Using New Technologies to Improve Quality of Care

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Excellence in Optometric Education

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Resolvyx 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***

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 I-CAM-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 (Focus Labs)

- "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%/Specificty 92%
    - No other clinical sign or test is better than 62%

Tear Lab (Focus Labs)

- 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 AmJOphth 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
    - Laculose 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
- Tearscience.com

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

Steroids for Corneal Ulcer Trial (SCUT)

- Multi-centered, double blind, randomized
- N=500
- Ulcers major cause of corneal scarring
- 4th leading cause of blindness worldwide
- Treatment goals
  - Elimination of bacterial (now within days)
  - Prevention of scar formation (occurs in "successful" cases)
- Prednisolone 1% not started for 48 hrs pending cultures
- Results – no improvement in BVA at 3 mos, no increase in adverse events either

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

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/cm2)
  - 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)

Impantable 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

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***

Glaucoma Evaluation is Transforming

- In the past, detection & management relied on functional assessment
  - Visual fields (white-on-white)
    - Insensititve 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?

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RAPDX (Konan Medical)

- Automated pupillographer
- Assesses differential amplitudes and latencies of pupil responses
- Far better than human clinical assessments
- Earlier detection of glaucoma, normal tension glaucoma, MS, infarcts, tumors

Salzberg Reading Desk (SRD Vision)

- Device precisely & automatically measure reading performance parameters under conditions of changeable luminance & contrast
- Consists of stereo infrared webcams, laptop, high resolution monitor, operating software
  - Subjects read into microphones with progressively smaller type size with software signal processing
- Advantages – measures at subjects preferred reading distance
- 2-5 min test time

Salzberg Reading Desk (SRD Vision)

- Applications
  - Pre & post-op reading acuity
  - Compare efficacy of reading devices
  - Acuity measurements for multifocal IOLs & contact lens
  - Real world understandable objective measurement of reading performance
- Future applications
  - Determine add powers for multifocal IOLs
  - VA measurements at all distances
  - Monitor progression of retinal diseases (AMD)

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

EyeQuick Digital Ophthalmoscopic Camera

- Bilateral
- Requires Interpretation
  - separate report form
  - narrative in body of medical record, on date of service
- Hand-held device, portable, bedside, prone
- Can capture anterior segment or posterior segment images, both still or video
- View images on LCD or Transfer to computer
- www.EyeQuick.com 800.596-8335

JAM

Volk Pictor

- Bilateral
- Requires Interpretation
  - separate report form
  - narrative in body of medical record, on date of service
- Hand-held device, portable, bedside, prone
- Non mydriatic, automatic focusing, 1920x1440, -20to+20D
- Can capture anterior segment or posterior segment images, otoscopic or dermatologic, still or video
- View images on LCD or Transfer to computer via USB
- www.volk.com 309.854.1408 Peter Bergstrom

JAM

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)

JAM

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

Current Perimeters are Highly Variable

- After *one* abnormal visual field test:
  - 86% of patients test within normal limits on next exam

- After *two* consecutive abnormal test results:
  - 66% of patient test within normal limits on next exam[1]

3.Keltner JL, et al. *Arch Ophthalmol* 2003; 121:643.

Closing 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

Time Domain OCT vs Fourier Domain OCT

Time Domain

- A-scan generated sequentially one pixel at a time in depth
- Moving reference mirror
- 400 A scans / second
- 10 micron depth resolution
- B scan (512 A scans) in 1.28 sec
- Slower than eye movements

Fourier Domain

- Entire A scan generated at once based on Fourier transform of spectrometer analysis
- Stationary reference mirror
- 26,000 A scans per second
- 5 micron depth resolution
- B scan (1024 A-scans)in 0.04 sec
- Faster than eye movements

Glaucoma Analysis with the RTVue: Nerve Head Map

Nerve Head Map (NHM)

- Data Captured: 9,510 A scans (pixels)
- Time: 370 msec
- Area covered: 4 mm diameter circle

Provides
- Cup Area
- Rim Area
- RNFL Map

TSNIT graph

Ganglion Cell Map (MM7)

- Data Captured: 14,810 A scans (pixels)
- Time: 570 msec
- Area covered: 7 x 7 mm

Provides
- Ganglion cell complex assessment in macula
- Inner retina thickness is:
  - NFL
  - Ganglion cell body
  - Dendrites

3-D Optic Disc

- Time: 2 seconds
- Data Captured: 51,712 A scans (pixels)
- Area covered: 4 x 4 X 2 mm

Provides
- 3 D map
- Comprehensive assessment

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

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, intrcranial 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 chemo-therapy, and renal diseases
- Others under study include brimonidine, memantine, BDNF
- Future will be neuroprotection to improve environment and neuroregeneration with stem cells

Vitrectomy Causes Cataract & Glaucoma

- Chang,S AJO 2006
- Vitrectomy well known to result in cataract within 2 years
  - O2 now discovered to be responsible
  - After cataract and vitrectomy angle oxygen changed from 12mmHg to 32mmHg
- Study found increased IOP in operated eye compared to fellow eyes
  - 68% of OAG developed in operated eye
  - Presence of natural lens at time of vitrectomy associated with 28 month delay in OAG

Nanosensor IOL

- Fraunhofer Institute in Germany
  - Microelectric Circuits and Systems IMS
- Implant sensor for continuous IOP monitoring
- Integrated a 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%

- 1st & 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

Biologics in Recalcitrant Uveitis

- Standard treatment - includes topical steroids & cycloplegics, oral steroids, injectable steroids, sustained release formulations of steroids
- Steroid sparing agents – methotrexate, azathioprine are antimetablolite treatments
- Biologics – developed in the 1990s, targeted proteins for inflammatory mediators (cytokines or surface receptors)
  - Off label in US

Biologics in Recalcitrant Uveitis

- Anti-cytokines – the proinflammatory cytokine tumor necrosis factor-alpha (TNF-a) plays a role in pathogenesis of uveitis
  - Infliximab (Remicade) – most commonly used in uveitis (Bechet's, sarcoid, intermediate, birdshot, sympathetic opthalmia)
  - Adalimubab (Humira)
  - Etanercept (Enbrel)
- Interferons – IFN-a is a cytokine responsible for autoimmune disease
  - 83-94% of uveitis with Bechets recovered within 2-4 weeks

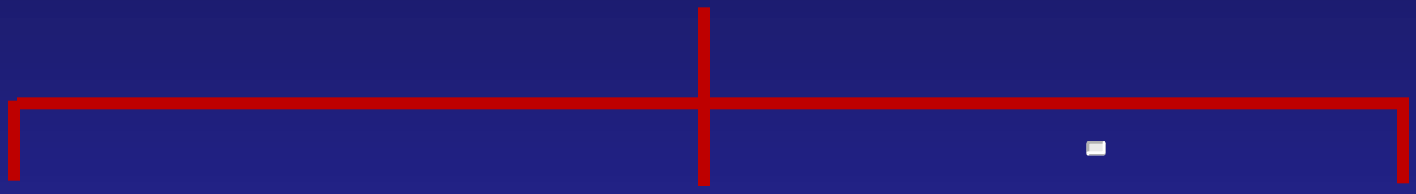
AMD Risk Factors

- 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 waiste/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 (63-124μ in diameter), or RPE abnormalities

AMD stages - Intermediate

Intermediate AMD

(AREDS category 3)

Consists of extensive intermediate drusen (63-124μ in diameter), at least one large druse (>125μ 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

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*

Average CNV Presentation

- Average size:
  - 3300μ
- Location:
  - 80% Subfoveal
  - 20% Extrafoveal
- Initial Vision:
  - 20% ≥ 20/40
  - 40% 20/50 – 20/200
  - 40% < 20/200

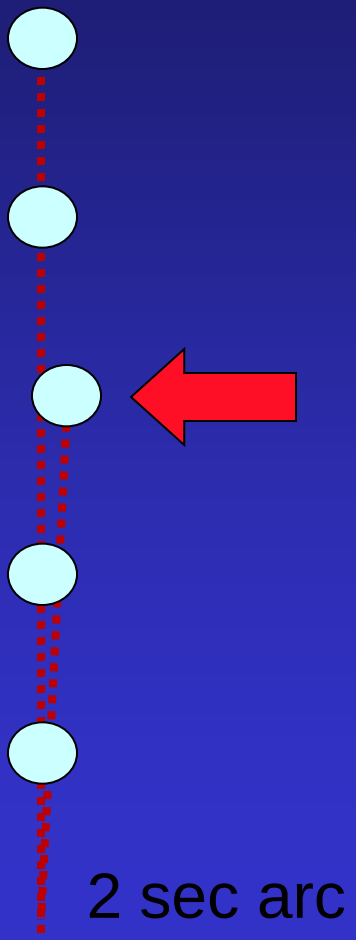
Olsen, TW *Ophthalmology* Feb. 2004

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

Foresee PHP™ Technology

Vernier Acuity



- The human ability to perceive minute differences in the relative spatial localization of two objects in space
- The brain is exceptionally sensitized to the detection of small shifts in the co-linear arrangement of photoreceptors.

Hyperacuity

- ***Snellen 20/15 Resolution***
  - 1minute of arc
  - 0.017 degrees
- ***Vernier Resolution***
  - Two seconds of arc
  - 0.03 minutes of arc
  - 0.00051 degrees
  - **The width of a pencil viewed at 300 m !**

The Future *of AMD Monitoring*

Foresee PHP™

- Easy operation
- Comfortable for patient
- Noninvasive Rapid threshold test ~ 5 min/eye
- Automated results analysis
- Generates visual field map of disturbance patterns consistent with the progression of AMD

Graduated Height of Artificial Distortions

0.1 deg.

0.2 deg.

0.3 deg.

During the test, signals containing artificial distortions of various magnitudes are presented to the patient

ForeseeHome™ AMD Monitor

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

ForeseeHome™
AMD Monitor

- 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 autoflourescence 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

JAM

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

JAM

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

Emerging Treatments for Dry AMD

- MacuClear's MC-1101
  - G. Choiu, 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

AMD Research on Genetics

- Age related macular degeneration gene located
- Encodes for a protein called Compliment 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

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 Ophthal 2010;117:1554-1559
- Growth rates of geographic atrophy NOT associated with varients in CFH, C2, C3, APOE, TLR3 genes
- Nominal association in LOC387715, ARMS2, HTRA-1 genotypes

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 cardiovacular disease
    - Homocystein concentration in blood increases risk AMD
    - Daily supplements reduce homocytein 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

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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

JAM

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 / PotentiaPhama, 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)
  - 1st 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 Epiretinal 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

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 canulated in very young children
- Deliver high concentration (low dose) chemotherapy infusion on outpatient basis
- Prevents radiation, enucleation, and systemic chemotherapy

Thank you

McGreal Educational Institute

Missouri Eye Associates

Excellence in Optometric Education