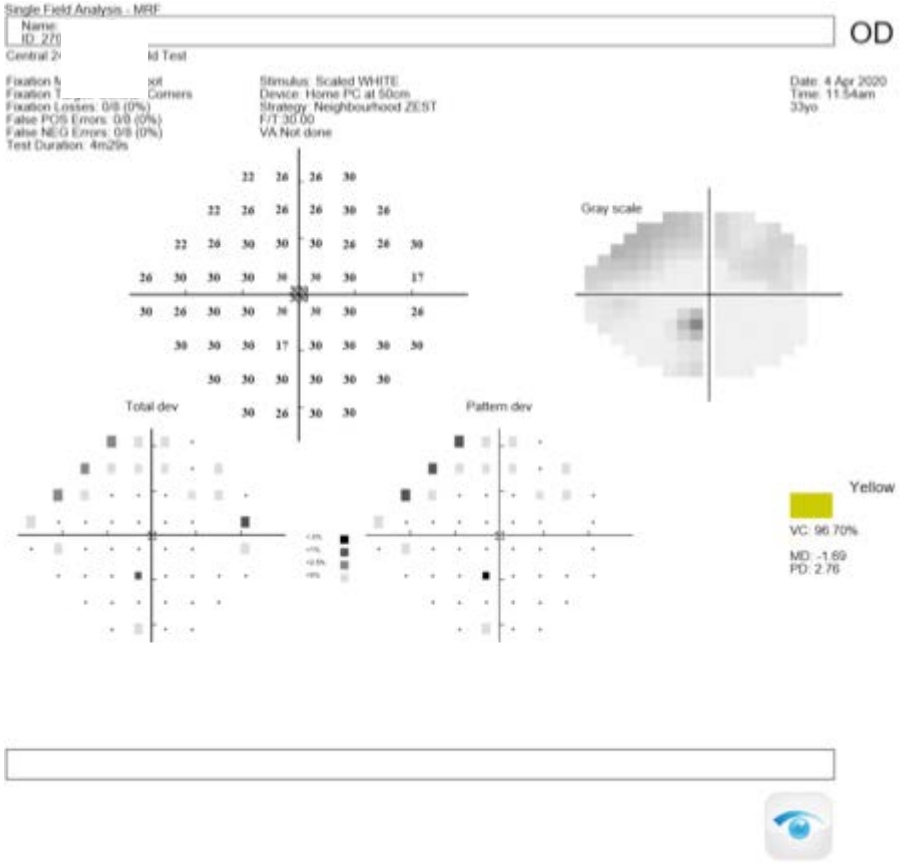
- make early losses easier to find

# Results: outputs in familiar formats

## HFaA

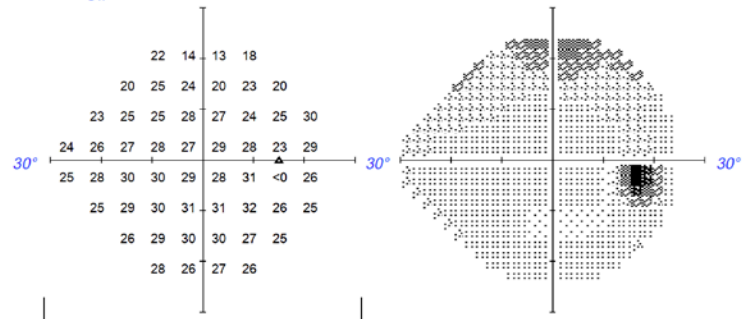


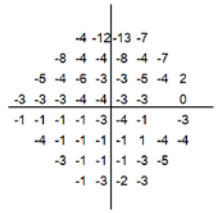

## MRF



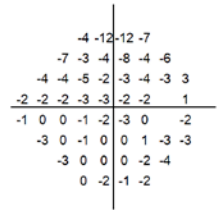
OD | Single Field Analysis | Central 24-2 Threshold Test

| | | | | | |
|---|---|---|---|---|---|
| Fixation Monitor: | Gaze/Blind Spot | Stimulus: | III, White | Date: | Jul 12, 2018 |
| Fixation Target: | Central | Background: | 31.5 asb | Time: | 10:57 AM |
| Fixation Losses: | 1/10 | Strategy: | SITA Faster | Age: | 73 |
| False POS Errors: | 8% | Pupil Diameter: | | | |
| False NEG Errors: | Off | Visual Acuity: | | | |
| Test Duration: | 03:22 | Rx: | +1.00 DS | | |
| Fovea: | Off | | | | |



Total Deviation

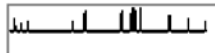


Pattern Deviation

GHT: Outside Normal Limits

VFI: 94%
MD24-2: -3.08 dB P < 1%
PSD24-2: 2.61 dB P < 2%

:: P < 5%
P < 2%
P < 1%
P < 0.5%



Single Field Analysis - MRF

Name: [redacted]
ID: 17

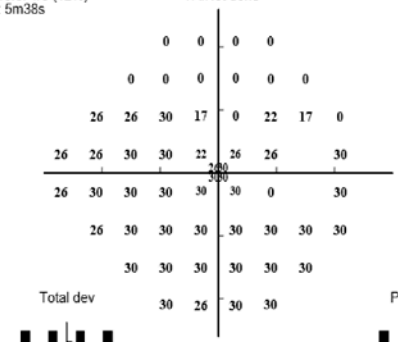
OD

Central 24-2 Grid Threhold Test

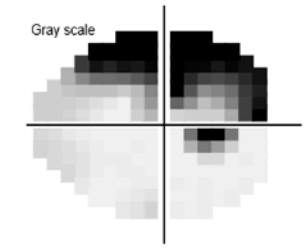
Fixation Monitor: Blind Spot
Fixation Target: Central+Corners
Fixation Losses: 2/8 (25%)
False POS Errors: 1/8 (12%)
False NEG Errors: 1/8 (12%)
Test Duration: 5m38s

Stimulus: Scaled WHITE
Device: Home PC at 50cm
Strategy: Neighbourhood ZEST
F/T:29.00
VA:Not done

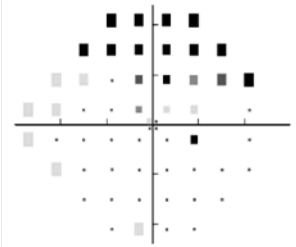
Date: 7 Apr 2020
Time: 5:38pm
76yo



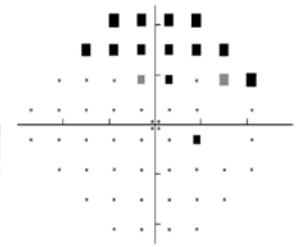
Gray scale



Total dev



Pattern dev



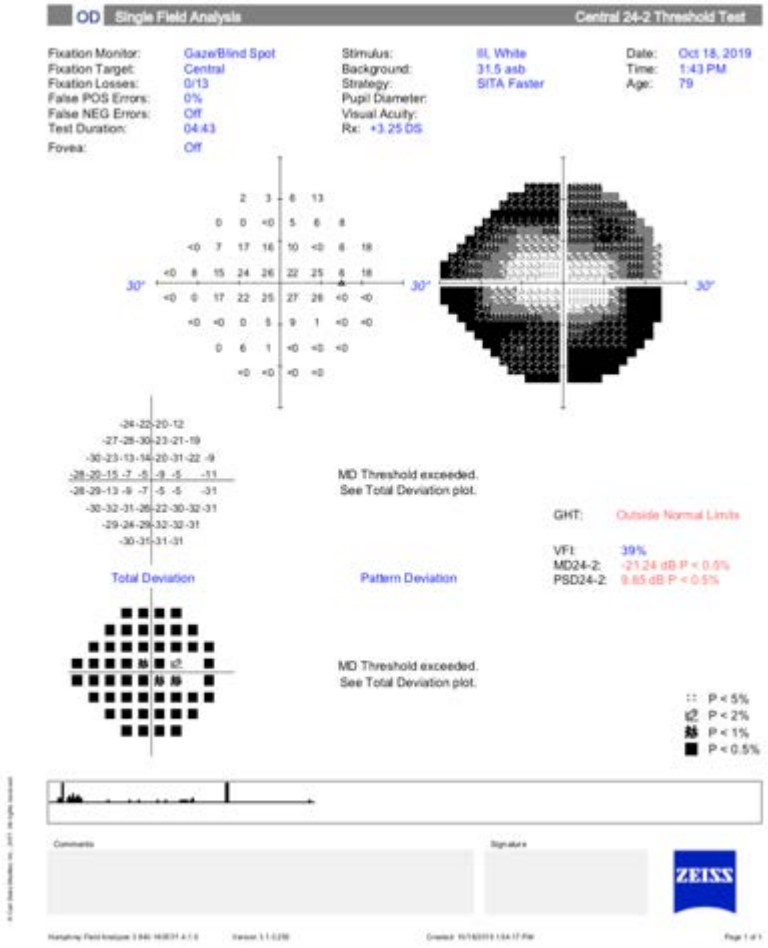
Abnormal

VC: 74.08%

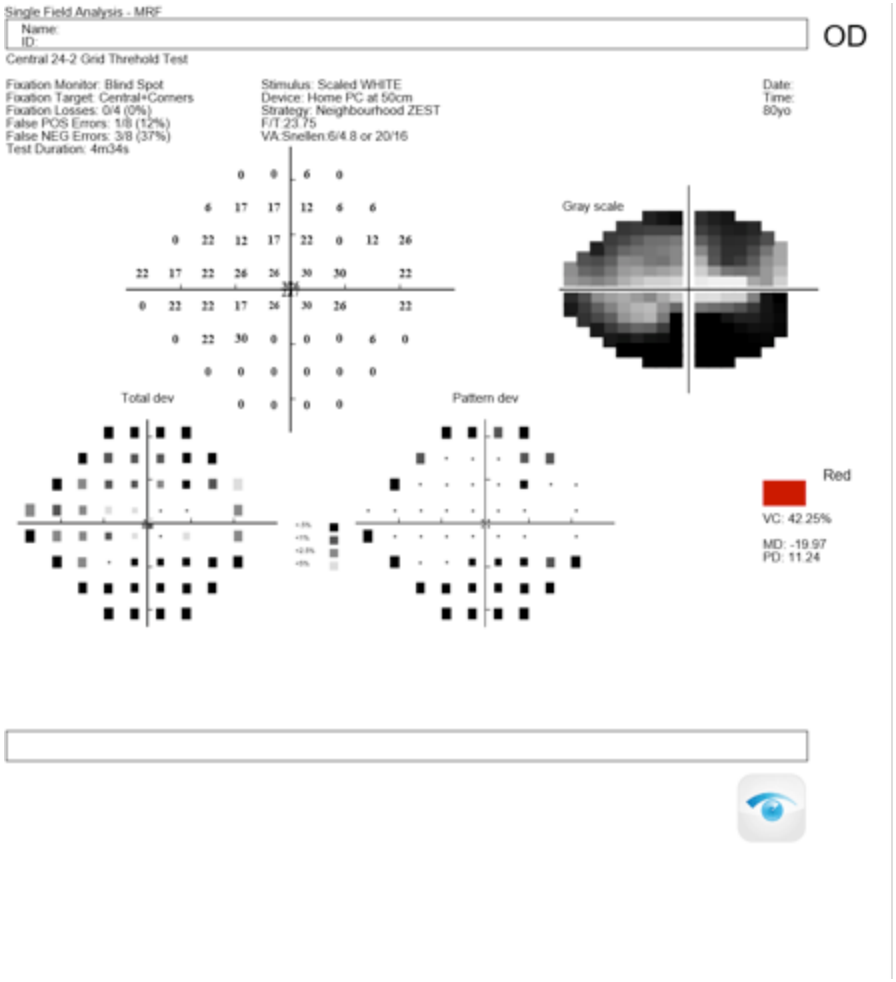
MD: -9.33
PD: 12.21

# Results: outputs in familiar formats. Advanced defect

## HFA




## MRF



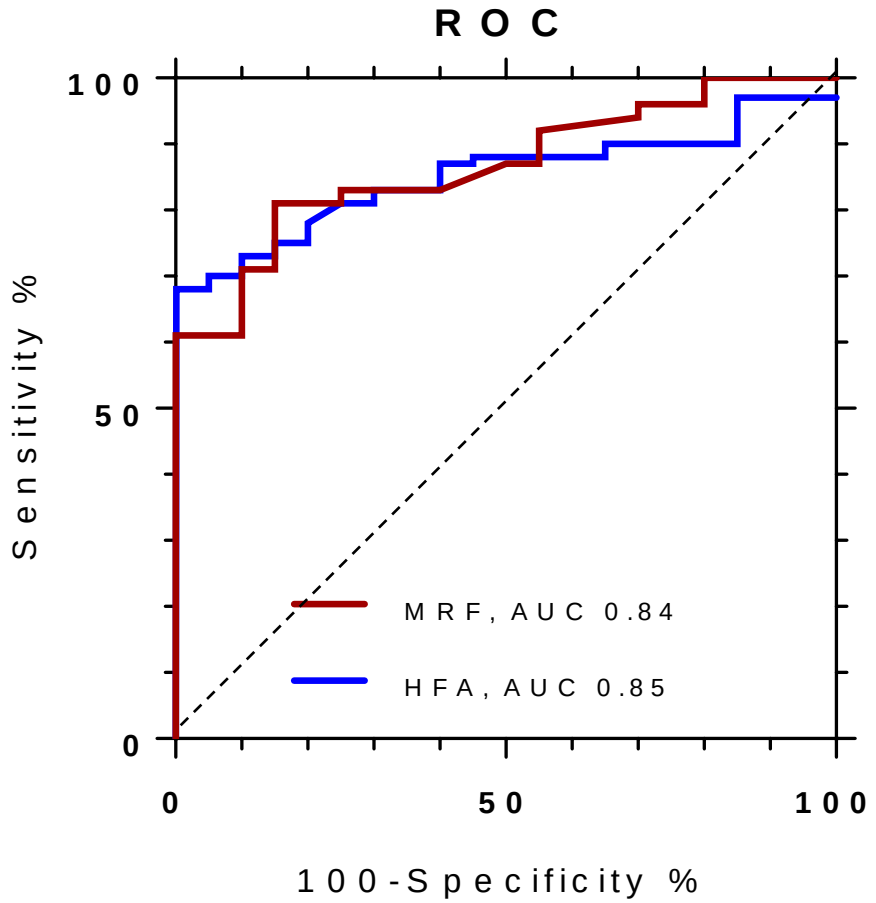
# Equivalent diagnostic ability between MRF and HFA

**Independent study from Macquarie University, NSW**

N=60 OAG: 43 manifest HFA defects, 17 GS: 20 controls

Diagnoses based on Optic Disc

*Schultz et al Clin Exper Ophthalmol 2017.*




MACQUARIE University
SYDNEY·AUSTRALIA

# Olleyes

- Visual Field:
  - All common protocols e.g. 24-2, 10-2, 30-2, etc).
  - Testing time is about 3 minutes for threshold and 1.5 minutes for screening.
- Visual Acuity (near and far acuity).
- Color Vision.
- Pediatrics Visual Field.

# Olleyes

- The VisuALL is a VR visual field perimeter designed for standardized and mobile assessment of the visual field. VisuALL automatically analyzes the retOLLEYES VIRTUAL VISUAL FIELD PRODUCTS
- The VisuALL is a VR visual field perimeter designed for standardized and mobile assessment of the visual field. VisuALL automatically analyzes the retinal sensitivity in patients with Glaucoma and other visual disorders. VisuALL enables the examination of multiple patients at a time increasing office productivity.

ORIGINAL STUDY

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

*Reza Razeghinejad, MD,* Alberto Gonzalez-Garcia,† Jonathan S. Myers, MD,* and L.J Katz, MD**

**Precis:** The VisuALL head-mounted perimetry in normal subjects and glaucoma patients had a moderate to strong correlation with the Humphrey Field Analyzer (HFA).

**Purpose:** Visual field testing has a vital role in diagnosing and managing glaucoma. The current clinical practice relies on large, table-based testing units. This study investigated the performance of a novel virtual reality head-mounted visual perimetry device (VisuALL), in normal and glaucoma patients.

**Methods:** This prospective observational study was conducted on 50 eyes of 25 healthy subjects (normal group) and 52 eyes of 26 patients with a controlled mild or moderate stage of glaucoma (glaucoma group). All participants had visual field testing with VisuALL and the HFA (24-2, Swedish Interactive Threshold Algorithm). The mean sensitivity of the whole visual field and each quadrant were compared between both machines and the receiver operating characteristic was used to compare the diagnostic abilities and the Bland-Altman plot to evaluate the agreement of the 2 perimeters.

**Results:** The global mean sensitivity of the Visu*ALL* and the HFA correlated significantly in both normal ($r=0.5$, $P=0.001$) and glaucoma ($r=0.8$, $P<0.001$) groups. The mean sensitivity of all quadrants also correlated significantly in both groups. The Visu*ALL* mean sensitivity had a greater (0.98) receiver operating characteristic curve than HFA (0.93) mean sensitivity ($P=0.06$) in discriminating normal versus glaucoma.

**Conclusion:** There was an excellent correlation between the VisuALL and the Standard Automated Perimetry in normal and glaucoma patients and VisuALL showing high diagnostic performance.

**Key Words:** glaucoma, visual field, perimetry, virtual reality, head-mounted device

(*J Glaucoma* 2020;00:000–000)

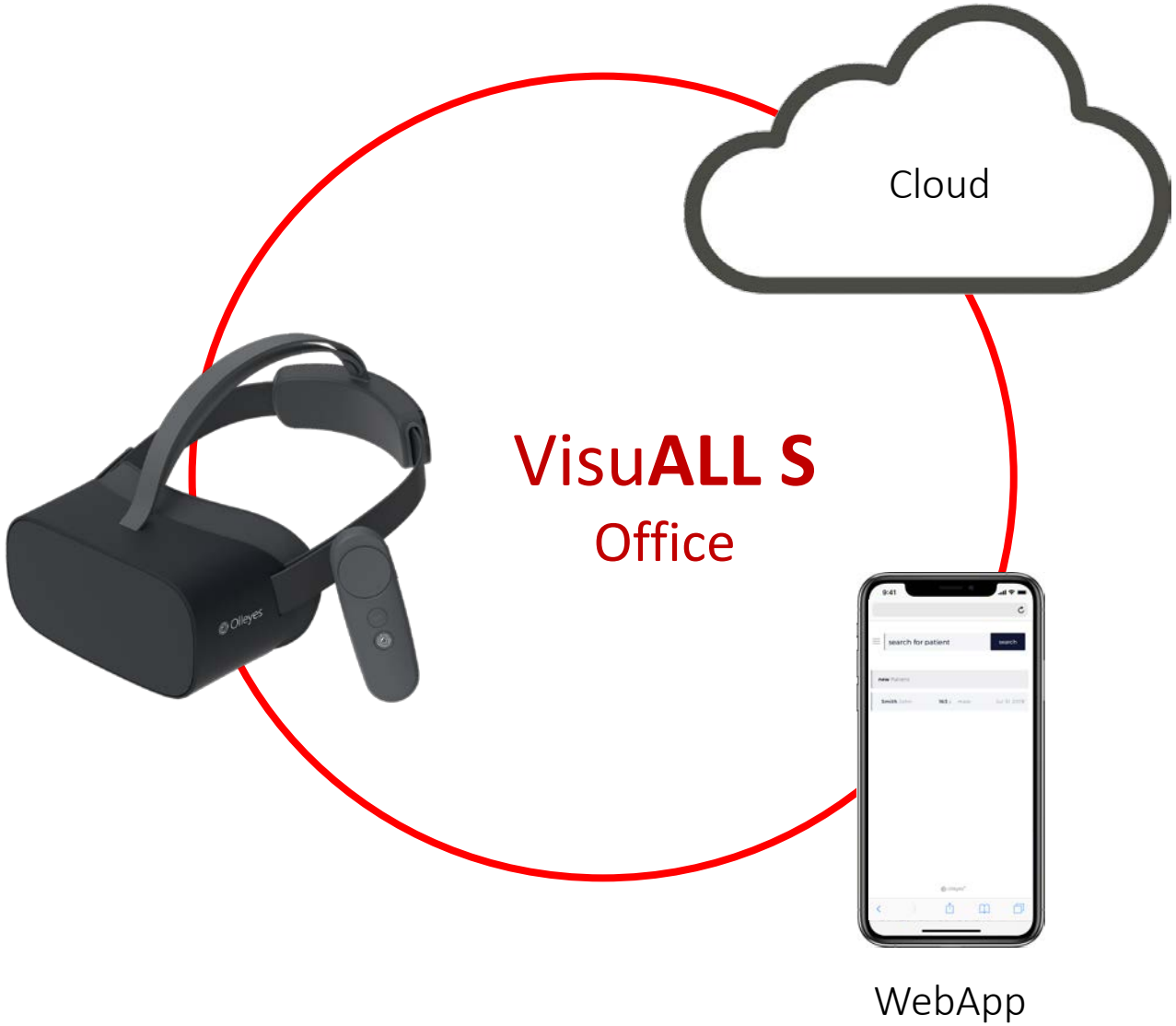
neurological diseases and for detecting the disease progression.[1]

The SAP requires maintenance of constant fixation for several minutes and conscious decision making in identification of near the threshold level stimuli.[2,3] In addition, it has a number of disadvantages including being stressful for debilitated, claustrophobic, ill, or elderly patients to keep their heads still in the perimeter bowl during the test. Patients with musculoskeletal problems and admitted patients in the hospital that are not able to position their head in the proper position for visual field testing may have unreliable, artifact laden results or be unable to take the test.

Several devices have been developed since the advent of the HFA and the Octopus perimeters, in an effort to improve the detection of visual field defects and make the test easier for patients.[4–6] Examples include the use of laptops and iPads.[7–9] These modalities bring portability, but lack of fixation monitoring methods and hardware standardization have been the limiting factors in their widespread use. In addition, specificity and sensitivity studies have been mixed.[7,8,10,11] The majority of these devices are composed of a head-mounted device (HMD) controlled by a laptop or a tablet.[8,12] The size and cost of current tabletop perimeters limit their use in screening efforts as well as clinical care in remote and rural settings. HMD perimeters may allow in-office, remote, and home visual field testing owing to their lower cost and portability and could promote a change in the screening protocol.

The aim of this study was to characterize a novel perimeter that includes an HMD with eye-tracking capabilities, to evaluate the age influence on the resultant retinal sensitivity, and to compare its results with the HFA.

# Visu**ALL VRP**




Perimetry Adults

Perimetry Ped

Visual Acuity

Color Vision

More…

# VisuALL VRP

## Perimetry **Kids**

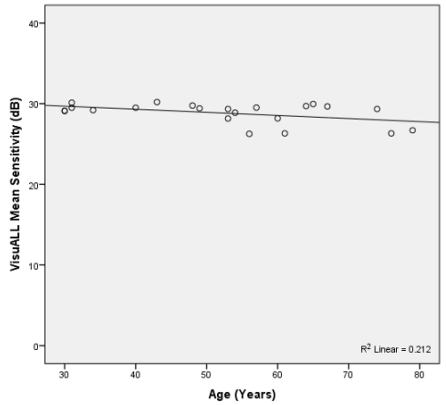
Gamified

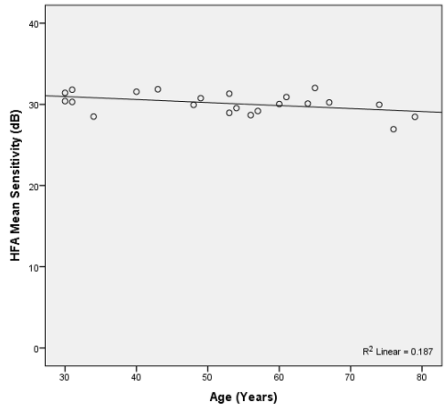
Binocular

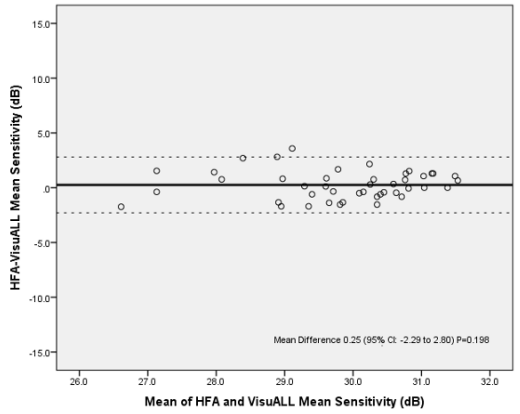
Patch-Free

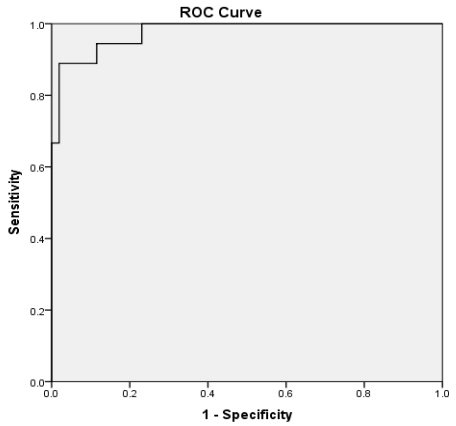
Validated

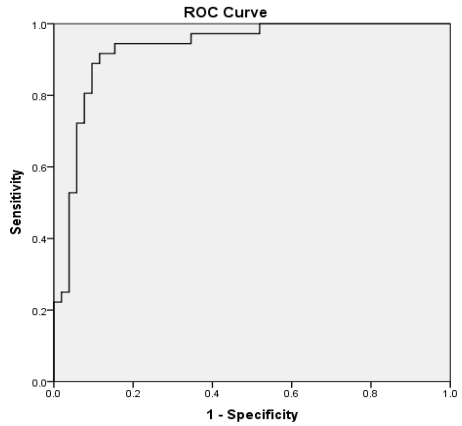
# Validation



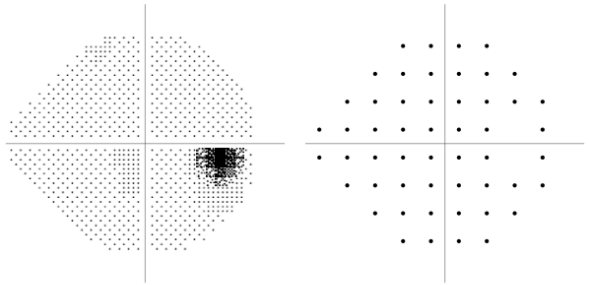

* Reza Razeghinejad, Alberto Gonzalez-Garcia, Jonathan S Myers, L Jay Katz. Preliminary Report on a Novel Virtual Reality Perimeter Compared with Standard Automated Perimetry. J Glaucoma. 2020 Sep 15. Online ahead of print.

Visu**ALL VRP**

| name | dateOfBirth | gender | eye | degrees | strategy |
|---|---|---|---|---|---|
| | | | OD | 24 | NormalT |

Grayscale | Pattern Deviation

05-07-2020



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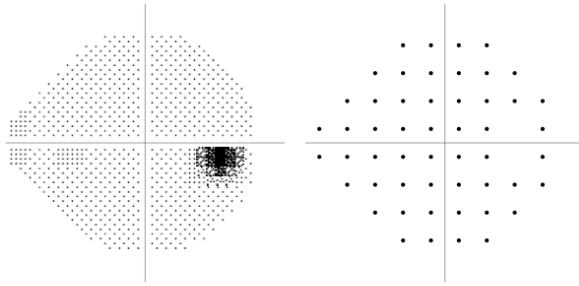
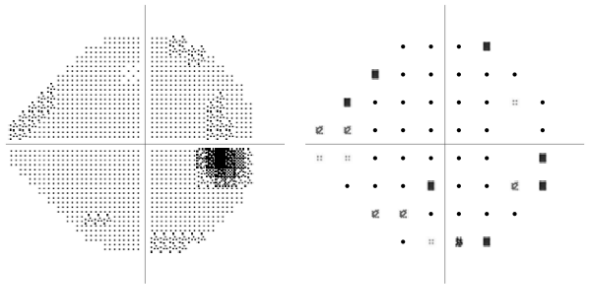
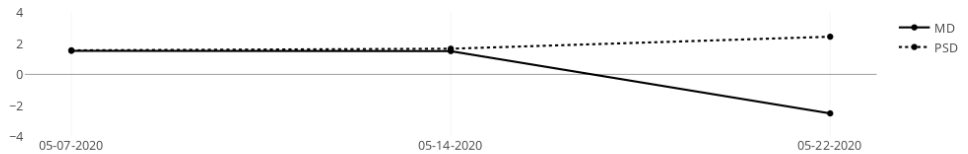


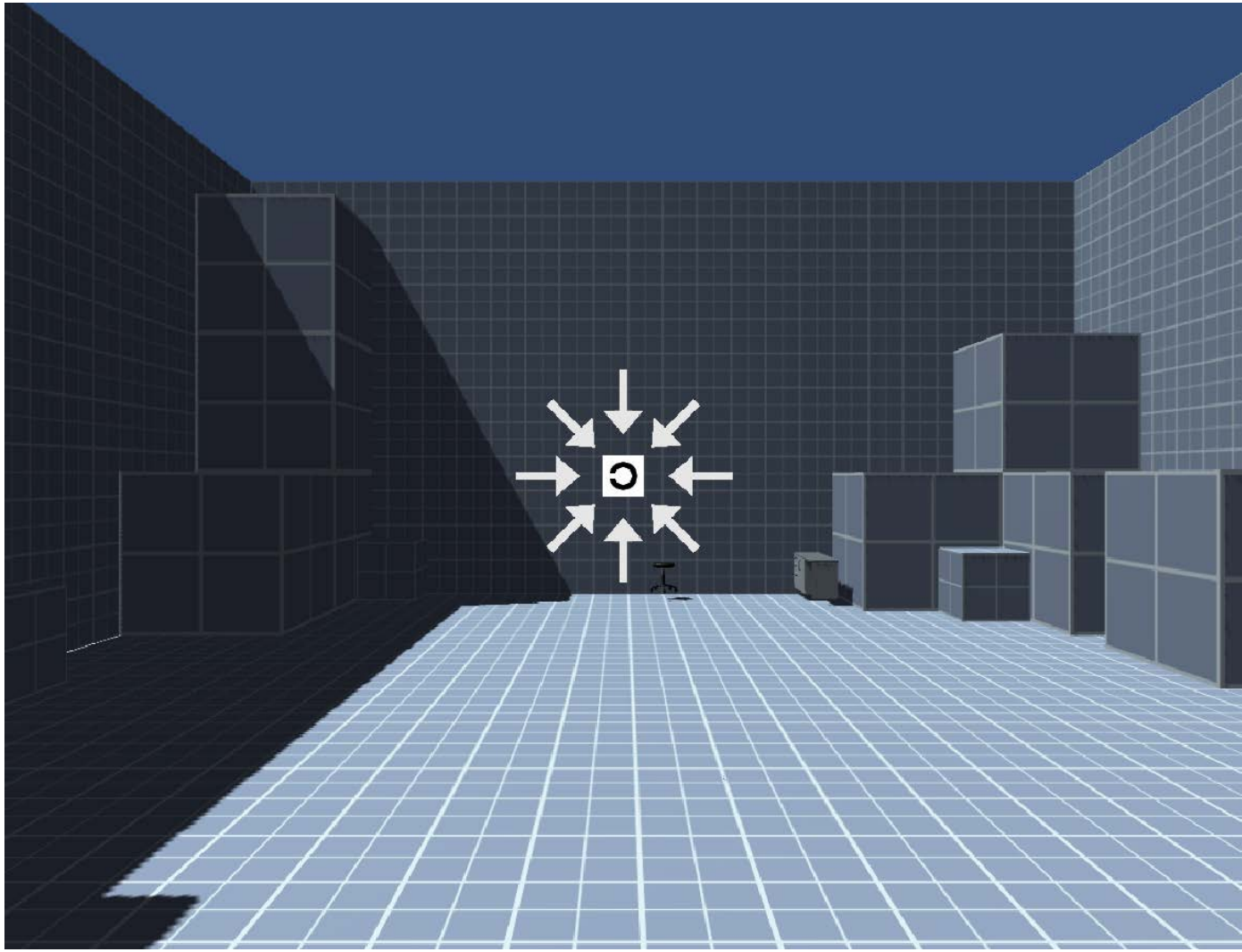
05-22-2020





Visual Acuity

(immersive)



VisuALL VRP

# Color Vision

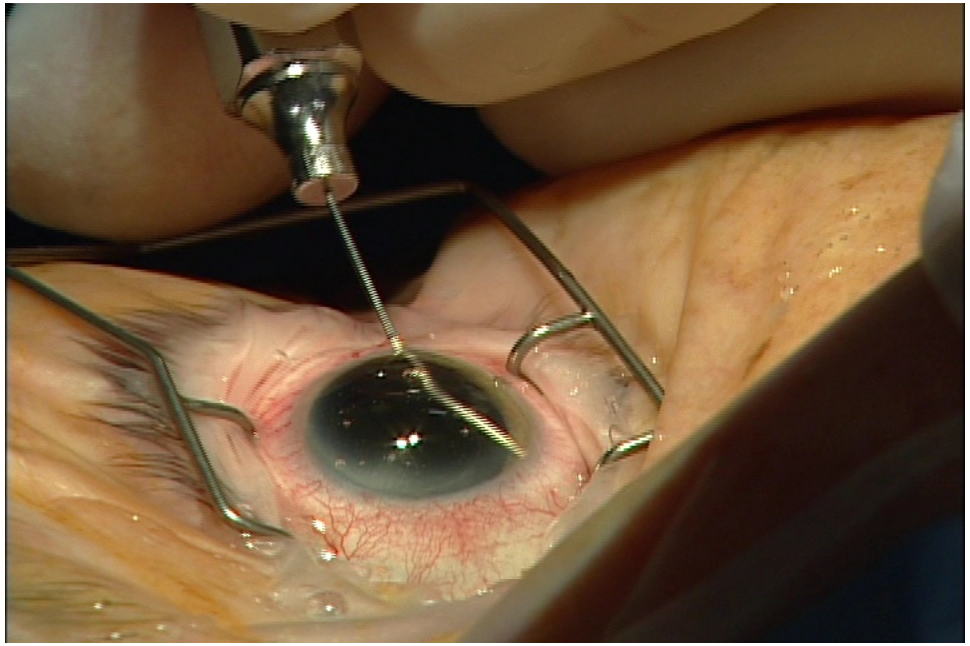

# Visu**ALL VRP**

# Annie

VisuALL

Virtual Assistant

# iStent Surgery



- Inject a viscoelastic into the anterior chamber.  Use a miotic if desired to help open the angle.

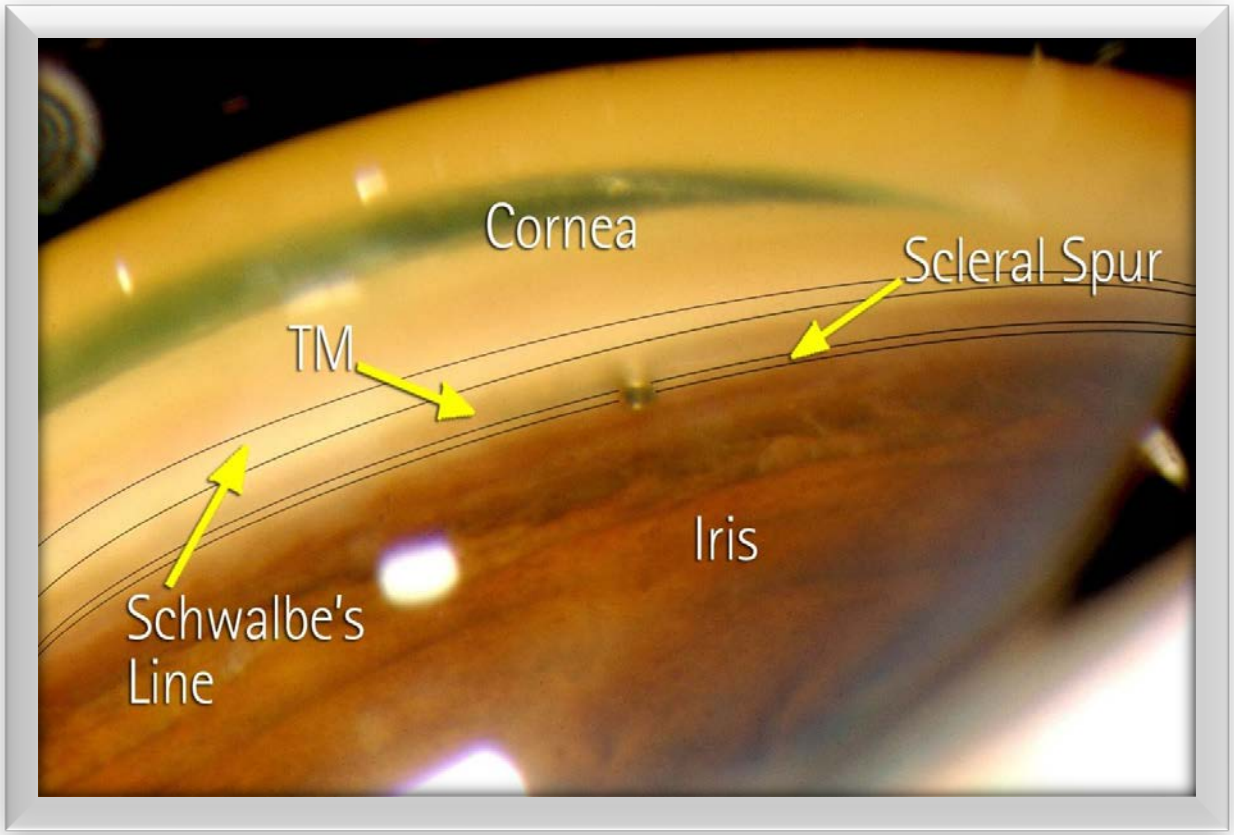
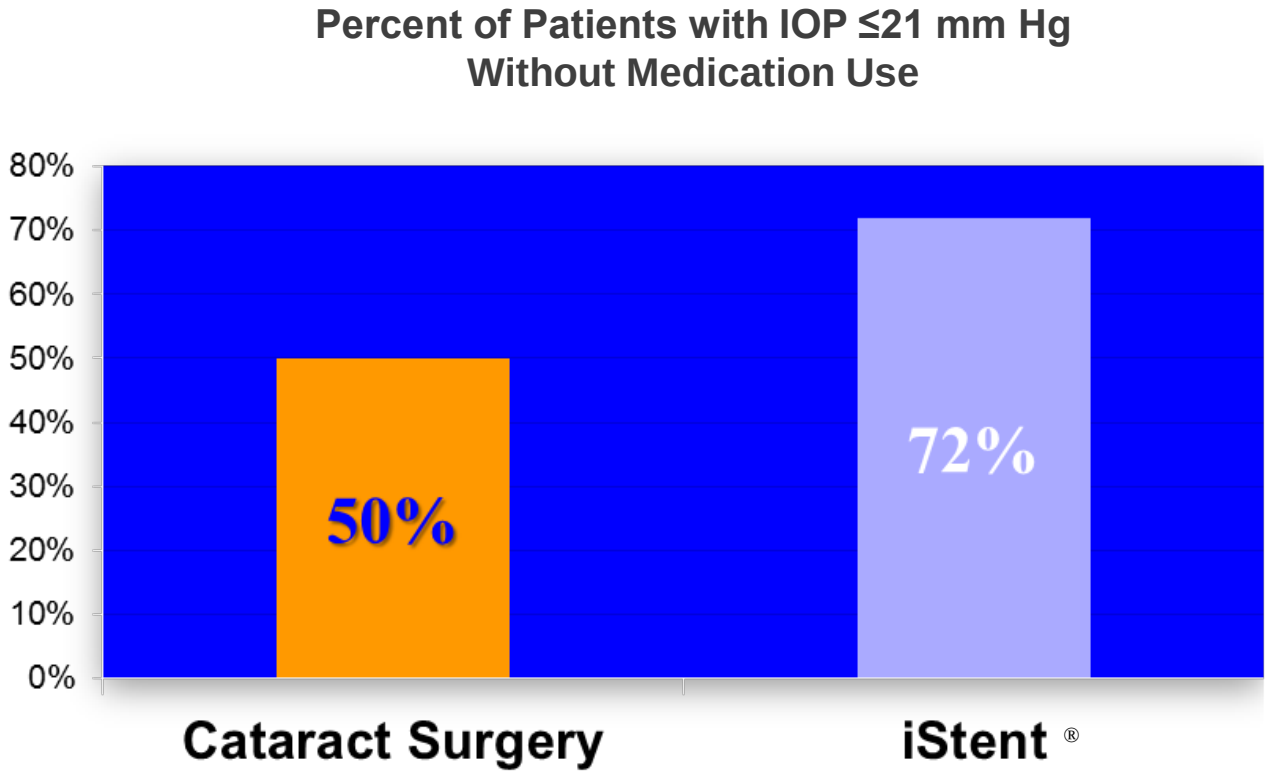



Photo courtesy of Tom Samuelson, MD

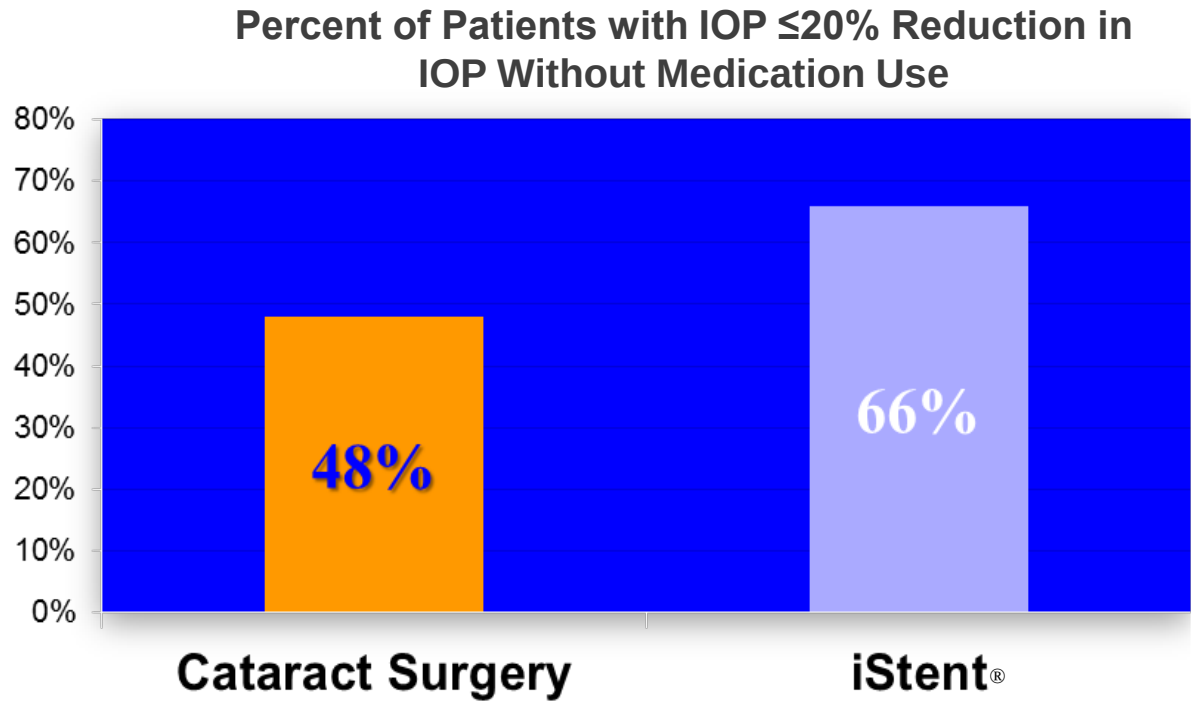
# US IDE Trial – Primary Endpoint




- **At 12 months, 72% of iStent® subjects with IOP ≤ 21 mm Hg without medication vs. 50% with cataract surgery alone (*P*<0.001)**

Samuelson TW, Katz LJ, Wells JM, Duh Y-J, Giamporcaro JE, for the US iStent Study Group. Randomized evaluation of the trabecular micro-bypass stent with phacoemulsification in patients with glaucoma and cataract. Ophthalmology 2011; 118:459–467.

# US IDE Trial – Secondary Endpoint

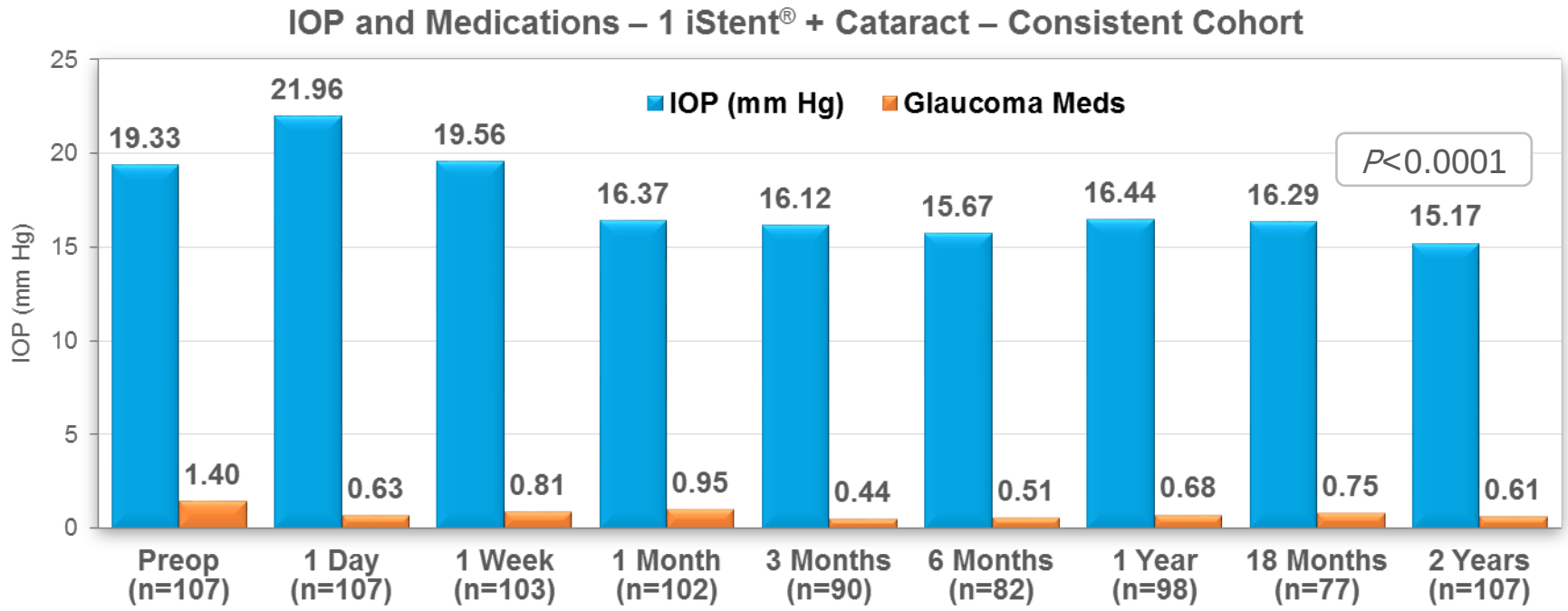



- **At 12 months, 66% of iStent® subjects with ≥ 20% IOP reduction without medication vs. 48% with cataract surgery alone (P=0.003)**

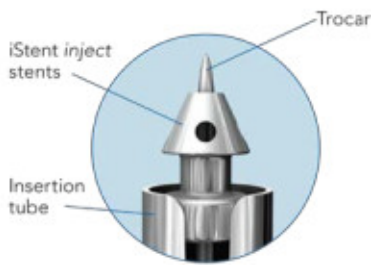
Samuelson TW, Katz LJ, Wells JM, Duh Y-J, Giamporcaro JE, for the US iStent Study Group. Randomized evaluation of the trabecular micro-bypass stent with phacoemulsification in patients with glaucoma and cataract. Ophthalmology 2011; 118:459–467.

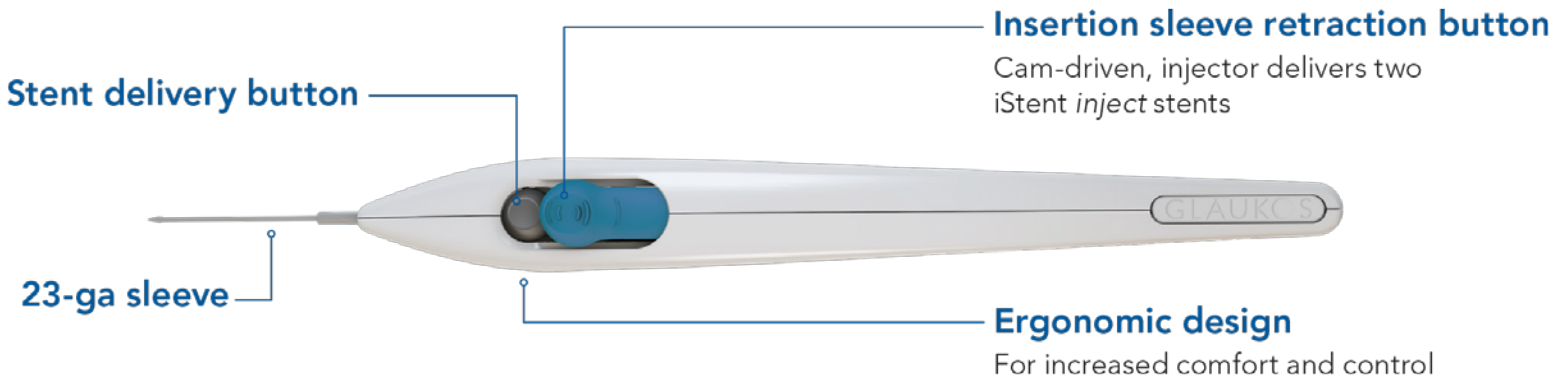
# Retrospective Case Series (Ferguson, Berdahl)

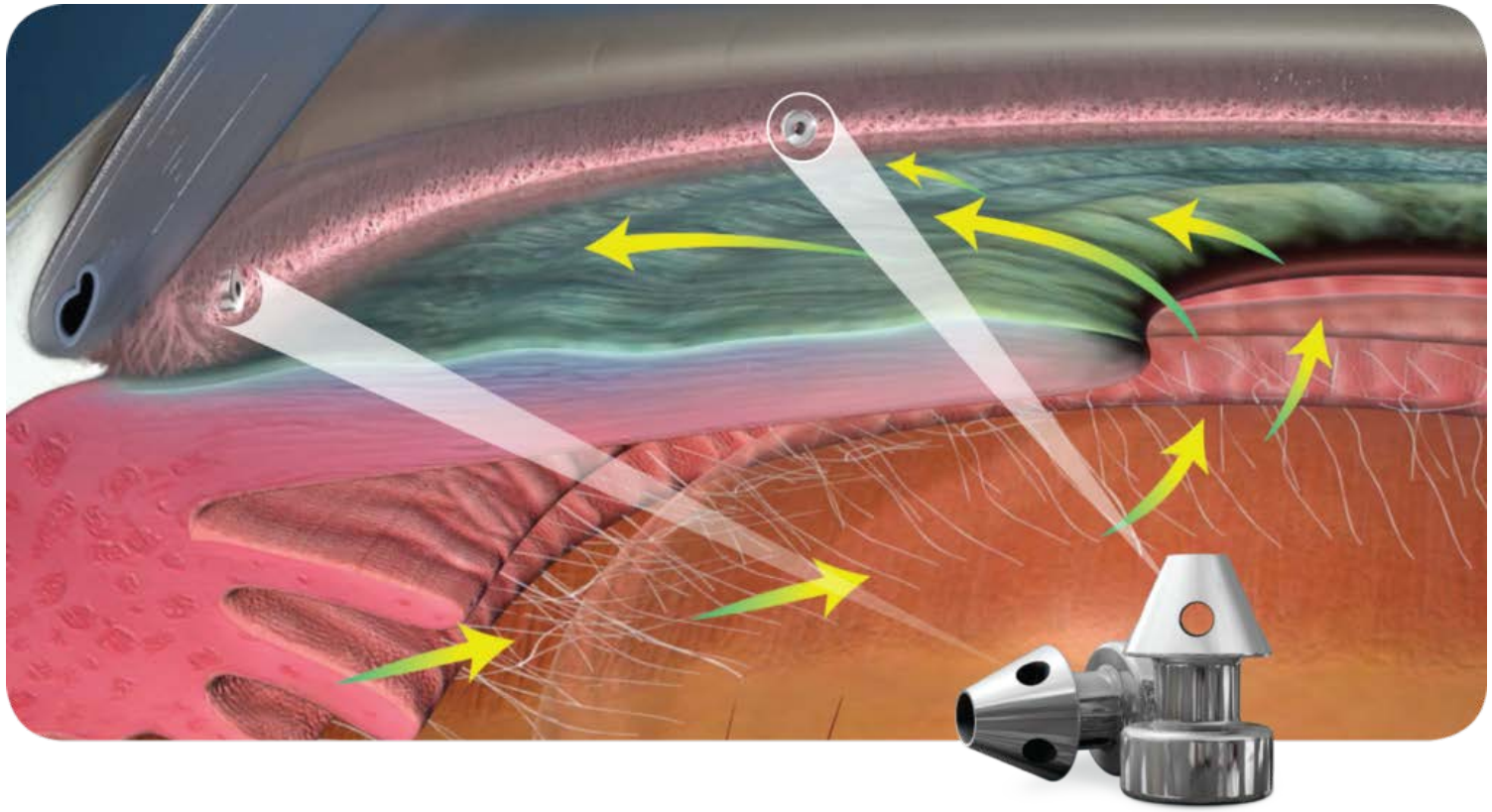
- Large series (n=107)
- At 2 years, mean IOP reduction was **22%** with a **56%** reduction in mean medications




*Ferguson TJ, Berdahl JP, Schweitzer JA, Sudhagoni RG. Clinical evaluation of trabecular microbypass stents with phacoemulsification in patients with open-angle glaucoma and cataract. Clinical Ophthalmology 2016:10 1767-1773*


Trocar
iStent *inject*
stents
Insertion
tube


Insertion sleeve retraction button
Cam-driven, injector delivers two iStent *inject* stents
Stent delivery button
23-ga sleeve
Ergonomic design
For increased comfort and control
GLAUKOS

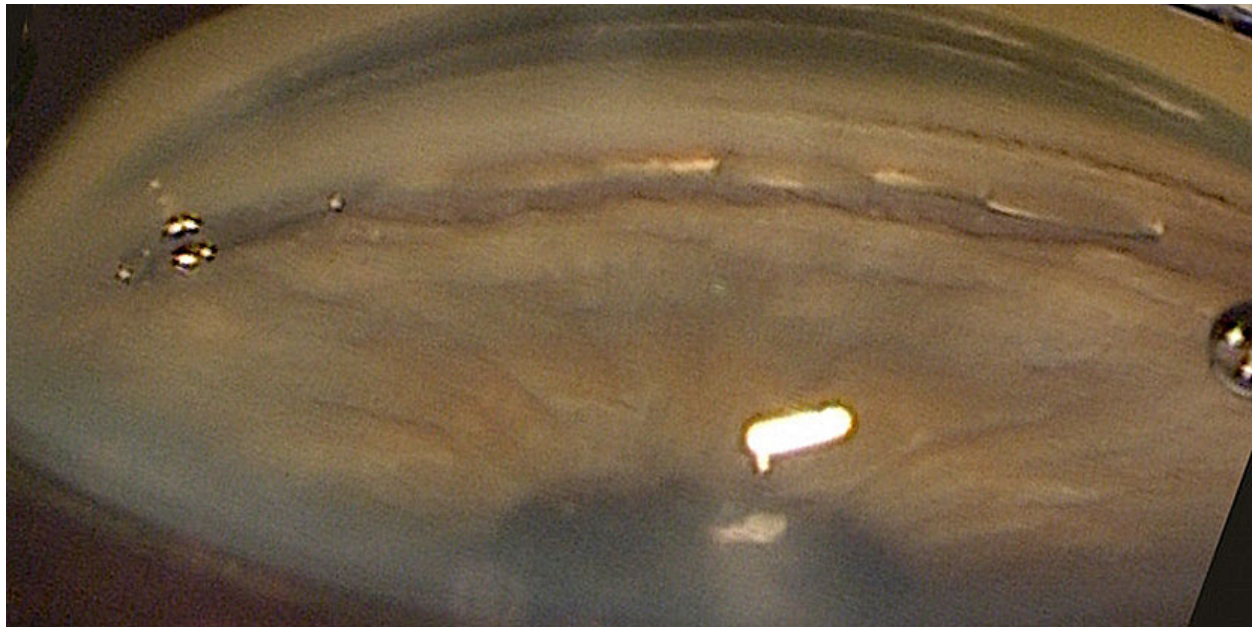


Noecker

# Ivantis /Hydrus Microstent

- The FDA's approval was based on the 24-month results from the HORIZON trial, the largest MIGS study to date.
- The study included 556 mild to moderate glaucoma patients randomly assigned to undergo cataract surgery with or without the microstent.
- More than 77% of patients with the implant exhibited a significant decline in unmedicated IOP, compared with 58% of the control group.
- On average, the device reduced IOP by 7.5 mmHg, approximately 2.3 mmHg more than the cataract surgery-only group.

# Hydrus Microstent

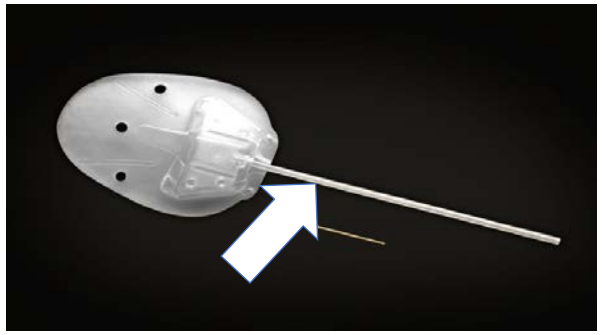


# XEN

# XEN Glaucoma Implant™ Mechanism of Action

**Ab Interno Sub-Conjunctival Drainage**

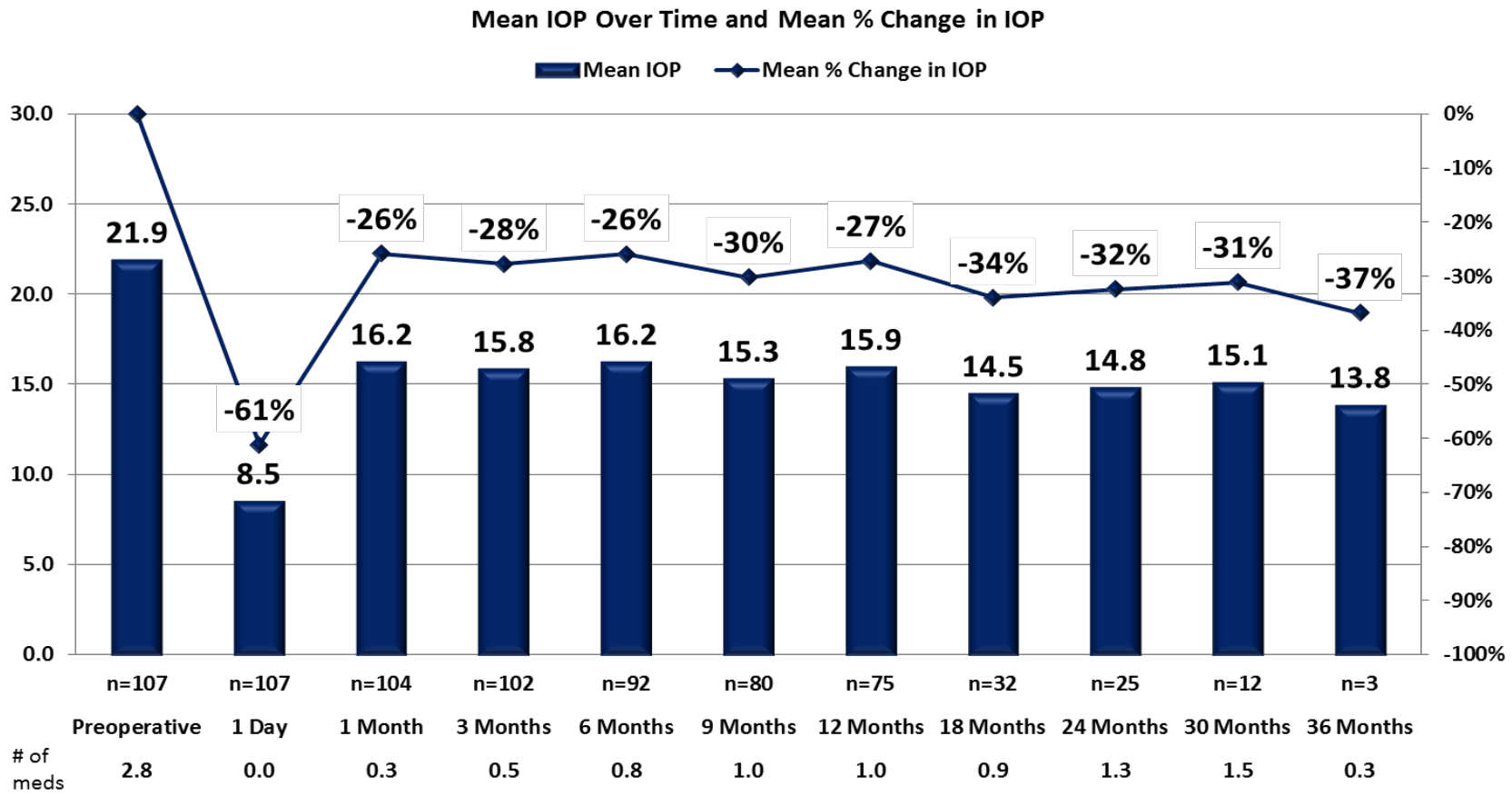
- Surgical "Gold Standard" IOP reduction in minimally invasively procedure
- Clinically proven outflow pathway
- Bypasses all potential outflow obstructions
- Conjunctiva sparing: alternative surgical options remain
- Single implant delivers desired effectiveness



Gelatin Material is Tissue Conforming

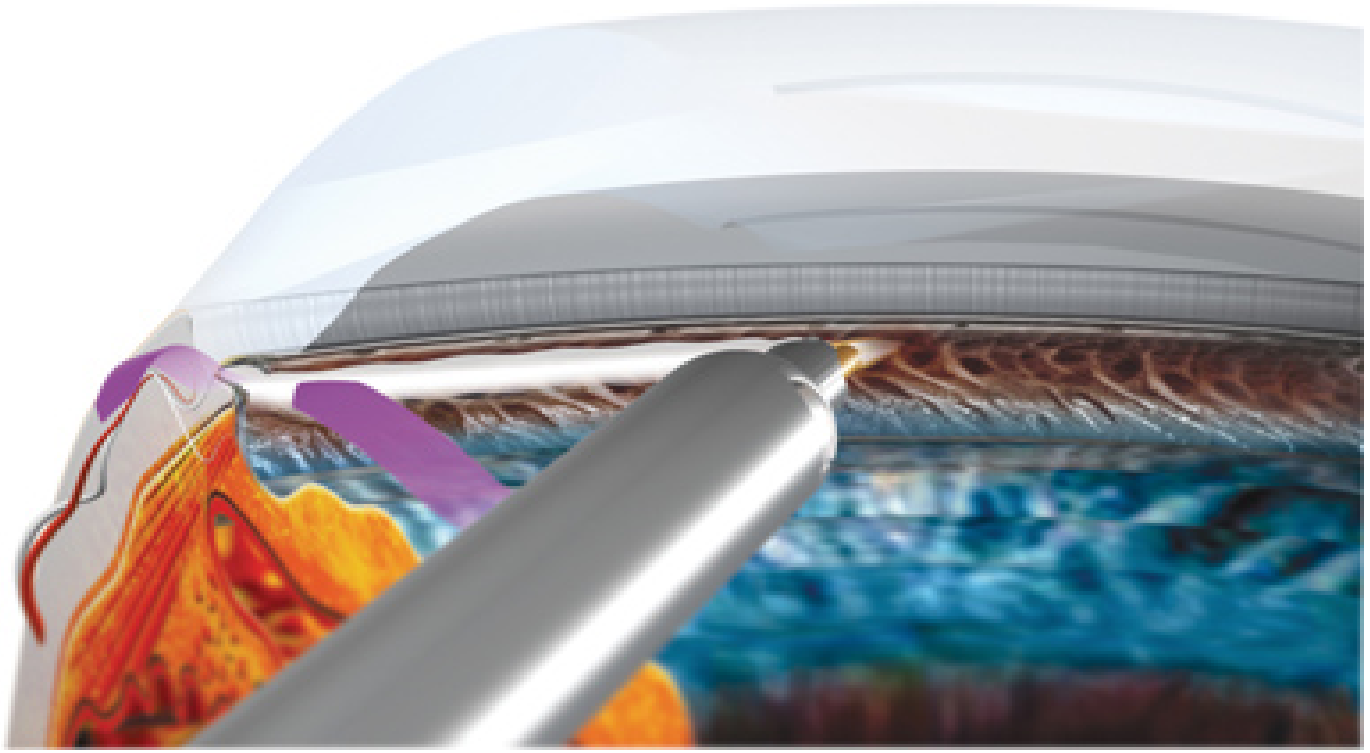
# POAG Only

Summed patients: primary, combined and refractory




**Mean preoperative IOP is best medicated. Patients were not washed out prior to surgery.*

# Trabectome



# Evaluation of the long-term results of Trabectome surgery
# Yildrum,Y etal Int. Ophthalmology 2016

A total of 70 eyes followed up with a diagnosis of open-angle glaucoma (OAG) and undertaken trabectome surgery were included in the study.

The criteria of success were accepted as an IOP value ≤21 mmHg or ≥30 % reduction in IOP and no need for a second operation.

Mean IOP was decreased by 38 % from a preoperative value of 28.77 ± 5.34 to 17.62 ± 2.81 mmHg at the end of 18 months.

Likewise, mean drug usage was decreased by 48 % from a preoperative value of 3.3 ± 1.01 to 1.7 ± 1.16 at the end of 18 months. Both decreases were statistically significant ($p < 0.05$).

Postoperative success rates were:

1. 82.8 % in the 6th month
2. 81.4 % in the 9th month
3. 77.1 % in the 12th month
4. 470 % in the 18th month.

Most common complication observed was intraoperative reflux hemorrhage and no serious complication was observed.

# What is AI?

- Artificial intelligence (AI) is a general term that means to accomplish a task mainly by a computer, with minimal human beings involved[1]. In other words, the purpose of AI is to make computers mimic the way of our thinking, and improve our work efficiency in the modern fast-pace life. It has become one of the most influential information technology revolutions.
- Obermeyer Z, Emanuel EJ. Predicting the future - big data, machine learning, and clinical medicine. *N Engl J Med*. 2016;375(13):1216–1219.

- Machine learning provides techniques or algorithms that can automatically build a model of complex relationships by processing the input available data and generalizing a performance standard[7]. And it can be briefly described as enabling computers make successful predictions or judgments by repeatedly learning existing representative materials.
- To be able to form an accurate model, machine learning often requires a large number of training data. And most of them need to be labeled its features in advance by relative authoritative experts.

- **Deep learning with convolutional neural networks (CNNs).** The term “deep learning” is used because there are multiple interconnected layers of neurons—and because they require new approaches to train them. This latest iteration of AI comes closer to resembling “thinking,” because CNNs learn to perform their tasks through repetition and self-correction.
- A CNN algorithm teaches itself by analyzing pixel or voxel intensities in a labeled training set of expert-graded images, then providing a diagnostic output at the top layer. If the system’s diagnosis is wrong, the algorithm adjusts its parameters (which are called weights and which represent synaptic strength) slightly to decrease the error. The network does this over and over, until the system’s output agrees with that of the human graders.
- This process is repeated many times for every image in the training set. Once the algorithm optimizes itself, it is ready to work on unknown images.

- Current Limitations
- The groundswell of research interest in AI can't mask the fact that the field is grappling with some significant challenges.
- **Quality of the training sets.** If the training set of images given to the AI tool is weak, the software is unlikely to produce accurate outcomes. "The systems are only as good as what they're told. It's important to come up with robust reference standards," Dr. Chiang said.
- Dr. Abràmoff agreed. "You need to start with datasets that everyone agrees are validated. You cannot just take any set from a retinal clinic and say, well, here's a set of bad disease and here's a group of normal," he said.
- **Problems with image quality.** "The state-of-the-art systems are very good at finding diabetic eye disease. But one thing they're not very good at recognizing is when they're not seeing diabetic eye disease. For example, these systems will often get confused by a patient who has a central retinal vein occlusion instead of diabetic retinopathy," Dr. Chiang said.
- He added, "Another challenge is that a certain percentage of images aren't very good. They're blurry or don't capture enough of the retina. It's really important to make sure that these systems recognize when images are of inadequate quality."
- **The black box dilemma.** When a CNN-based system analyzes a new image or data, it does so based upon its own self-generated rules. How, then, can the physician using a deep learning algorithm really know that the outcome is correct? This is the "black box" problem that haunts some medical AI researchers and is downplayed by others, Dr. Abràmoff said.
- **Wrong answers.** Dr. Abràmoff concocted an experiment that he believes illustrates why there is reason for concern. His team changed a small number of pixels in fundus photographs of eyes with DR and then gave these "adversarial" images to image-based black box CNN systems for evaluation. The changes in the images were minor, undetectable to an ophthalmologist's eye. However, when these CNNs evaluated the altered images, more than half the time they judged them to be disease-free, Dr. Abràmoff said.[13]
- "To any physician looking at the adversarial photo it would still look like disease. But we tested the images with different black box CNN algorithms and they all made the same mistake," he said. "So, it's easy for this type of algorithm to make these kinds of mistakes, and we don't know why that is the case. I believe feature-based algorithms are much less prone to these mistakes."

**Eye (Lond). 2018 Jun; 32(6): 1138–1144.**
**Published online 2018 Mar**

# Automated diabetic retinopathy detection in smartphone-based fundus photography using artificial intelligence

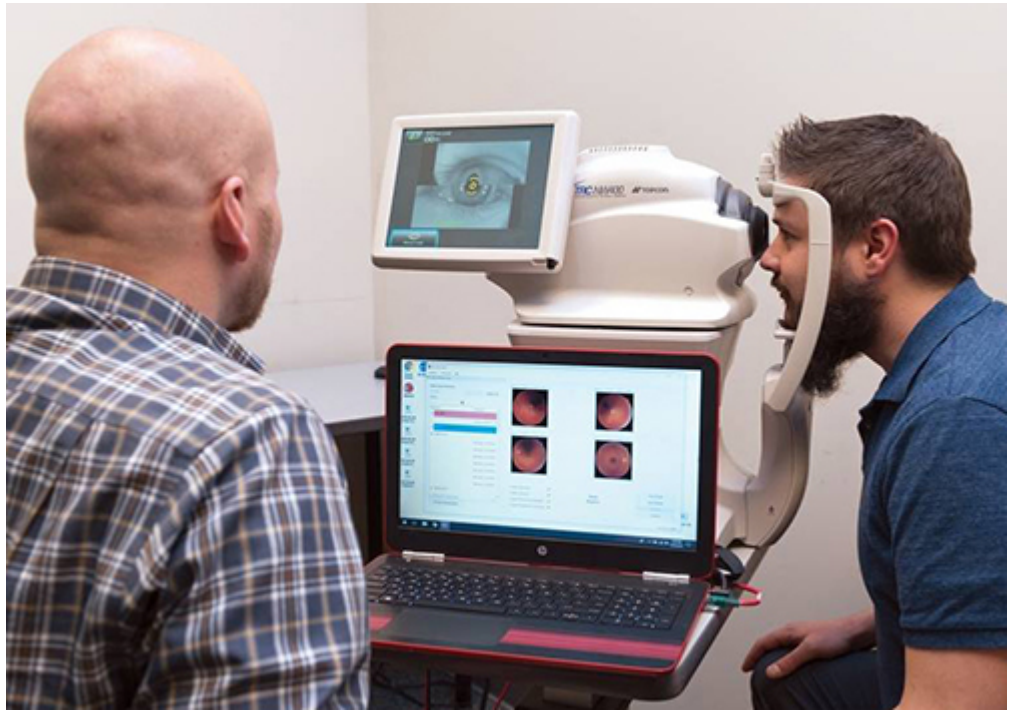
Ramachandran Rajalakshmi, Radhakrishnan Subashini, Ranjit Mohan Anjana, and Viswanathan Mohan

- Three hundred and one patients with type 2 diabetes underwent retinal photography with Remidio ‘Fundus on phone’ (FOP), a smartphone-based device
- 98 % agreement with retinal specialists

# IDx-DR

- **The IDx-DR system (above) delivers a binary result. When signs of diabetic retinopathy are present, the system recommends a follow-up with an ophthalmologist. If it detects no signs of the condition, the system recommends a follow-up screening in one year. All of this happens without input from a clinician or the services of a medical laboratory.**

# IDx



# idx

- The hybrid system’s sensitivity (the primary measure of safety) was 96.8% (95% confidence interval [CI]: 93.3% to 98.8%). This was not significantly different from that of the previously published results with the unenhanced algorithm (CI of 94.4% to 99.3%), the scientists reported.[11] But the specificity level was much better: 87.0% (95% CI: 84.2% to 89.4%, vs. a CI of 55.7% to 63.0% previously).

- Krause J, Gulshan V, Rahimy E, Karth P, Widner K, Corrado GS, Peng L, Webster DR. Grader variability and the importance of reference standards for evaluating machine learning models for diabetic retinopathy. *Ophthalmology.* 2018;125(8):1264–1272

- For the moderate or worse DR, the sensitivity of deep learning models is about 97.1%, compared with the ophthalmologists' 83.3%. Maybe the quality of input images is responsible for the minimal lesions missing, they think

- Google’s deep learning algorithm taught itself to correctly identify diabetic lesions in photographs even though it was not told what the lesions look like, said Peter A. Karth, MD, MBA, a vitreoretinal subspecialist from Eugene, Oregon, who is a consultant to the Google Brain project. “What’s so exciting with deep learning is we’re not actually yet sure what the system is looking at. All we know is that it’s arriving at a correct diagnosis as often as ophthalmologists are,” he said.

# DR AI Outcomes

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Gulshan *et al* **12** | 2016 | Messidor-2 | 1748 | Inception-V3 | 0.99 | 87 | 98.50 |
| | | | | | | 96.10 | 93.90 |
| | | EyePACS-1 | 9963 | | 0.991 | 90.30 | 98.10 |
| | | | | | | 97.50 | 93.40 |

- Treder M, Lauermann JL, Eter N. Automated detection of exudative age-related macular degeneration in spectral domain optical coherence tomography using deep learning. *Graefes Arch Clin Exp Ophthalmol*. 2018;256(2):259–265

# Age-related macular degeneration

| Age-related macular degeneration | | | | | | | |
|---|---|---|---|---|---|---|---|
| Ting *et al* **11** | 2017 | SiDRP 14–15 | 35 948 | VGG-19 | 0.932 | 93.20 | 88.70 |

- But also, there exist researches combined spectral domain OCT with deep learning about AMD, including the macular fluid quantity of neovascular AMD (nAMD) and the retinal layers segmentation of dry AMD like. After an iteration training, the training and validation accuracy are both 100%. They believe that other macular diseases will obtain the same effective results.

- The available AI devices for detecting glaucomatous optic neuropathy from fundus photos are the Pegasus (Orbis Cybersight Consult Platform), NetraAI (Leben Care Technologies Pte Ltd) and the Retinal Image Analysis - Glaucoma (RIA-G). RIA-G is the AI device based on DL made by the Indian startup Kalpah Innovations (Vishakapatnam, India). It is a cloud-based software that uses advanced image processing algorithms to measure the cup disc size and ratio, NeuroRetinal Rim Thickness and Disc Damage Likelihood Score[39].

  Panda BB, Thakur S, Mohapatra S, Parida S. Artificial intelligence in ophthalmology: A new era is beginning. *Artif Intell Med Imaging* 2021; 2(1): 5-12 [DOI: 10.35711/aimi.v2.i1.5]

- Asaoka R, Murata H, Iwase A, Araie M. Detecting Preperimetric Glaucoma with Standard Automated Perimetry Using a Deep Learning Classifier. Ophthalmology. 2016;123:1974-1980.

  Panda BB, Thakur S, Mohapatra S, Parida S. Artificial intelligence in ophthalmology: A new era is beginning. *Artif Intell Med Imaging* 2021; 2(1): 5-12 [DOI: 10.35711/aimi.v2.i1.5]

- AI can also augment the interpretation of visual fields in studies showed by Asaoka et al[40] and Andersson et al[41] using a Feed-Forward Neural Network to identify pre-perimetric visual fields (VF). Goldbaum et al[42] used unsupervised ML and variational Bayesian independent component analysis mixture model (vB-ICA-mm) to analyze VF defects. Bowd et al[43] used the variational Bayesian

  Panda BB, Thakur S, Mohapatra S, Parida S. Artificial intelligence in ophthalmology: A new era is beginning. *Artif Intell Med Imaging* 2021; 2(1): 5-12 [DOI: 10.35711/aimi.v2.i1.5]

BJO

•Volume 103, Issue 2

Review

# Artificial intelligence and deep learning in ophthalmology

1.Daniel Shu Wei Ting1,
2.Louis R Pasquale2,
3.Lily Peng3,
4.John Peter Campbell4,
5.Aaron Y Lee5,
6.Rajiv Raman6,
7.Gavin Siew Wei Tan1,
8.Leopold Schmetterer1,7,8,9,
9.Pearse A Keane10,
10.Tien Yin Wong1
1.Correspondence to Dr Daniel Shu Wei Ting, Assistant Professor in Ophthalmology, Duke-NUS Medical SchoolSingapore National Eye Center, Singapore 168751, Singapore; daniel.ting.s.w@singhealth.com.sg

# Glaucoma Suspect AI Outcomes

| Glaucoma suspect* | | | | | | | |
|---|---|---|---|---|---|---|---|
| Ting *et al* **11** | 2017 | SiDRP 14–15 | 71 896 | VGG-19 | 0.942 | 96.40 | 93.20 |
| Li *et al* **16** | 2018 | Guang dong | 48 116 | | 0.986 | 95.60 | 92.00 |

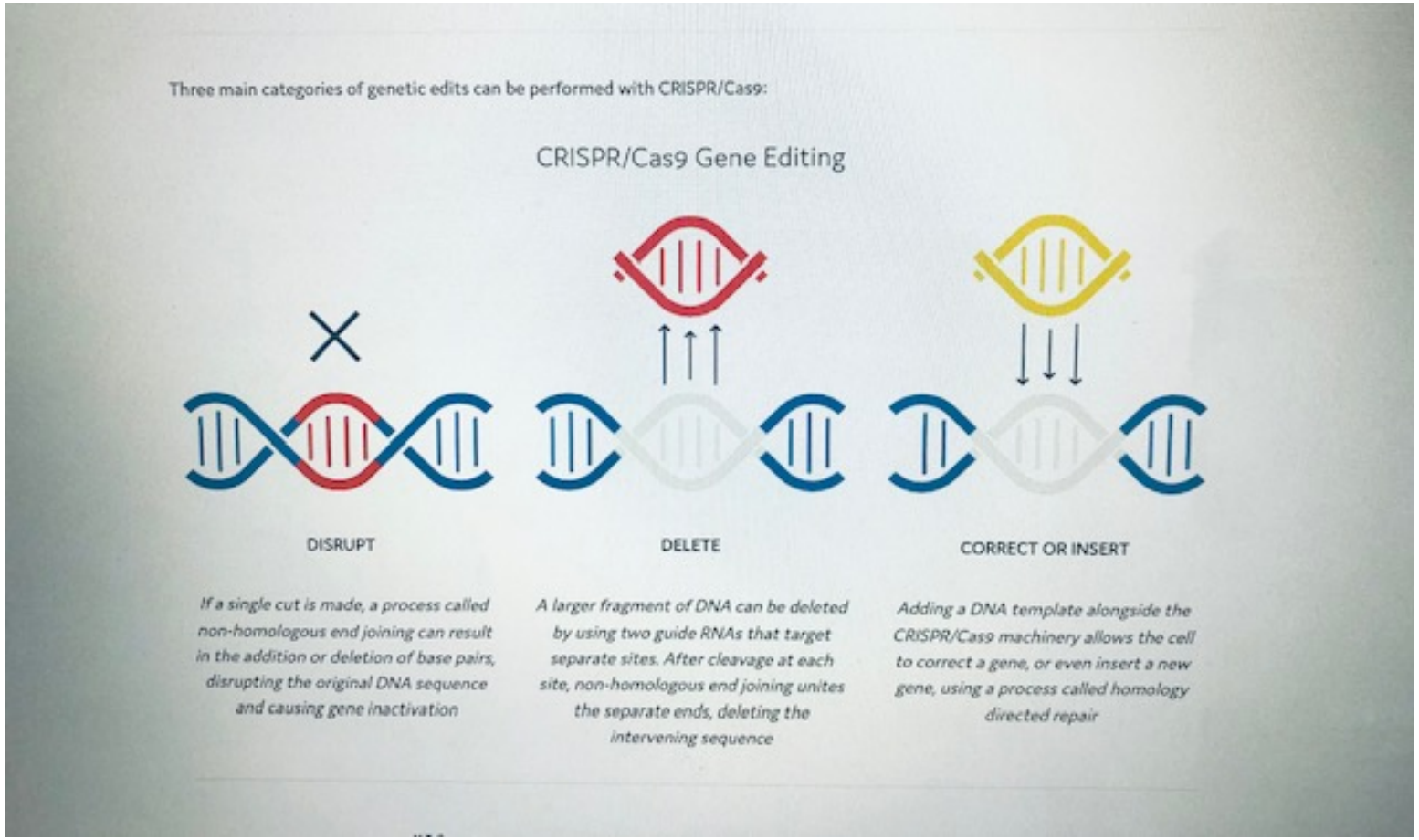
# DeepMind

- An especially exciting development in the field of ophthalmology AI came with the report of a system developed as part of a collaboration between Moorfields Eye Hospital in London and another Google AI team, DeepMind.
- These teams created an AI system that combines two DLS with the ability to detect 50 ophthalmic diseases based on analysis of three-dimensional OCT data.
- The first DLS uses the raw OCT data to create a tissue map, and then the second DLS analyzes the tissue map for potential markers of disease.[12,13]

# DeepMind

- The DeepMind system was validated in a study that showed it was 94% sensitive, catching most positive cases of each disease.
- In fact, DeepMind performed as well or better than human clinical experts (retina specialists and optometrists with medical retina training), depending on who the experts were and how much additional information they had to work with (e.g. fundus images, patient medical histories).
- What's also impressive is that the system gives more than just a yes-or-no diagnosis, but provides multiple levels of actionable information.
- For instance, the system provides probabilities for multiple similar diseases in addition to the top pick. The system also provides an accompanying recommendation on urgency of referral, with options of 'observation only', 'routine', 'semi-urgent', and 'urgent'.[12,13]

# Crispr: The future of medicine



- **CRISPR Lexicon**
- **CRISPR:** Clustered Regularly Interspaced Short Palindromic Repeats of genetic information that some bacterial species use as part of an antiviral system. A group of scientists, including our co-founder Dr. Emmanuelle Charpentier, discovered how to use this system as a gene-editing tool (Jinek, *et al.* Science 2012)
- **Cas9:** a CRISPR-associated (Cas) endonuclease, or enzyme, that acts as "molecular scissors" to cut DNA at a location specified by a guide RNA
- **Deoxyribonucleic acid (DNA):** the molecule that most organisms use to store genetic information, which contains the "instructions for life"
- **Ribonucleic acid (RNA):** a molecule related to DNA that living things use for a number of purposes, including transporting and reading the DNA "instructions"
- **Guide RNA (gRNA):** a type of RNA molecule that binds to Cas9 and specifies, based on the sequence of the gRNA, the location at which Cas9 will cut DNA

- At CRISPR Therapeutics, we aim to develop transformative gene-based medicines based on CRISPR/Cas9 gene editing. For genetically-defined diseases, we can use a guide RNA that directs Cas9 to cut DNA at a specific site in a disease-causing gene, or at a different site, such as a region that regulates genes, to ameliorate the genetic defect through gene disruption or correction. For cell therapies, we can target genes that when disrupted may improve the safety or efficacy of the therapy, or precisely insert new genes to give the cells new abilities. In either case, we may edit cells either *ex vivo* (outside the body) or *in vivo* (inside the body).