

## ***Technology & Innovation***

**John A. McGreal Jr., O.D.**  
**Missouri Eye Associates**  
**McGreal Educational Institute**

*Excitement in Optometric Education*

## **John A. McGreal Jr., O.D.**

- Missouri Eye Associates
- 11710 Old Ballas Rd.
- St. Louis, MO. 63141
- 314.569.2020
- 314.569.1596 FAX
- mcgrealjohn@gmail.com

JAM

## **2Win Binocular Handheld Refractometer & Vision Analyzer**

- Fully automated binocular refraction
- Operates at 1 m
- 7 second exam, no drops
- Small portable
- Battery operated
- Ideal for infants, children, disabled or non cooperative patients
- Acoustic and light targets built in
- [www.2winforvision.com](http://www.2winforvision.com) 408 716 3271

## **DRS Digital Retinography System**

- Fully automated retinal imaging
- Auto-sensing, auto-alignment, auto-focus, auto-flash adjustment
- Both eyes in one minute
- Compact clean design
- Motorized chin rest
- 40-45 degrees field of view
- Embedded PC, ethernet & Wi-Fi connectivity
- [www.centerview.com](http://www.centerview.com) Padova, Italy, Santa Clara CA

## **Eyewearable Technology**

- Hottest emerging consumer category
- Young tech-savvy early adopters
- Google's Glass will galvanize the interest
- Wearable devices in variety of form factors
  - Smart glasses with screens
    - View data, images
  - Sunglasses allowing HD video capture & uploads to social
  - Ski goggles with GPS and speedometers

## **Google Glass**

- Wearable computer
- High resolution display – 25" HD screen at 8ft
- Camera 5mp & video at 720p
- 12 GB usable memory, Synced with Google cloud storage (16GB)
- Audio delivered through bone conduction transducer
- WiFi connectivity, Blue tooth to any phone
- GPS & SMS messaging
- MyGlass companion app requires Android 4.0.3, higher
- USB charger, lasts one day
- Durable frame fits all with two extra nose pads in 2 sizes

### Epiphany Eyewear – Vergence Labs

- Thick black frame shape memory nylon
- Polarized, UV blocking
- HD recording with audio, HD streaming through tablet to Facebook and YouGenTV
- Lithium ion battery, USB charge (1-2days)
- Plano front lens impact resistant
- Back lens Rx -2.00D to +2.00D
- Electromagnetic lens in between, activated by a switch on front, changes to sunless in 1 millisecond
- \$299 (8GB), \$399 (16GB), \$499 (32GB)

### VUSIX M100 Smart Glasses – Vusix Corp

- 1<sup>st</sup> Hands free display & communication system
- To access data from internet & smart phones
- Virtual display, integrated camera (still & video)
- GPS & visual navigation
- Android OS
- Wireless via Bluetooth or WiFi to smart phone (iOS, Android)
- Augmented reality – merges virtual & real world
- Most award winning in multiple categories

### VUSIX M100 Smart Glasses – Vusix Corp

- HD camera & Ski goggle
- HD video camera 1080p. 8 mp photo
- Sleek, 84 degree field, up to 170 degree wide angle, built-in microphone, temperature gauge, filming options (120 frames/sec) in-goggle view finder, instant replay. Real time stats, speed, temp, distance, airtime, altitude
- 14" screen at 8ft, Bluetooth, smart phone connectivity
- Caller ID, text messaging, buddy tracking, trail maps, navigation
- \$399

### Retinoblastoma Advance

- Super-selective Ophthalmic Artery Chemotherapy as Primary Treatment of Retinoblastoma Abrams, D Ophthal 2010;117:1623
- “Chemo-surgery”
- Ophthalmic artery can be safely and repeatedly cannulated in very young children
- Deliver high concentration (low dose) chemotherapy infusion on outpatient basis
- Prevents radiation, enucleation, and systemic chemotherapy

### Retinoblastoma Advance

- Ophthalmic Artery Chemosurgery for Retinoblastoma Prevents New Intraocular Tumors Abramson, D Ophthal 2013;120:560-565
- New anterior tumors are found after treatment of primary tumor (XRT or chemo) in 24-48%
- OAC eyes demonstrate fewer new intraocular retinoblastomas; suggests ophthalmoscopically undetectable tumors present at initial diagnosis
- Less EUA, lower costs, higher ocular survival, less anxiety, avoidance of sided effects of repeated focal treatments

### New Ideas in Glaucoma

- Minimally Invasive Glaucoma Surgery (MIGS)
  - Micro-stents emerging from trials, recent FDA approvals
  - Studies (COMPASS/phase 3) showing limited efficacy of third IOP lowering agent
  - Makes argument for MIGS after failing with two topical medications
- Glaukos iStent
- Solx Gold Implant

## Glaukos iStent Tabecular Bypass

- Smallest medical device approved by FDA
  - 1mm long, 0.33mm height, snorkle 0.25mm x 120um, 60ug
  - Nonferromagnetic titanium single use, sterile inserter
- Approved for mild-moderate glaucoma
- Placed during cataract surgery
- Spares tissues damaged by traditional procedures
- Contraindicated in NVG, PAS, primary or secondary angle closure glaucoma, angle abnormalities
- Adverse events – corneal edema, loss of BVA>1 line, PCO, stent obstruction

## New Ideas in Glaucoma - Genetics

- Multiple genes & environmental factors interact in this heterogenous complex disorder
- Family history is one of the most important risk factors
- First degree relatives of affected patients demonstrate glaucoma 10 times more than general population
- 16 loci contributing susceptibility identified
  - Of these four genes isolated
  - Myocilin - more likely in early age of onset, family hx, elevated IOP
  - Optineurin
  - WDR36
  - NTF4

## Prognostic Factors in VF Progression

- Ophth 2013;120:512-519 Ernst, et al, in order
- Age (for all OAG)
- Disc hemorrhages (for NTG)
- Baseline VF loss
- Baseline IOP
- Exfoliation syndrome
- CCT
- Peri-papillary atrophy (for NTG)
- Proven previous VF progression

## New Use for “Rejected” Corneas

- Journal of Glaucoma, Girkin UAB
- Donor corneas not suitable for cornea transplants (clarity) may be a better option to cover glaucoma shunts than traditional pericardium tissue
  - More durable, less likely to erode
  - Safer, lower risk of infection
  - Reduces subsequent surgery

## Human Allograft Tissue

- Biocompatible for leaking blebs or exposed implants
- Gamma sterilized
- 2.5 year shelf life
- Nominal thickness 0.5mm
- Freeze dried or hydrated
- Available as sclera, pericardium

## ExPress Mini-Glaucoma Implant (Optinol Ltd)

- Less time consuming than larger tubes
  - Allows for more extensive surgery later if needed
- Placed under sutured scleral flap
- Conjunctival dependent
- Creates posterior low diffuse bleb within 1-2 days
- Device is 400um wide x 3mm long stainless steel device
- Avoids trabeculectomy failure

## Trabectome (NeoMedix)

- One use disposable device
- Bipolar electro-surgical pulse 550KHz/0.1w incr
- Simultaneous irrigation & aspiration
- Ablation of TM and unroofing of schlemm's canal and juxtacanalicular tissue
- Average IOP decreases from 24mm to 15mm @60m
- Topical Rx's decrease from 3 to 1 @60m
- Advantage – easy, outpatient, option to delay trabeculectomy, less side effects

JAM

## Glaucoma Tube Implants

- Developed for patients with high risk of failure from standard surgery
- Design – silicone rubber tubing and ridged plastic or silicone rubber explant
  - Materials do not allow fibroblast to adhere to device
  - Equatorial placement of explant
    - Anterior edge of explant is 8-10mm posterior to corneoscleral junction
  - Tube into anterior chamber by 2mm
  - Superior temporal position is preferred
  - Patching material required to adequately cover implant
    - Sclera, dura, pericardium

## Glaucoma Tube Implants

- Drain – allows flow of aqueous from anterior chamber through tube into implant
  - Passive diffusion into surrounding peri-ocular tissues
  - Uptake by lymphatic system and venous capillaries
- Available Implants
  - Non-valved
    - Molteno
    - Baerveldt
  - Valved
    - Ahmed
    - Krupin
  - Single plate and double plate designs

## Glaucoma Tube Implants

- Indications
  - Failure of conventional therapies
    - Topical
    - Laser
    - Trabeculectomy with or without MMC
  - Conjunctival diseases, pemphigoid, chemical injuries, severe dry eyes, trauma related glaucoma with scleral thinning, uveitic glaucoma, congenital glaucoma,
  - Neovascular diseases – Neovascular glaucoma, diabetic retinopathy, retinal vascular occlusions.

## Glaucoma Tube Implants

- Special intra-operative and post-operative considerations
  - Temporary ligature of drain tube of non-valved implants
    - 2-4 weeks
    - Allows capsule to develop
    - Resistance to flow is established
    - Best completed with absorbable external suture or prolene suture placed into tube
      - Removed via small conjunctival incision in office
- Complications
  - Corneal endothelial issues in vicinity of tube, hypotony, obstruction of tube with fibrin, vitreous, blood, epithelial ingrowth

## Baerveldt Implants (Abbott Medical Optics)

- 3 models
- Larger surface area plate than single quadrant devices
  - Single quad insertion
  - Decreased bleb height
- Smooth polished pliable silicone plate
- 4 fenestrations to promote fibrous adhesions
  - Reduces bleb height
  - Open drainage tube
  - Fixation sutures holes
- Requires stitch or tie off suture to control flow initially

## Ahmed Implant (New World Medical Inc)

- One way valve design
  - Prevents post op hypotony
- Immediate IOP reduction
  - Best for cases which are high pressures
  - Best for cases where any spike in IOP cannot be tolerated
- Single stage procedure
- Eliminates “rip chord” sutures, occluding sutures, or tube ligature sutures

## Molteno Implants (Molteno Ophthalm Ltd)

- Single or double plates devices
- Double plate devices allow for greater aqueous drainage
- Silicone
- Low profile
- Larger, thinner devices

## Tafluprost

- Topical prostaglandin, first preservative-free preparation
- Indications: open angle glaucoma or ocular hypertension
- Supplied: 10 PF ampules per pouch, 3 pouches/box
- Side effects – same as other PGA
- Dosage: once daily at bedtime
- Storage: refrigeration necessary until pouch is opened, then once opened room temperature is fine
- Available as *Zioptan*

## Brinzolamide 1.0%/Brimonidine 0.2%

- Anti-glaucoma suspension
- Indications
  - POAG/OHTN
- Benefits
  - fixed combination, *ONLY* beta blocker free, reduces burden
- Action – 21-35% decrease IOP (5-9mmHg at 3 mos)
- Side effects – blurred vision, irritation, dysgeusia, DE
- Precautions – brinzolamide is a sulfonamide, BAK
- Dose – TID
- Available as
  - *Simbrinza* / Novartis-Alcon

## New Ideas in OCT

- Ultra-widefield with angiography
  - Extends multi-modality of Spectralis platform
  - Diseases are underestimated for lack of peripheral angiography
  - Can image out to 150 degrees
- Multi-color Imaging – Spectralis
  - High contrast, noise reduction, eye tracking
  - 3 simultaneously acquired selective color laser images
  - Versatility to view individual or multicolor images
  - Identifies pathology unclear on fundus images

## Peripheral Autofluorescence in AMD

- Colin, et al Ophthalmol 2013;120:127-1277
- Distinct patterns of peripheral FAF abnormalities were seen in 68.9%
- AMD type correlates with Peripheral FAF changes
  - Neovascular type more common, non-neovascular type, then normals
- Age – any peripheral FAF abnormality was associated with older age
- Female patients had a higher risk of abnormal peripheral FAF compared to males

## Multi-Spectral Imaging (MSI)

- “virtual angiography”
- Non-invasive alternative to IVFA
- Valuable adjunct to OCT
- LEDs from 550-950nm
  - Image in pairs
  - Full series is 6 flashes/12 images
  - Shorter wavelengths image inner retina layers (ex VMA)
  - Longer wavelengths image outer retina layers (ex AMD)
- Useful to gauge effects of drugs, nutraceuticals, major benefit in dry AMD

## Optos OCT SLO

- Microperimetry assesses retinal sensitivity
  - Monitors course of disease and response to treatments
- Precise correlation between pathologic structure & functional defects
- Only device on market conducts OCT & functional MP testing
- MP testing runs in conjunction with high confocal SLO
  - With tracking of vessels
  - Faster perimetry
  - More accurate change over time assessments compared to SAP

## Super-dose Anti-VEGF Trial (SAVE) in AMD

- Brown, et al. Ophthalmology 2013;120:349-354
- Intravitreal injections of 2.0mg ranibizumab led to significant VA gains & anatomic improvements in patients with persistent intraretinal, subretinal, or subRPE fluid during a period of chronic monthly 0.5mg ranibizumab injections
- CATT demonstrated persistent fluid on OCT in 53.2% of ranibizumab & 70.9% of bevacizumab
- A significant unmet need for more potent, longer lasting or complementary mechanism of action

## Anti-platelet derived growth factor in AMD

- Ophthotech Corp, NJ – anti-PDGF aptamer Fovista
- Solution to overwhelming, non-sustainable treatment burden of anti-VEGF
- ANCHOR, MARINA, CATT, HORIZON all show vision recovery for first 2-3mos, stabilizing around 4mos, then plateau for extended period with strict monthly injections
  - All demonstrate quick worsening with decreased dosing
  - Medicare claims data – fewer than 6 injections in 1<sup>st</sup> year
  - Nationwide outcomes must be worse than we want to admit!

## Anti-platelet derived growth factor in AMD

- Roots of resistance – angiogenesis involves thousands of chemical factors, occurring over stages
  - Initiation/progression/differentiation/maturation/remodeling
  - Numerous cell types contribute to this growth
- Pericytes and endothelial cells show significant “cross talk” cell signaling
- “Tip” endothelial cells blaze trails, create sprouts, secrete PDGF-B which recruits pericytes to proliferate and migrate, protecting the endothelial cells and over time secreting more VEGF, diminishing the effect of anti-VEGF therapy

## Anti-platelet derived growth factor in AMD

- Combination therapy of anti-VEGF & anti-PDGF in phase 2b demonstrate +10.6 letters improvement or 62% improvement over Lucentis monotherapy
- This appears to inhibit pericyte recruitment, strip pericytes from NV complex without negatively affecting host non-cardiovascular vessels, causing both inhibition & regression of NV complex

## Pharmacogenomics & Treatment in AMD

- Currently only phenotypic/anatomic predictors of response to anti-VEGF therapy
- Technology emerging to stratify and predict responses to antiangiogenic treatments
  - Using known disease causing SNPs and haplotype odds ratios of these SNPs, drusen size, smoking history we can predict risk of progressing to advanced sight threatening AMD
- Rapidly evolving field to help individualize care and design new therapies
- In office genetic testing available soon to assess the response to AMD vitamins, down to exact ingredients

## Lutein+Zeaxanthin & O3FA for AMD

- Chew, et al. JAMA May 15, 2013-Vol309, No19
- AREDS 2
  - Addition of Lutein+zeaxanthin, DHA+EPA, or both to AREDS formulation in primary analysis did not further reduce risk of progression to advanced AMD.
  - Because of the potential increased incidence of lung cancer in former smokers, lutein+zeaxanthin could be appropriate carotenoid substitutes in the AREDS formulation

## AREDS 2 The Rest of the Story

- AREDS 2 subjects far better than national average in nutrition status
- In US dietary intake of Z is 1mg/D, similar to intake of participants showing greatest reduction in risk
  - In line with lowest quintile in study
- Addition of L+Z to AREDS formulation resulted in a 10% reduction in conversion from AREDS 3 or 4 to advanced AMD, and 11% reduction of CNV
- Comparing AREDS w/o beta carotene vs original AREDS w beta carotene resulted in an 18% reduction in progression to advanced AMD

## AREDS 2 The Rest of the Story

- Former smokers showed more lung cancers in beta carotene group than no beta carotene group
  - 50% of AREDS 2 subjects were former smokers
  - Suggests half AMD patients at greater risk of lung cancer if using AREDS I supplement
  - Competitive inhibition of carotenoid uptake
  - Beta carotene more than doubled lung cancer in previous smokers (current smokers excluded from beta carotene group)
- NEI issued recommendation to modify original AREDS formulation by adding 10mg lutein & 2mg zeaxanthin while removing beta carotene

## CARMA – Secondary Outcomes / Benefits

- Carotenoids w Coantioxidants in ARM (CARMA study)
  - Beatty et al Ophthal 2013;120:600-606
- Randomized, double masked controlled trial of patients at highest risk of progression to advanced AMD
  - BVA, MPOD, CS, morphologic grading, serum antioxidants
  - Excluded b carotene, reduced zinc to 20mg, reduced vitamin C to 150mg, Lutene 12mg & Zeaxanthin 0.6mg, vitamin E 15mg
- Results: no BVA change at 12mos, but increased beyond, MPOD (declined in placebo grp) increased, morphologic benefits observed

## Diabetic Eye Diseases – The Next Wave

- 27% of Americans over 65 have DM (ADA)
- 100 million people worldwide
- 1 in 3 Americans will be DM by 2050 (CDC)
- 40-45% of Americans with DM have retinopathy (NEI)
  - 7.7 million people
  - 89% increase since 2000!
  - ANY degree of DR are 61% higher risk of CVD (CHD, stroke) events & all cause mortality independent of traditional risk factors (Ophthal 2013;120:574-582)
- DM 40% more likely to have glaucoma
- DM 60% more likely to have cataracts

## Diabetic Eye Diseases – The Next Wave

- 2012 US diabetic care cost \$245 billion
  - 41% increase from 2007
  - Forecast to be 3.35 trillion by 2020
- 200,000 deaths/year in US
- 25.8 million Americans have DM
- 79 million Americans have pre-diabetes
- 7 million have undiagnosed DM
- Recent work finds DM strongly associated with AD, CA

---

## Diabetic Eye Diseases – The Next Wave

- Three Level Surge
  - Baby Boomers – 28% US population
    - AMD & DR
  - DM surge
  - Affordable Care Act (ACA)
    - Adds 32 million new covered lives
    - Many have not had proper medical care
    - Many have not had proper eye care
- “Gluttons for Punishment” – Lancet 21 July 2012, 380
  - Americans comprise 5% of world population and account for 33% obesity, overfed for first time in history, inactivity results in as many deaths as smoking

---

## Lens Fluorescence Biomicroscope

- ClearPath DS-120 / Freedom Meditech
  - Recently approved
  - Non-invasive, biophotonic quickly detects lens autofluorescence
    - 8 seconds
    - Quantitatively
  - Confocal scanning laser reflectance microscope
  - Pupil tracker
  - Long life blue LEDs
  - Electronic transmission to HER or other referral sources
- Eliminates fasting, blood draw, waiting time, biohazard burden

---

## Lens Fluorescence Biomicroscope

- Screens for Elevated Advanced Glycolated End products (AGEs)
  - High correlation to uncontrolled glucose
  - Irreversible AGEs in crystalline lens
    - Benefit as a screening tool compared to HgA1c
  - Linear relationship exists between age & autofluorescence
  - Uncontrolled glucose causes deviation in the relationship
- Available in three configurations to fit any office layout

---

## New & Emerging Treatments for DME

- Ranibizumab - FDA approved for DME recently
  - READ-2: for DME
  - RISE/RISE: rapid, sustainable increase in VA & decrease in ME
  - RESOLVE/RESTORE: drug alone or drug + laser better than standard therapy
- Bevasizumab
  - CATT: B vs R SAME
  - BOLT: drug vs laser in DME
    - drug better at year 1 & year2
- Afibercept - Phase III for DME

IAM

## New & Emerging Treatments for DME

- Topical drops
  - Mecamylamine (Comentis/SanFran) – endothelial nicotinic acetylcholine receptor blocker, decreases angiogenesis & vascular permeability
  - Bromfenac
  - Nepafenac
- Intravitreal
  - Triamcinolone
  - Ozurdex – FDA approved for RVO & uveitis

IAM



## New & Emerging Treatments for DME

- Subconjunctival
  - Sirolimus (Perceiva/MacuSight/CA)
    - FDA approval for systemic use in renal transplants
  - Rapamycin – immunosuppressant, anti-angiogenesis, anti-proliferative, anti-fibrotic, anti-permeability, anti-migratory mechanism
    - Injected subtenons or intravitreal
    - Effect is for 180 days, getting better with time
    - CHANGES THE COURSE OF DR, rather than reversing macular edema!

JAM

## Anisokonia Solved – The Shaw Lens

- Designs a precision, atoric, aspheric, position of wear iseikonic, isophoric, binocular spectacle lens system
- Difference in both eyes ability to make compensated eye movements to achieve foveal fixation of a peripheral target
- Due to
  - Spectacle correction of anisometropia
  - Meridional aniseikonia from asymmetrical astigmatism
  - Curvature at spectacle plane (face form)
  - Prism
- Problem = “you get used to it”

----

## Anisokonia Solved – The Shaw Lens

- Spectacle correction of anisometropia
- CL wearer unhappy with spectacles
- Refractive changes due to cataract progression
- Myopic progression in CL wear
- Scleral buckle with/without subsequent cataract surgery
- Mixed mode cataract surgery (ACIOL with PCIOL)
- Infantile amblyopia w anisometropia, +/-strabismus
- Adolescent Amblyopia with/without CL
- Adult hyperopic anisometropic amblyopia (BVA 20/200)

----

## Anisokonia Solved – The Shaw Lens

- Lens design tool (software app) uses prescription, motor fusion limits, position of wear information
  - Bridges refractive physical optics and physiology of individual binocular vision system
- Vergence testing required – base down to break OD/base up to break OD/base in to break OU/base out to blur/break OU
  - Tolerance of static and dynamic anisokonia varies widely between patients
- Complex mathematics automatically determines appropriate index, corridor length, base curve and center thickness to solve aniseikonia to prescribed limits for best binocular dynamic results

----

## Anisokonia Solved – The Shaw Lens

- Digitally surfaced multilayer, antireflection, hydrophobic, oleophobic scratch resistant coatings
- PAL in 4 ergo designs, FT 28, single vision, indices from 1.49-1.74, Transitions, Polarized, custom tints, and hard resin
- Available as finished uncuts ready for edging or completely edged and mounted
- Better medicine in good business (loyalty/differentiating)
- Distribution in Toronto, and Dallas
- [www.shawlens.com](http://www.shawlens.com), [answers@shawlens.com](mailto:answers@shawlens.com)  
877.796.9944

----

## Resolvix Pharm/Cambridge Mass

- 10,000 times more potent than fish oil in anti-inflammatory effect
- Improves corneal disease
- Increases goblet cells
- Safe
- Synthesized form dietary lipids like fish oil
- Finished phase II, starting phase III
- Will be available as *Resolvin Analogues*

## Rebamipide 2% / Otsuka

- Quinolone derivative with mucin secretagogue activity
- Recently the role of ocular mucins have been attracting attention
- Reduced goblet cell density, changes in mucin amounts, distribution and glycosylation reported
- Effective in improving both objective and subjective symptoms of dry eye, with HA 01%
- Well tolerated safety profile
  - Approved in Japan for oral administration for gastritis and gastric mucosal disorders
- Randomized, multicenter, phase 3 trial Ophthal 2013;120

## Lifitegrast/SARCode Biosciences Brisbane CA

- T cell modulator similar to cyclosporin but FASTER
  - Starts in 2 weeks!!
  - Phase II
- Lymphocyte function-associated antigen (LFA-1) inhibitor of intracellular adhesion molecules (ICAM-1)
- Prevents binding of T-cell mediated inflammation (LFA-1 to ICAM-1)
- Works on *active* T lymphocytes
- Cyclosporin works on the *production* of T lymphocytes which takes 100-110 days to complete a cycle of inflammation

## InflammaDry (Rapid Pathogen Screening)

- Matrix Metalloproteinase (MMP-9) is the best biomarker for ocular surface disease & dry eye
- Developed as a simple in office test to predict and prevent problems after LASIK and other surface surgery
- Also as a test for dry eye disease
- FDA reviewing now
- Will be available as *InflammaDry*

## Tear Lab

- "Lab on a Chip"
  - We have a test!
    - Analogy of treating DM without BG, HA1c etc
    - No longer needs CLIA, COLA, inspection, etc
- Gold cartridge draws nl of fluid and processes
- Osmolarity is the global marker of Dry Eye (DEWS Report)
  - Least variable test for DE
  - Central mechanism in pathogenesis of DED
  - More variable results seen in more advanced disease
  - Large differences between eyes noted, increasing with disease severity
  - 308mosmsl = Dry Eye
  - Sensitivity 72.8%/Specificity 92%
  - No other clinical sign or test is better than 62%

## Tear Lab Severity Scale

- |           |          |
|-----------|----------|
| ■ 280-300 | Normal   |
| ■ 300-320 | Mild     |
| ■ 320-340 | Moderate |
| ■ 340+    | Severe   |

## Osmolarity Highest Positive Predictive Value of DED

- |                   |     |
|-------------------|-----|
| ■ Osmolarity      | 87% |
| ■ Schirmer's      | 31% |
| ■ TBUT            | 25% |
| ■ Staining        | 31% |
| ■ Meniscus height | 33% |
- Dry Eye Workshop Report 2007 OculSurf 2007;5:2 Tomlinson A, et al IOVS. 47(10) 2006

## Tear Lab

- Corneal tests and symptoms DO NOT correlate with disease
  - 30% of DE patients are ASYMPTOMATIC
  - Took 7 times for FDA to clear Restasis
  - May not see another drug
- 2007 DEWS Report - MGD most common cause of DE
  - Mucin is everywhere in the three layers of tear film
- Tear Osmolarity in Diagnosis & Management of Dry Eye, Lemp.M AmJOpht 2011;151:792-798
- Objective Approach to Dry Eye Disease Severity, Sullivan,B InvestOphthVisScience Dec 2010 Vol 51 No 12

## Rifaximin for DE in Rosacea

- Semi-synthetic rifampin-based non-systemic antibiotic
  - Very little drug passes GI wall into circulation
- Indications
  - Small intestine overgrowth, IBS, Travelers' diarrhea
    - 98% of papillo-pustular rosacea have SIBO
  - Diagnosis requires GI consult and breath test
    - Lactulose test
  - Different mechanism than doxycycline
  - Interfers with transcription of B subunit of bacterial RNA polymerase
  - Cure for rosacea in one treatment
- Available as *XIFAXAN 550mg tid x 14 days*

## DE Pipeline

- Interleukin (IL-1) blocking agents
  - Different mechanism than cyclosporin
- Steroid subclass – SEGRAs
  - Selective glucocorticoid receptor agonists
  - Mapracorate – compound offers steroids' breath of effects without the cataracts or IOP side effects

## Lipiflow Thermal Pulsation System

- Device for treating dry eye and blepharitis/MGD
- 12 min in office procedure
- Applies heat to posterior eyelids and intermittent pressure to front of eyelids
  - Releases MG obstruction
- FDA approval July 2011
- MG regain function in 4 weeks
- Results last one year
- Tearsience.com

## Contacts-Just Give Me the Numbers

- CL materials are 16% of total gross
- CL capture rate is 77.3%
- Dollars / pt wearing CL = \$400.40
- Independent ECP purchase \$10.6K/mos
- 1 in 5 adult pts wear PT CLs
- ECP purchase 14% daily disposables
- ECP purchase 25% 2 weeks
- ECP purchase 50% monthly
- High performance practices 43% Daily (and growing)

## Contacts-Just Give Me the Numbers

- 70% of ECPs stock lenses
- 85% of ECPs of \$1million + practices do
- 33% dispense CL on exam day
- 50% fill rates feasible
- OD share of exams vs materials is now 65%
- What is the "as is" situation in your office?
- What are the best practices in the industry?
- What can you do to close the gap?

## Dailies Total 1 (Alcon/Ciba)

- Water Gradient Contact Lens
  - New category in Tyler's Quarterly
  - For chronic dry eye to increase wearing time
- Silicone core 33%
  - Good O<sub>2</sub> transmission
  - DK = 156
- Outer Transition zone to water gradient material of 80%
- Edge is 100% water gel for outstanding lubricity and comfort
- Powers = -0.50D to -6.00D, expanding to -10D, then +6D
- Trends shifting into daily away from planned replacement

## The Science Behind Water Gradient Contact Lenses

### DAILIES TOTAL<sup>1</sup>® Water Gradient Contact Lenses

- First and only water gradient contact lens
- Gradual transition from 33% water at the core to over 80% at the surface<sup>2</sup> - approaching 100% at the very outer surface<sup>1</sup>
- Transitions from a highly breathable\*\* silicone hydrogel material at the core to a non-silicone hydrophilic polymer structure at the surface<sup>1</sup>

Change for Reusable processes only.  
\*For full development of water gradient.  
\*\*High oxygen permeability material, Dk=156 @ 30°C.  
© 2010 Alcon, Inc. All rights reserved. Alcon, Inc. is a subsidiary of Novartis. All other trademarks are the property of their respective owners. All other trademarks are the property of their respective owners. All other trademarks are the property of their respective owners. All other trademarks are the property of their respective owners.

## Hyaluronidate Gel Contact Lens

- Composition
  - Hydrogel component - structural support
  - Hyaluronidate - soluble biopolymer
  - Minerals found in tear film
- Material - methafilcon A
- Water - 55%
- DK/T - 31 (-3.00D)
- BC- 8.6 Diam-14.1 CT-0.08mm
- Front surface - Aspheric
- Power - +4.00 to -8.00

## Hyaluronidate Gel Contact Lens

- Asphericity - masks -1.00D cylinder, adds +0.75 for near
- 1 HA molecule binds 3000 times its weight in water!
- Warmth releases HA on both sides of lens
- Blinking releases HA into tear film
- Only available to ECPs and no on-line channels
- Available as **SAFIGEL 1 day**
- 877.723.4435
- [www.safigel.com](http://www.safigel.com)

## Ganciclovir ophthalmic gel 0.15%

- Anti-viral
- Indications
  - HSV keratitis
- Action - inhibits DNA replication
- Side effects - blurred vision, irritation, SPK
- Dose - one drop 5 times per day until dendrite resolved, then TID for one week
- Available as
  - Zirgan/Sirion

## Bromfenac 0.07%

- NSAID - lower concentration with better penetration
- Indications
  - Post-operative inflammation, CME, wet AMD
  - Retina(2012;32(9):1804 NSAIDs Use May Reduce Frequency of anti-VEGF Injections
- Benefits
  - Once daily dose
- Side effects - AC inflammation, FBS, eye pain
- Precautions - sulfite allergy, delayed healing, CL wear
- Dose - QD
- Available as
  - **Prolensa** / Bausch & Lomb

### **Nepafenac 0.3%**

- NSAID – lower concentration with better penetration
- Indications
  - Post-operative inflammation & Pain, CME
- Benefits
  - Once daily dose
- Side effects – decreased VA, FBS, sticky sensation
- Precautions – corneal effects, delayed healing, CL wear
- Dose – QD
- Available as
  - *Ilevro* / Alcon

### **Loteprednol etabonate 0.5%**

- Corticosteroid for treatment of post-operative inflammation and pain after cataract surgery
- Indications
  - Post-operative inflammation, CME, DE, allergy
- Benefits
  - Mucoadhesive technology, dose uniformity (no shaking), 2 moisturizers, low preservative
- Side effects – AC inflammation, FBS, eye pain
- Precautions – IOP increases, cataracts, viral infection
- Dose – QID
- Available as
  - *Lotemax GEL* / Bausch & Lomb

### **Anakinra 2.5%**

- IL-1 receptor antagonist
- Indications
  - Rheumatoid arthritis
- Harvard Trial for Dry eye showed benefits
  - 6 fold decrease in symptoms
  - JAMA Ophthalmology 2013 Apr 18:1-9
- Dose – TID
- Not approved for eyecare / Available as
  - *Kineret* / Amgen

### **Tofacitinib 5mg**

- Moderate – Severe rheumatoid arthritis
- Indications
  - Rheumatoid arthritis
- Precautions – test first for TB
- SE – severe infections, HA
- Available as
  - *Xeljanz* / Pfizer

### **Apixaban 2.5 or 5mg**

- Anticoagulant
- Indications
  - Reduce stroke risk in atrial fibrillation
- Precautions – D/C 48 hrs prior to surgery
- SE – bleeding related
- Available as
  - *Eliquis* / PfizerBMS

### **Autologous Serum for PED, DES**

- Tears contain EGF, vitamin A, TGF-B, fibronectin and other cytokines.....all found in serum
- 40ml of blood from venipuncture centrifuged for 5 min
  - diluted to 20% by physiologic saline (empiric)/UV bottle
  - Dosed at 6-10 X/D with additional AFTs
- Results
  - 43% healed within 2 wks, all within several months
  - Serum accelerates migration of corneal epithelial cells
  - Serum upregulates mucin expression of corneal epithelium

## Amniotic Membrane Transplantation (AMT)

- Ocular surface reconstruction in SJS, severe dry eye, and severe chemical burns
- Human amniotic membrane prepared from placenta of elective cesarean section in seronegative (HIV, HepB & C, syphilis)
- Facilitates epithelialization, reduces inflammation, vascularization and scarring
- Limbal stem cell transplantation is needed in concert with AMT in the most severe chemical burns

## Amniotic Membrane Transplantation (AMT)

- Acelagraft (Dehydrated Human Amniotic Membrane Allograft)
  - Highly organized matrix
  - 100% human derived
  - Non-immunogenic
- Cost
  - 1x2 \$315
  - 2x3 \$390
  - 4x4 \$480

## Corneal Collagen Cross-Linking

- Progressive keratoectasia
  - progressive corneal disease
  - Refractive surgery
  - No treatment
- New treatment, old concept
  - Natural occurrence within cornea and lens
    - 4.5% increase in fibril diameter
  - Dentistry- hardens material for fillings
  - Polymer industry-hardens adhesives
  - Cardiology-glutaraldehyde hardens heart valve
  - Uses UV light & riboflavin

## Collagen Cross-Linking (CXL)

- Riboflavin – photosensitizing agent
  - Excited to triple state by UV
  - Releases radicals
  - Causes hydrogen bonds between AA in collagen chains
    - At the intra & interhelical levels
    - Increases collagen diameters and spacing
- Treatment for keratoconus (1/2000, 20% need PK)
  - Pellucid marginal degeneration
  - Bullous keratopathy
  - Corneal melts/Infectious keratitis
  - LASIK ectasia

## Collagen Cross-Linking (CXL)

- Contraindications
  - <400u corneal thickness (endothelia damage)
  - Incisional refractive surgery
- Procedure overview
  - Epithelial debridement (+/-)
  - Ribo 0.1% apply every 2-5 min for 30 mins
  - Exposure to UVA irradiation for 30 mins (370nm, 3mW/cm<sup>2</sup>)
  - Add ribo every 2-5 min for shielding
  - Treatment diameter 7-9mm
  - Post-op treatment same as PRK
- Results last 2-7 years, may need retreatment

## Collagen Cross-Linking (CXL)

- Future applications
  - Keratoconus
  - Poor refractive surgery candidates - can now have surgery
  - Better outcomes - for good candidates for refractive surgery
  - Adjunctively in all laser refractive procedures to provide better structural support of the cornea long-term
- Not FDA cleared here yet but access is available

## Tomorrow's Best IOLs

- Calhoun Vision, Inc.
  - Next generation "adjustable" material, unique, unstable, silicone, foldable
    - Cross-linked silicone polymer matrix - Mechanical and optical properties
    - Macromer - Low molecular weight links to photoreactive group
    - Photoinitiator - Organic molecule dissociates into free radicals, begins polymerization on exposure to special wavelengths, moving macromer down diffusion gradient into radiation area thickening the lens

## LAL - IOLs

- 2 weeks post-operative UV protection required
- Adjust refractive error at 2 week post-op
  - Uses 380nm exposure of light at slit lamp system
- Next perform lock-in
  - Pink tint is commonly reported 1-2 days post lock-in
- Not cleared in US but Canada, Europe etc

## Accommodating IOLs

- Electro-optic diffractive IOL (Elenza)
  - Monofocal IOL with central aspheric modification
    - Far & intermediate vision
  - Smart electro active diffractive liquid crystal
    - Near
    - Microsensors detect physiologic triggers of accommodation (pupil)
    - Onboard processors & algorithms to control power sequence
    - Lithium ion power cells - weekly charge

## Implantable Miniature Telescope

- Indicated in advanced AMD
  - 75 years of age, no previous cataract surgery in one eye
  - Adequate Endothelial cell counts and Anterior chamber depth
- FDA & CMS approved
- Wide angle micro-optics in combination with cornea create telephoto system
- Galilean design
- 2.2-2.7X enlargement of retinal image
- 3.6mm diameter, 4.4mm length (size of pea)

## Implantable Miniature Telescope

- Prosthetic device sealed into carrier plate
  - Fused quartz crystal
  - PMMA clear carrier
  - PMMA (blue tint) light restrictor
- Vision Care Ophthalmic Technologies
  - Saratoga, CA
  - 408.872.9393

## Cataract Surgery in The Future

- Biconvex optic of 9mm, injectable copolymer
- Accommodative
- 1 piece design
- Wavefront adjustable
- Power customizable
- Photochromic
- Surface modified or drug impregnated
- Implantable through a 1mm incision

## Cataract Surgery “with a Laser”

- Femtosecond laser for cataract surgery is here
- Fast accurate capsulorrhexis
- Programmed primary incision
- Lens fragmentation/softening of nucleus
- Limbal relaxing incisions for astigmatism
- Benefits – accuracy, bladeless, all skill levels perform better surgery
- Problems – slower operation, multi step process, not covered, difficulty in up-charging Medicare patients
- “Million dollar mousetrap”

JAM

## Cataract Surgery “with a Laser” (LCS)

- LenSx (Alcon)
- LensAR (LensAR, Inc)
- Catalys (OptiMedica)
- iFS (Abbott Medical Optics)
- Victus (B&L)
- FemtoLDV Z6 (Zeimer)
- Systems include videomicroscopy, real-time integrated OCT, deliver ultrashort near infrared wavelength pulses
- Costs - \$300,000 - \$500,000 plus maintenance

JAM

## New Era in Cataract Surgery

- Optimization – continuous improvement of a technique or technology
- More accurate incision, capsulotomy, and astigmatic correction, better placement of IOL, more accurate vision outcomes
- Reduced energy, less wound leak, less endothelium trauma, less capsule tear, fully exploit potential of multifocal IOLs
- If less dependence on glasses is the goal, femto is best
- Keep new technology in proper perspective
  - Traditional is very effective and successful

## Next Gen IOLs – Softec HD

- Bi-aspheric *zero aberration* IOL
- ¼ D powers
- Enhanced depth of focus
- Less sensitive to tilt
- Tolerance of IOL labeling is +/-0.4D
  - Untenable risk for surgeons expected to deliver uncorrected vision
- Only IOL addressing Defocus & Spherical aberration
- -0.25D defocus is more significant than all other higher order aberrations combined!

JAM

## Glaucoma Evaluation is Transforming

- In the past, detection & management relied on functional assessment
  - Visual fields (white-on-white)
    - Insensitive for detecting early POAG
    - High degree of variability
- Recently, structural change over time longitudinal studies have validated the role of structural imaging
  - Are structural defects with normal functional tests false positives or POAG?

JAM

## i-Care Tonometer

- Hand held, portable
- NO ANESTHESIA
- Disposable probe
- Accurate
- Power – AA batteries
- Measurement in 0.1 sec
  - Measures motion of cornea
- Digital display
- Memory – last 10 results



## i-Care Tonometer

- Applications
  - Eye MDs
  - ODs
  - General practitioners
  - Pharmacy
    - Screenings
  - Veterinarians
  - Consumers
    - Self screenings

## NEW Icare® PRO

- Professional expertise for glaucoma diagnostics and clinical follow-up
- Rechargeable batteries and docking station with integrated charger & data transmission

## Icare® Tonovet

- Useful tool for measuring intraocular pressure on animal patients (dog/cat, horse)
- Painless => creates no anxiety in the animal
- Measurement barely noticed by the animal
  
- Veterinary ophthalmologists
  
- Other veterinary medical personnel

## Visual Field 9208x

- Bilateral
- Requires Interpretation
  - separate report form
  - narrative in body of medical record, on date of service
- Fee \$43.88- (-81) \$57.37+ (-82) \$65.92- (-83)

IAM

## Other Important VF Studies

- Paczka (2001) - found FDT better overall performance in detecting damage than RNFL photographs
- Kondo (1998), Wu (2001) - In patients with SAP VFDs restricted to 1 hemifield, FDT has shown to be able to detect functional losses in the other hemifield
- Medeiros (2004) – functional defects in FDT predict future defects on SAP

## Other Important VF Studies

- Kim (2007/AAO) – when SAP is normal, some patients with VFD detected by FDT showed decreased NFL thickness (OCT)
  - Provide evidence that coincident FDT & OCT abnormalities may be an early sign of glaucoma
- Fan, X (2010/Ophthal 117:1530) – FDT detected defects in 2/3rds of study eyes, predicted future defects in SAP

## Visual Field Testing for Specific Functions

- Short wavelength autoperimetry (SWAP)
  - Bistratified ganglion cell (9%) short-wavelength cones
- Frequency doubling technology (FDT)
  - Magnocellular ganglion cells
- Motion automated perimetry (MAP)
  - Magnocellular ganglion cells (3%)
- High pass resolution perimetry (HPRP)
  - Parvocellular ganglion cells

## Opto-Global /Optos

- New perimeter
- AP 100, AP 200
- Flicker
- SWAP
- SAP
- Screening and threshold testing
- Network ready
- Competitive aggressive pricing

## Octopus 301 Perimeter

- Motorized auto eye tracking
- 100% fixation control
- Blazing fast speed, testing 30 degree field
- Ergonomic design patient friendly
- Blue yellow testing in 3 min/eye
- Critical fusion testing
- One min screen
- Three min full threshold
- PeriTrend Analysis
- LAN ethernet
- 900 series tests 90 degree field
- 800.787.5426 [www.haag-streit.com](http://www.haag-streit.com)

## Clinical Statements

- Advances in perimetry are continuing
  - Faster third generation algorithms reduce test time by 50%
- Customization for specific needs
  - Early detection / established glaucoma / screening
- Early VF loss is often selective, with specific types of axons disturbed
  - SWAP allows early recognition, HPRP follows progression
- SAP perimetry will continue to be preferred for established glaucoma with VFDs
  - Considerably improved methods of computer-assisted interpretations of serial VFs
- Screening methods will sacrifice sensitivity for specificity and ease of use to detect the half of glaucoma patients who have undiagnosed disease
  - Deployed in non-professional environments

## Ophthalmic Genetics

- Researchers have identified genes for OAG
  - TIGR/Myocilin = juvenile OAG
  - OPTN (optineurin) = Primary OAG (NTG)
    - Optineurin may provide neuroprotection to optic N
  - CYP1B1 = Congenital glaucoma
- Genetic testing will allow clinicians to determine if Pt is predisposed to or affected with specific type of glaucoma, even before symptoms appear
- OcuGene (InSite Vision/Alimeda) – simple, in office test, 99% accurate detection of TIGR (trabecular meshwork inducible glucocorticoid response gene)
  - Positives may be treated more aggressively, earlier

## Surgical Glaucoma Therapy

- Future directions
  - Newer antifibrinolytics
    - CAT-12, a monoclonal antibody to TGF-B2
  - Photodynamic therapy
  - Novel drug delivery systems
    - Collagen implants, bioerodable polymers, liposomes & microspheres
  - Glaucoma drainage implants instead of filtering surgery
    - Shunts aqueous from AC tube through an episcleral plate
  - Ocular genetics
    - Discover genes, gene therapy, primary prevention of glaucoma may become a reality

## Glaucoma & the Brain

- Researchers view Glaucoma as a disease of the brain
  - Neurodegenerative disease
- Glaucoma shares common features with AD, Parkinson's and Lou Gehrig's diseases
- Offers potential for new treatments that promote nerve health, neurotrophic factors which can help at multiple places in the visual pathway
  - Neuroprotection – Ciliary neurotrophic factor (CNTF)
  - Neuroregeneration – increase axon regrowth
  - Neuroenhancement – improve support between dying RGC and surrounding cells in brain and retina

## New Functional Testing

- Pattern ERG (PERG) – improves with decreased IOP
- Multifocal VEP – higher flicker VEP
- Isolated Check VEP
  - Tests central vision
  - Bright Check Pattern (M-cells)
  - Dark Check Pattern (off pathway cells)
- Pupil perimetry (True Field Analyzer)
  - Computer measures pupil (involuntary) diameter in response to retinal visual stimulation

JAM

## Visual Evoked Potential

- Nova-DN VEP Vision Testing System (Diopsys)
  - Not new technology, but clinically useful and affordable is
    - Improves sensitivity & specificity in glaucoma diagnosis
  - Short duration transient VEOP (SD-tVEP) to record electrical responses of the entire visual system
  - Objective test, 4-6 minutes
  - Low contrast testing – health of magnocellular pathways
  - High contrast testing – health of parvocellular pathways
  - Serial tracking of disease progression
  - Useful in MS, TBI, Stroke and other CNS disorders

## Visual Evoked Potential - Coding

- Nova-DN VEP Vision Testing System (Diopsys)
- CPT: 95930
  - Bilateral
  - No CCI bundling edits in office setting
- ICD – includes many optic nerve and retina disorders, visual disturbances (amblyopia, SVD, night blindness, sudden vision loss, et al), neurological (aphasia, MS, Lyme, TBI, intracranial diseases, conversion, gait abn, coordination, etc)
- Fee: \$133.19 (range \$60-\$180 commercial)

## Nova-VEP

- Device - \$35,000
- Patches - \$80
- Skin gel - \$23
- Wires - \$22/set
- CPT code – 95930 VEP
- Fee - \$159
- 5 Year financing requires 5 pts/month to break even
- Available as *Nova-VEP*

## Neuroprotection in Glaucoma

- Tsai Curr Eye Res 2005
- EPO (erythropoetin) found to have protective effect on RGCs
  - Currently approved and well understood for anemias, post chemotherapy, and renal diseases
- Others under study include brimonidine, memantine, BDNF
- Future will be neuroprotection to improve environment and neuroregeneration with stem cells

## Nanosensor IOL

- Fraunhofer Institute in Germany
  - Microelectric Circuits and Systems IMS
- Implant sensor for continuous IOP monitoring
- Integrated 2.5 by 2.6 millimeter sensor in an IOL
- The top and bottom of the sensor are electrodes
  - The top electrode is flexible, bottom of the sensor is rigid
  - When the intraocular pressure increases, the top electrode is pushed in, reducing the distance between the top and bottom of the sensor and thus increasing the capacitance
- Implant sends the pressure data to a reader that is fitted into the frame of a pair of spectacles
- The patient can download the results on an auxiliary device
- An antenna in the spectacle frame supplies the sensor with the required energy via an electromagnetic field
- Currently undergoing clinical trials
- Could come available in two to three years time
- The sensor is not only suitable for use in the eye it can also help patients with chronic hypertension with implantation into a blood vessel

## Nanosensors IOP

- MIT Technology Review
- A pressure sensor to measure glaucoma IOP
- Tiny microchip implanted subretinal
- The sensor is designed to measure IOP
  - wirelessly transmit the data to computer
- One of the major obstacles in creating this type of device is designing a tiny but highly functional chip that uses very little power
  - Sensor runs on nanowatts rather than on microwatts
- The researchers will begin testing the implant in animals by December

## Promise of Implantable Drug Delivery Systems

- Humans are clumsy, forgetful, imprecise and undependable...high tech drugs are not
- Benefits - longer lasting, highly localized, accurate concentration, fewer side effects
- Reservoir implants – require surgical placement/replacement, simple, longevity, steady state
  - Retisert, Iluvien, I-vation
- Biodegradable implants – no need for removal, less toxicity
  - Ozurdex

## Promise of Implantable Drug Delivery Systems

- Vitrasert – 1996 approved for CMV implant of gancyclovir, pars plana insertion
- Retisert – next generation, better target and duration, pars plana insertion and suture, good for uveitis but IOP elevations and cataract are problematic
- Iluvien – fluocinolone intravitreal implant, for AMD (wet & dry) and DME
- Ivation – treatment of DME, implantable titanium screw coated with triamcinolone, self anchors into sclera

## Promise of Implantable Drug Delivery Systems – Innovations on Tap

- Biosilicone Technology – pSividia nano-structured porous silicone, bioerodable, handles any molecule size
- Replenish Media Pump – microelectromechanical device delivers continuous or bolus targeted drugs to ant/post segments via flexible cannula and refillable reservoir system (30 g needle), most of device is outside eye...“reverse-drainage glaucoma device”
- Encapsulated Cell Technology (ECT) – delivers large molecules to retina, stores complex proteins at 37degrees C without degradation

## Promise of Implantable Drug Delivery Systems – Innovations on Tap

- Encapsulated Cell Technology (ECT) –
  - Genetic engineering of RPE cells via plasmid transfection
  - Plasmids encode a therapeutic protein, in to cell genome
  - Engineered cells loaded into polymer membrane capsule and inserted into vitreous
  - Continually produce the therapeutic protein
  - No need for long term drug storage
  - “makes the bread fresh daily”
  - Testing now with ciliary neurotrophic factor (CNF) in retinal disease

## Ozurdex – Dexamethasone Intravitreal Implant 0.07%

- 1<sup>st</sup> & only injectable dexamethasone implant
- For non-infectious uveitis of the posterior segment
- For macular edema following BRVO or CRVO
- Solid polymer matrix biodegrades to lactic acid and glycolic acid
- Delivered by injection as in office procedure (22-gauge)
  - Ergonomically designed applicator for single use, preloaded
- Contraindicated in advanced glaucoma

## Ozurdex – Dexamethasone Intravitreal Implant 0.07%

- Posterior uveitis results
  - 46.8% of treated patients had resolution of vitreous haze at 8wks
  - 42.9% gain >15 letters (3 lines) from baseline at week 8
- BRVO / CRVO
  - 9.8 letters gained at day 60
- IOP data
  - 13.9% with >10mmHg increase from baseline IOP at day 60
  - 3.2% with >35mmHg increase from baseline IOP at day 60

## AMD Risk Factors

- Age > 60
- Race W>B, Sex F>M
- HTN/Smoking
- Nutrition
- Family History
- Fair complexion
- Cardiovascular disease/CRP/obesity/high saturated fat diet
  - AmJEpidem Mar2011 abdominal obesity in men each 0.1 increase in waist/hip ratio increases odds of early AMD by 13%, late AMD by 75%

## Forecasting ARMD Through 2050

- Arch Ophthal 2009; 127 (4):533-540
- Early AMD 9.1mil in 2010 to 17.8mil in 2050
- CNV & GA 1.7mil in 2010 to 3.8mil in 2050
- Visual Impairment from AMD is 620,000 in 2010 to 1.6mil in 2050

## AMD stages - Early



*Consists of a combination of multiple small drusen, few intermediate drusen (63-124 $\mu$  in diameter), or RPE abnormalities*

## AMD stages - Intermediate

*Intermediate AMD  
(AREDS category 3)*

*Consists of extensive intermediate drusen (63-124 $\mu$  in diameter), at least one large druse (>125 $\mu$  in diameter), or geographic atrophy not involving the center of the fovea*

## AMD stages - Advanced

Advanced AMD  
(AREDS category 4)

- Neovascular maculopathy such as
  - Choroidal neovascularization (CNV)
  - Serous and/or hemorrhagic detachment of the sensory retina or RPE
  - Lipid exudates
  - Subretinal & sub-RPE fibrovascular proliferation
  - Disciform scar
- Geographic atrophy of the RPE & choriocapillaris involving the center of the fovea

## Nutritionals

- First degree relatives of ARM pts 2-4 times greater risk of ARM compared to controls
- Twin studies show high levels of concordance of the disease among monozygotic sibs
- Vitamin E may cause bleeding
- Vitamin D may be of benefit
- Diets high in omega-3 FAs are of benefit
- Control of weight, HTN & cholesterol is important
- Diet of green leafy vegetables increase lutein, zeaxanthin which increase optical density of macular pigment providing protective role

## Nutritionals

- EyePromise (ZeaVision)
  - Zeaxanthin 6mg
    - in the same 1:1 ratio as found in healthy macula
  - Lutein 6mg
  - Beta carotene – none
  - Vitamin C – 120mg
  - Vitamin E – 60 IU
  - Zinc – 15mg
  - Copper – none
  - Fish oil (omega-3) – 250mg
  - Alpha Lipoic acid – 10mg

## Nutritionals

- EyePromise Vizual Edge (ZeaVision)
  - Zeaxanthin 26mg
  - Lutein 8mg
  - Vitamin C – 240mg
  - Vitamin D3 – 2000 IU
  - Vitamin E – 120 IU
  - Zinc – 30mg
  - Fish oil (omega-3) – 380mg, total fish oil 500mg
  - Alpha Lipoic acid – 20mg
- New NSF certified product to enhance & improve visual performance (glare recovery, contrast, temporal processing speed, light sensitivity)

## Nutritionals

- Zeaxanthin & Visual Function Trial (ZVF) Richer, S Optom Nov 2011
  - Randomized, controlled trial from 2007-2010
  - Zeaxanthin 8mg/day + Lutein 8mg
  - Visual improvement in elderly AMD pts of 2 lines
- Macular Re-pigmentation Enhances Driving Vision in Elderly Adult Males with AMD Richer, S JClinExpOphthal
  - Zeaxanthin 8mg/day for one year
- Pearls – enhanced functional vision with higher doses of ZX

## Nutritionals

- Lutein+Zeaxanthin & Omega-3 Fatty Acids for ARM (AREDS 2 Clinical Trial) Chew JAMA May 15, 2013
  - Randomized, controlled trial
  - Lutein+Zeaxanthin, DHA+EPA, or both to the AREDS formulation in primary analysis did not further reduce risk of progression to advanced AMD
  - Because of the potential increased incidence of lung cancer in former smokers, Lutein+zeaxanthin could be an appropriate carotenoid substitute in the AREDS formulation

## Why Is Early Diagnosis Important?

*Earlier Diagnosis  
Means Better  
Final Visual Acuity*

- **Lesion size** was a more significant factor affecting treatment benefit than either:
  1. Lesion composition
  2. Baseline visual acuity

■ *TAP and VIP Report 1, AJO, Sept., 2003*

## Inherent Faults of the Amsler Grid

- **Completion**
  - The Amsler Grid does not overcome cortical completion
- **Fixation**
  - The Amsler Grid does not force fixation
- **Crowding**
  - Inhibition by neighboring peripheral lines reduces detection



- First FDA cleared home based monitoring system for AMD, cellular modems
- Personalized patient monitoring, between physician exams
- 85% sensitivity, specificity
- Robust normative database
- Quantifies changes in function
- Notifies doctor and patient of significant change



- Patient pays \$250 placement fee
  - No contracts, service fees, 30 day money back guarantee
- Patient pays \$60 monthly fee for testing
  - \$15 rebate to doctor (database access)
- Practice gets \$100 Clinic training fee, demo device
- ForeSeeHome.com has good video clips
- Contact: garrett@notalvision.com

## BlueLaser Autofluorescence Track Dry AMD

- Functional indication of retinal health
  - Measures metabolic activity of RPE
- Geographic Atrophy Progression Study (GAP)
  - Use autofluorescence to track progression
  - 10 new therapies for dry AMD
    - Combine BluePeak & OCT
    - May change the world like ranibizumab & OCT changed wet AMD
- Spectralis multimodality design platforms
  - 7 models available

IAM

## Dry AMD is the Next "Wet Degeneration"

- Drusen Volume & Area "Map"
  - G. Hagemen of University of Utah
    - Drusen are toxic waste of RPE cells react to light = GA = cell death
- Highly reproducible
- Fundus image does not correlate to volume analysis
- "Life cycle" of drusen
  - Clinically always look the same
  - Drusen "die"
- New OCT applications to identify, count and monitor drusen for change over time

IAM

## Emerging Treatments for Dry AMD

- Fenretinide in Geographic Atrophy (GA)
  - Phase II oral capsules of Vit A derivative
  - Binds retinol
  - Stimulates photoreceptors & RPE
  - Downregulates Vit A
  - Downregulates lipofusin
  - Side Effects: poor night vision

JAM

## Emerging Treatments for Dry AMD

- MacuClear's MC-1101
  - G. Choi, PhD – AMD pathogenesis may begin with decreased choroidal blood flow
- Topical (tid), vasodilating, anti-inflammatory, anti-oxidant
- Favorable safety profile
- Significant increase in choroidal blood flow in phase I
  - 500%!
- Fast track approval granted and moving into phase IIIa
- Potential for glaucoma being investigated

JAM

## AMD Research on Genetics

- Age related macular degeneration gene located
- Encodes for a protein called Complement Factor H
  - Increases inflammatory proteins
  - Increases C-reactive protein
- We now know a genetic component of the disease exists!

## New Wet AMD Clinical Concepts

- Defining AMD Risks will become routine
- Complement Factor H + Loc387715 + CFB/C2 gene mutation
  - 285 times risk of AMD
  - <1% risk of AMD without these genes!!
- Useful clinical test available by end 2011
  - Swab of mouth

## SequenomCMM

- RetnaGeneAMD
  - Simple in-office DNA cheek swab
  - Tested in 1132 CNV cases and 822 controls in Caucasians
    - Multi center (Boston, Utah, Australia)
  - Results in 8-10 days
  - Genetic counseling for doctors and patients
  - Impact of 13 genetic variants (SNPs) of 8 genes on 4 chromosomes (1,6,10,19)
    - 3 SNPs increase risk
    - 10 SNPs decrease risk
- SequenomCMM – prenatal & ophthalmic
- 877.821.7266 [www.sequenomCMM.com](http://www.sequenomCMM.com)

## SequenomCMM – Calculating Risk Score

- Gene
  - ARMS2 +1.45
  - CFH +0.81
  - C3 +0.42
  - F13B -0.01
  - CFHR5 -0.13
  - CFHR4 -0.15
  - CFH -0.19
  - F13B -0.45
  - CFHR5 -0.60
  - CFH -0.76
  - CFH -0.79
  - CFB -0.82
  - C2 -0.95



## SequenomCMM – Calculating Risk Score

- Impact on disease
  - ARMS2 = 3.39x's increased risk
  - CFH = 2.5x's increased risk
  - C3 = 1.25x's increased risk
  - C2/FB = 0.3 protective
- Log odds established for each SNP in multiplex panel and risk scores calculated based on individual genotype assignment yielding wide spectrum of disease risk (reflective of case controlled population)
- Low risk <25% CNV probability
- High risk >75% CNV probability

## What is Macula Risk Gene Test?

- Macula Risk® is a prognostic DNA test intended for patients who have a diagnosis of early or intermediate AMD.
- Using the complete combination of AMD genes, and smoking history, Macula Risk® identifies those most likely to progress to advanced AMD with vision loss.
- Macula Risk® allows you to stratify patients for appropriate monitoring as recommended by the AOA and the AAO Preferred Practice Patterns - *"in an effort to detect asymptomatic CNV at a treatable stage."*
- The patient sample is a cheek swab taken in the doctor's office. Macula Risk® is reimbursed by most providers including Medicare.

## AMD – A Genetic Disease

- Macula Risk
- A test that identifies AMD
- patients who will progress
- to vision loss.
- Samples DNA

• Cheek Swab

## Dry AMD / GA & Genetics

- Progression of GA & Genotype in ARMD, Klein, M Ophthalm 2010;117:1554-1559
- Growth rates of geographic atrophy NOT associated with variants in CFH, C2, C3, APOE, TLR3 genes
- Nominal association in LOC387715, ARMS2, HTRA-1 genotypes

JAM

## Importance of Multivitamins in AMD

- ArchInternMed 2009; 169(4):235-341 Christen et al
  - Folic Acid, Pyridoxine and Cobalamin Combination Treatment & ARMD in Women: The Women's Antioxidant & Folic Acid Cardiovascular Study
    - Trial data from large cohort (N=5442) of Women at High risk of cardiovascular disease
    - Homocystein concentration in blood increases risk AMD
    - Daily supplements reduce homocystein in blood and risk of AMD

## Importance of Multivitamins in AMD

- ArchInternMed 2005; 165(4):854-7 Reeves et al
  - Healthy Lifestyle Characteristics among adults in US
    - Trial data suggests importance of getting people to stop smoking, start proper diet, and exercise
    - Only 3% of Americans do
    - Once we understand a person's dietary & lifestyle status we can better "prescribe" nutritional therapy
  - Leading antioxidant in US is \_\_\_\_\_?
  - Leading vegetable in US is \_\_\_\_\_?

## **Omega-3s Beneficial in AMD**

- Arch Ophthal 2008 Chong et al
  - Australian meta-analysis of many studies (N=88,000)
  - High O-3s associated with 38% reduction in risk late AMD
- IOVS 2008 Nguyen et al
  - Australians fed rats O-3s, tested with ERG
  - Conclude beneficial across all retina layers, especially GC
- Arch Ophthal 2009 Tan JSL; 127(5):656-665
  - Dietary Fatty acids and 10 year incidence of ARMD/Blue Mountain Eye Study
  - Protection against early AMD demonstrated with regular consumption of fish, omega-3 polyunsaturated fats and low intake of linoleic acid. Benefit of regular consumption of nuts

## **Omega-3s & Vitamin D Beneficial in AMD**

- Arch Ophthal Christen WG 2011;129(7):921
  - N=39,870 female health professional
  - Regular consumption of DHA & EPA & fish significantly decrease risk of AMD
- ArchOphthal, MillerAD 2011;129(4):481-489
  - CAREDS study of postmenopausal women
  - N=1330
  - High 25(-OH) D concentrations protect against early AMD in women less than 75 years old

## **Macular Pigment Studies in Cataracts**

- ArchOphthal 2008; Mueller et al
  - CAREDS/WHI
  - N=1802 women with highest levels of L/Zx had 32% lower incidence of NSC
- Ophthal 2008 115(8) Sperduto et al
  - NEI Trial of Centrum Silver
  - N=1020 18% less lens events
- AmJClinNut 2008; Tan et al Blue Mountain Group
  - N=2464 Vit C and dietary antioxidants decreased NSC 50%

## **Macular Pigment Studies in Diabetes**

- IOVS 2008; Gierhardt et al
  - Proved Zx mechanism of protection in early DR
    - Anti-inflammatory & VEGF regulation
- CAREDS 2007 Diabetic women have 30% lower MPOD
- Graetes 2008 Spanish Group
  - Fed diabetic rats lutein and found it to be as effective as insulin at preventing cataract

## **Ranibizumab / Lucentis**

- for injection
- Dose – 0.5mg/monthly
- Administration – 27g needle intravitreal injection
- Indication – neovascular “wet” macular degeneration
- Contraindications – ocular infection
- Warnings – risk of endophthalmitis, increased IOP
- Dose – may decrease to q3m after 4 monthly injections
  - Less effective
- Studies – ANCHOR, SAILOR, PIER, MARINA, FOCUS

IAM

## **Bevacizumab / Avastin**

- for injection, twice the half life of Lucentis, fraction cost for AMD
- Effect – Anti VEGF for CA of lung and colorectal CA
- Dose – 0.5mg/monthly
- Administration – 27g needle intravitreal injection
- Indication – neovascular “wet” macular degeneration
- Contraindications – ocular infection
- Warnings – risk of endophthalmitis, increased IOP
- Dose – may decrease to q3m after 4 monthly injections
  - Less effective

IAM

## Avastin for EVERYTHING ocular

- AMD
- PDR
- PDR with vitreous hemorrhage
- DME
- Vein occlusions
- ROP
- Choroidal melanoma
- NVG
- The future is topical eyedrops, oral formulations

JAM

## Aflibercept / Eylea

- for injection,
- Effect – Anti VEGF
- Dose – monthly for 3 months, then every other month
- Administration – 27g needle intravitreal injection
- Indication – neovascular “wet” macular degeneration
- Contraindications – ocular infection
- Warnings – risk of endophthalmitis, increased IOP
- Benefit – less injections, less cost

JAM

## Pazopanib / GlaxoSmithKline

- TOPICAL
- Effect – Anti VEGF-A, targets receptor tyrosine kinase so inhibition is after VEGF binds to receptor
- Dose –5mg/ml TID
- Accumulates in high concentration in posterior retina through trans-scleral route (end around on anterior segment)
- Indication – neovascular “wet” macular degeneration
- Approved now for renal cell cancer
- Benefit – no injections, less cost, 4.3 letters at day 29 trend toward improvement at day 8

## New Wet AMD Clinical Concepts

- Ciliary Neurotrophic Factor (CNTF)
  - Immuno-isolation
  - Implanted pars plana releasing drug for over one year
  - Outer nuclear layer & photoreceptor layer thickens
    - No correlation with VA improvement
- Anti-Platelet Derived Growth Factor (PDGF)
- POT-4 / PotentiaPharma, Inc
  - Binds to C3 – Potent inhibitor of C3
  - SMALL cyclic peptide (not large 3-D protein)
    - Lasts for MONTHS!!
  - Studies using depo form combination with VEGF drugs

## New Wet AMD Clinical Concepts

- Complement is MOST IMPORTANT
- Human Genome Project – completed in 2005
  - Chromosome 1 is location of complement factor H (CFH)
  - 1<sup>st</sup> to be mapped!
  - C3, C3a, C5, C5a are all pathways of activation of VEGF
- **VEGF expression is result of complement activation!!**
  - Compliment is the bomb of inflammatory system
    - Requires detonator – 30 proteins in blood for triggers
      - Membrane Attack Complex (MAC) & Fc-Fragment

## Comparative Clinical Trials

- Avastin vs Lucentis
- CATT Comparative ARMD Treatment Trial
- IVAN
- LIBERA Trial – OCT guided (high dose)
- LUCAS Trial – OCT guided (trial & extended)
- MANTA Trial – 3 Rxs & treat as needed
- PrONTO – 3 Rxs, Monthly OCTs & +/-injections
- RADICAL – Triple therapy
  - Reduced fluence PDT / dexamethasone / ranibizumab
- All results will come in 2011

## Comparative Clinical Trials

- **RADICAL** – Triple therapy
  - Reduced fluence PDT / dexamethasone / ranibizumab
- **Anti-VEGF & Radiation**
  - NeoVista – Strontium-90 applicator (stainless steel 20-ga tube) via core vitrectomy channel
  - Positive results in CNV in AMD
  - Better results when used in combination with two injections of bevacizumab
- **CABERNET** (CNV secondary to AMD treated with BETA Radiation Epi-retinal Therapy)
  - Brachytherapy/ranibizumab vs ranibizumab alone

## Nanotechnology Vision Chip

- **NASA** developing the Nanotechnology Vision Chip
  - Technology for stimulating retinal neural cells using an array of carbon nanotubes (CNTs)
  - NASA Ames Research Center, in conjunction with Stanford University School of Medicine
- **Use:** to restore vision in patients suffering from age-related macular degeneration
- An array of electrically conductive CNT towers grown directly on the surface of a silicon chip
- Each CNT tower in the array is connected to its own electrical circuit, so that electrical signals generated by the pixels of a light detector can be transmitted to the CNT towers

## Nanotechnology Vision Chip

- Thousands of CNT towers are closely spaced in an array, to match the spacing of the neurons within the retina
- Implanted into the retina, so that the CNT towers come in direct contact with the retinal neurons
- Electrical signals generated by a CCD camera are delivered to the implanted device via telemetry
- Prototypes have used towers that are 100 microns in diameter and approximately 150 microns tall

## Nanotechnology Vision Chip

- An alternate version of this technology, the CNT towers are coated with special growth factors to stimulate growth of retinal neurons toward the CNT towers
- CNT can be coated with a variety of growth factors and cytokines to stimulate attachment of neural cells to the CNT towers
- With this enhancement, only minimal penetration of the retinal tissue (25–50 microns) may be needed to promote neural cell/CNT tower connections and may restore vision

## Nanotechnology Vision Chip

- Short-term in vitro tests of the implant materials with retinal ganglion cells suggest excellent biocompatibility
- Optimization of dimensions and spacing serves to maximize retinal layer stimulation
- Small, nano-sized components allow an image resolution density similar to that of native retinal photoreceptors

## Retinal Tissues Templates

- Researchers at Purdue University have created scaffold-like patterns on the surface of a pig's retina
  - Make templates out of molecular peptides
  - Each of the lines was less than 100 nanometers wide
- Biomedical engineers used an atomic force microscope to lay down lines of peptides in a process known as dip-pen nanolithography
  - Analogous to the lithography, or patterning, process used for semiconductor
- Hypothesized that placing templates on the retina could enable transplanted cells to take hold and grow
  - Implant retinal pigment epithelial cells, could be guided or organized if a template or scaffold were present
  - Could promote the growth of transplanted healthy cells
    - To treat age-related macular degeneration

## **Virus Modification for AMD**

- Virus Vector for treatment of CNVM
  - Using Adenovirus model
  - Genetically modified to contain DNA strand to stop the production of VEGF
  - Injected intra-vitreally
  - Virus infects retina
  - DNA incorporated into the cell matrix
  - Inhibits the production of VEGF
  - Even with direct laser damage no neovascularization occurs
  - One year post injection the protection remains
  - Animal model only at this time

***Thank you***

McGreal Educational  
Institute

Missouri Eye Associates