Can We Do Better in AMD?

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Theories on Aging and Eye Disease

- Age related macular degeneration and cataracts are associated with age
  - Leading causes of blindness worldwide
  - Elderly
  - Family history, gender, cardiovascular disease
  - Smoking – nicotine, benzopyrene, nickel, lead and arsenic
  - Light colored irides and hair
  - Exposure to UV radiation
  - Diet – saturated fat intake, obesity increases risk for AMD
- Mechanisms – free radical damage, UV damage
Smoking Cessation

- 1-7% chance of quitting without help
- Antidepressants
  - Bupropion (Wellbutrin/Zyban)
- Nicotine replacement
  - Nicoderm CQ Patch (Transdermal Nicotine 21mg, 14mg, 7mg steps over 10 weeks)
  - Nicorette Gum (2mg if <25 cigarettes/D, 4mg if >25 cigarettes/D)
  - Nicotrol Inhaler
  - Nicotrol Nasal Spray
  - Nicotrol Patch

Smoking Cessation

- Best new option
  - Varenicline (Chantix/Pfizer)
    - 43.9% quit vs 29.8% quit on bupropion
    - Treatment is for 12 weeks, if successful take it 12 more weeks to lessen chance of smoking again
    - Blocks nicotine receptors in brain and stops “reward” associated with smoking again
    - Side effects – nausea is mild and tolerable but occurs at 32%, 3% discontinued

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
Why is AMD the Leading Cause of Vision Loss & Blindness?

New Ideas in AMD
- Sub-specialty emerging in Retina
- Devices to measure Macular Pigment Optical Density
  - Macuscope (Marco)
  - QuantifEye (ZeaVision)
  - Good science behind both
- Hyperacuity perimetry
  - Forsee PHP (Reichert), ForseeHome (Notal)
- Zeaxanthin is considered important in supplementation
- Combination therapies more common in wet AMD

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!
- Companies bringing genetic testing to eye practitioners
  - Macula Protect (Canada), Sequenom (San Diego), Asper Biotech (Estonia), CyGene (Coral Gables)
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 & opthalmic
- 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
  - CFB -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

  - Check Swab
Considerations

- Certain vitamins possess antioxidant properties thought to enhance metabolic efficiency of RPE, quench free O2 radicals
- Carotenoid plant pigments comprising macular pigments reduce oxidative stress by absorbing blue light & reducing free radical formation
- Exactly which vitamins and minerals and dosages are optimal - strongly debated
- May be beneficial to “at risk” groups in ARMD
- Guard against over dosages of fat soluble vitamins
- Guard against drug interactions

Importance of Multivitamins in AMD

  - 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 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 ______________ ?
**Nutritional Conclusions**

- First degree relatives of ARM patients are 2-4 times greater risk of developing ARM in comparison to controls
- Twin studies have shown a high level of concordance of the disease among monozygous sibs
- Diets high in green leafy vegetables may increase macular pigment optical density and have a protective role
- Controlling HTN, lipids, obesity, stopping smoking, UV protection and high dietary intake of omega-3 FAs

**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

**Components of Ocular Supplements**

- **Vitamins**
  - Vitamin A as beta carotene
  - Vitamin C
  - Vitamin E
- **Minerals**
  - Zinc
  - Copper (Cupric oxide)
  - Selenium
- **Macular pigments**
  - Lutein – macular carotinoid
  - Zeaxanthin – foveal carotenoid
- **Bioflavenoids**
  - Ginko biloba – for AMD and glaucoma (blood flow) and memory
Nutrition / Supplement Successes

- Vitamin A – skin, conjunctiva, cornea
- Vitamin B1 – Beri Beri eradication
- Vitamin B12 – increased energy levels in elderly, pernicious enemia
- Vitamin C – scurvy erased, colds, cancer
- Vitamin D – Rickets vanished with fortified milk
- Vitamin E – reduces risk of heart attacks, prostate cancer
- Niacin – cholesterol treatment
- Folic acid – reduces birth defects in pregnant women
- Zinc
- Calcium - Osteoporosis
- Copper
- Selenium
- Lutein – macular carotinoid
- Zeaxanthin – foveal carotenoid

Nutritionals and OTC Vitamins

- Ocuvite Lutein (B&L)
- Ocuvite extra (B&L)
- Ocuvite PreserVision (B&L)
  - AREDS NIH Study
  - 2 tabs bid
- ICAPS Lutein & Zeaxanthin Formula (Alcon)
- ICAPS AREDS formula
- ICAPS MV
- ICAPS Lutein & O3s
- L-Sense OcuShield (Akorn)
- Maximize
- EyePromise (ZeaVision)

Nutritionals and OTC Vitamins

- Tozal Eye Health Formulation (Focus)
- OS2 (Amerisciences)
  - Formerly Tozal formulation
- Fortifeye Macular Defense and Super Omega (Fortifeye)
- Physicians Recommended Nutriceuticals (PRN)
**Treatment Modalities**

- **Dietary Supplements**
  - **Pro-Omega (Nordic Naturals)**
    - 2 softgels yield 1100mg EPA + DHA
    - 1 teaspoon yields 2750mg EPA & DHA
  - **Hydrate Essential (Cynacon/Ocusoft)**
    - Essential fatty acids - Flaxseed oil and bilberry extract encapsulated in hydroxylated lecithin
  - **HydroEye (Science Based Health)**
    - Blend of omega fatty acids and nutrients
  - **TheraTears Nutrition (Advanced Vision Research)**
    - EPA enriched flaxseed oil & omega-3s

**Nutritionals**

- **Ocuvite (B&L)**
  - 1000IU/200mg:60IU/2mg/40mg
  - General eye health along with multivitamin
  - 1 tablet qd or bid
- **Ocuvite extra (B&L)**
  - 1000IU/300mg:100IU/2mg/40mg plus select B vitamins
  - General eye health for those not taking multivitamins
  - 1 tablet qd or bid
- **Ocuvite Lutein (B&L)**
  - No A/60mg/30IU/6mg/15mg
  - For those at risk for ARMD, smokers, high exposure to UV
  - 1 capsule qd or bid

**Nutritionals**

- **PreserVision AREDS Tablets (B&L)**
  - Moderate to advanced ARMD
  - Can crush tablets
  - 4 tablets daily: 2 in morning and 2 evening with meals
  - 28,640IU/452mg/400IU/No Lutein/69.6mg = Daily dose
- **PreserVision AREDS Soft Gels (B&L)**
  - Moderate to advanced ARMD
  - For those with swallowing difficulties
  - 2 soft gels daily: 1 in morning and 1 in evening with meals
  - 28,640IU/452mg/400IU/No Lutein/69.6mg = Daily dose
- **PreserVision Lutein Soft Gels (B&L)**
  - For smokers, high UV exposure, difficulties swallowing
  - 2 soft gels daily: 1 in morning and 1 in evening with meals
  - No A/452mg/400mg/10mg/69.6mg = daily dose
Nutritionals

- ICAPS with Lutein & Zeaxanthin (Alcon)
  - Prophylaxis and mild-moderate-advanced ARMD
  - Yellow tablets
  - 4 tablets daily: 2 in morning and 2 evening with meals
  - 6,600 IU A/400mg C/150 IU E/60mg Zinc/4mg Lutein/zeaxanthin trace amount

- ICAPS AREDS formula (Alcon)
  - Moderate to advanced ARMD, for patients taking blood thinners
  - Red tablets
  - 2 in morning and 2 in evening with meals
  - 28,640IU A/452mg C/400 IU E/69.6 mg Zinc/No lutein

- ICAPS MV (Alcon)
  - For smokers, high UV exposure, enriched with multivitamins for smokers
  - Violet/blue tablets
  - No A/C/E/Zinc/lutein

Measurement of Macular Pigment

- Objective Techniques
  - Modified Fundus Cameras
  - Fundus Reflectence
  - Raman Spectroscopy
  - Autofluorescence Spectroscopy
  - Modified SLO

- Subjective Techniques
  - HFP (Heterochromatic Flicker Photometry) (psychophysical)
    - (Ability to detect a blue flickering light)

Is MPOD Related to AMD?

- Three donor eye studies published, all show 30-50% less pigment in AMD eyes vs controls
- Moran Eye Center (Bernstein) Raman method
- Manchester UK group HFP method found AMD patient eyes had 50% lower MPOD
- Germans found 50% lower MPOD in dry AMD patient eyes
- Dutch group did cross sectional prospective study using reflectance and found no difference on MPOD in early AMD
Macular Pigment Studies

- Optom 2008; 79:266-272 Lueng
  - Optometrist play key role in assessment & monitoring risk of AMD
- LAST Study (Lutein Antioxidant Supplement Trial)
  - 12 month study
  - 90 male VA patients
    - Lutein 10mg vs Lutein 10mg & MV vs Placebo
    - Lutein only or combination increases MPOD by >50%, Glare recovery, contrast sensitivity and visual acuity

Macular Pigment Studies

- OptomVisScience 2008; Stringham & Hammond
  - Six months of L/Zx increased MPOD
  - Decreased glare disability 58%
  - Decreased photostress recovery time 14%
- Ophthalm 2008 Feb 115(2):334-341 Blue Mountain Eye
  - Higher intake of L/Zx reduced risk of AMD
  - Confirmed protective benefit of zinc
  - Higher beta carotene increased risk AMD

Macular Pigment Studies in Cataracts

- ArchOphthalm 2008; Mueller et al
  - CAREDS/WHI
    - N=1802 women with highest levels of L/Zx had 32% lower incidence of NSC
- Ophthalm 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

- JOVS 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

The AREDS I & II Formulations

- AREDS (Age-Related Eye Disease Study)
- Vitamin C: 500 mg*
- Vitamin E: 400 IU*
- Beta-carotene: 15 mg (May be listed on the label as “25,000 IU vitamin A as beta-carotene) (eliminate!)
- Zinc oxide: 80 mg (40 mg)
- Copper: 2 mg (needed to prevent copper deficiency caused by high dosage of zinc)
- Lutein & Zeaxanthin: 10 mg & 2 mg
- Omega-3 fatty acids: 1 gram

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

- 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

- 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
**AREDS 2 The Rest of the Story**

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**Nutritionals**

- **EyePromise (ZeaVision)**
  - Zeaxanthin 8mg
  - in the same 2:1 ratio as found in healthy macula
  - Lutein 4mg
  - Beta carotene – none
  - Vitamin C – 120mg
  - Vitamin E – 60 IU
  - Zinc – 15mg
  - Copper – none
  - Fish oil (omega-3) – 250mg
  - Alpha Lipoic acid – 10mg

- **0S2 (Formerly Tozal/AmeriSciences)**
  - Taurine
  - Zeaxanthin 0.5mg
  - Lutein 10mg
  - Beta carotene – 18,640 IU
  - Vitamin A – 10,000 IU
  - Vitamin E – 60 IU
  - Zinc – 69mg
  - Fish oil (omega-3) – 250mg

- Study results tested supplement vs supplement & MCS
  - 57% of both groups improved at six months
Nutritionals

- **Tozal (Focus Labs)**
  - Taurine 400mg
  - Zeaxanthin 2mg
  - Lutein 10mg
  - Beta carotene – 18,640 IU, Vit A Palmitate 10.000IU
  - Vitamin A – 10,000 IU
  - Vitamin C 452mg
  - Vitamin E – 200 IU
  - Zinc – 69mg
  - Fish oil DHA-EPA omega-3) – 600mg
  - Vitamin D3 800mg
  - Copper 1.6mg

- Medical Food – RX only, at pharmacy or sold in office

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**MacuHealth Ocular Treatment**

- **Simple Focused Formula**
  - 10 mg Meso-Zeaxanthin
  - 10 mg Lutein
  - 2 mg Zeaxanthin

- **Meso has proven to be the key Carotenoid in the fight on AMD**
- **Proven to significantly increase Macular Pigment Density**

- **MZ is the dominant macular protective pigment found in the center of the macula**

- Kathy.rymer@youreyesolutions.com

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**Nutritionals**

- **ICaps Lutein & Omega-3 (Alcon Labs)**
  - Taurine 400mg
  - Zeaxanthin 2mg
  - Lutein 10mg
  - Vitamin A Palmitate 0.6mg
  - Vitamin C 45mg
  - Vitamin E 10mg
  - Vitamin B-12 2.4mg, Vitamin B61.3mg, Folic acid 240mg
  - Niacin 16mg, Riboflavin 1.3mg, Thiamine 1.2mg
  - Zinc – 7mg
  - Fish oil DHA-EPA omega-3) – 280mg
  - Calcium 1mg
  - Copper 0.9mg, Selenium 34mcg, Manganese 2.3mg
**Why Is Early Diagnosis Important?**

- **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*

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**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

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**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.

2 sec arc
Hyperacuity

- **Snellen 20/15 Resolution**
  - 1 minute 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

ForeseeHome™

- 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
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

Therapeutic Applications
- Fenretinide
  - Oral compound, vitamin A derivative
  - Lowers production of toxic fluorophores in RPE
    - Dose dependent manner
  - Competes with serum retinol for binding sites of retinol-binding protein
  - Promotes renal clearance of retinol
  - Bioavailability of retinol for RPE photoreceptors is reduced
    - Fewer toxic retinoid by-products (A2-E) generated

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
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 variants in CFH, C2, C3, APOE, TLR3 genes
- Nominal association in LOC387715, ARMS2, HTRA-1 genotypes

FAF Background Information

- Recording FAF is easy, fast & non-invasive
- FAF signals emitted across spectrum from 500-800nm
- CSLO
  - Excitation induced in blue (488nm)
  - Emission filter 500-700nm to detect
- Fundus camera
  - Excitation induced in green (535nm-580nm)
  - Emission filter in yellow-orange (615-715nm)
- Composition of images may vary between systems

FAF Background Information

- FAF imaging is in-vivo method for mapping of fluorophores in fundus
  - Naturally occurring and pathological
- Dominant source are fluorophores like A2-E in lipofuscin granules
  - Accumulates in post mitotic RPE
  - By-product of incomplete degradation of photoreceptor outer segments
- RPE captured by FAF lies just above choroid
  - Not captured by photography or FA photography
**FAF Background Information**

- Two filters required
  - One in conjunction with flash
  - Excites fluorescence of RPE/Bruch’s
  - Barrier – blocks all other wavelengths back to camera

- Any structure without fluorescence is BLACK
  - In pathology dead photoreceptor cells shed distal outer segments (POS) stacks for photoreceptor renewal
  - Dead cells trapped in RPE leave behind cell walls, lipid, blood
  - This debris is lipofuscin

- All others are SILVER

**FAF Signal as Predictive Marker**

- Extension of abnormal FAF & FAF Pattern impact enlargement rates over time
- Serve as predictive determinants
- Find “fast progressors”

**Progression rates MORE DEPENDANT on FAF pattern than any other risk factor!!**
- Baseline atrophy size, smoking history, HTN, DM, >80yrs, family history, hyperlipidemia

**FAF Imaging Systems**

- Autofluorescent Fundus Camera: Canon CX-1
- Optos Daytona
- Spectralis OCT /Heidelberg
- FAF Systems
  - No Standardization
    - Different protocols (RE correction, axial position), Different filters (may record different dominant fluorophore excitation)
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

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

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

- Geographic Atrophy Enlargement Rate
  - Valid marker
- OCT scan patterns
  - 200 A-scans x 200 B-scans (6x6mm)
  - “Fundus Image” shows true GA
    - Often ignored
    - Not SLO or photo
    - Compilation of A-scans and demonstrates integrity of RPE

Fundus Photography
92250

- Bilateral
- Not Bundled
- Requires Interpretation
- Fee $69.74

Fundus Retinal Photos ROI

- Synemed (Canon 15+MP)
- Cost $24,500.00
- Lease $543.90
- Breakeven 2 photos / wk
- 8-10 MP digital non-mydriatic
- 10 images / wk – lease = $22,273.20 annual revenue
Extended Ophthalmoscopy  
92225 / 92226

- Unilateral
- Initial (-225) vs. Subsequent (-226)
- Implies detailed, extra ophthalmoscopy
  - document fundus lenses used
- Modifiers RT /LT
- Requires retinal drawings & interpretation
  - sizes, colors and dimensions carrier specific
- Fee 92225 ($21.69)  92226 ($19.53)

Fluorescein Angiography 92235
Indocyanine-Green 92240

- Unilateral
- Not Bundled
- Requires Interpretation & Report
- Fee 92235 ($122.55)  92240 ($254.30)

Scanning Computerized Ophthalmic Diagnostic Imaging  
92134

- Unilateral or bilateral
- Applies to retinal evaluations
  - Heidelberg / Heidelberg Retinal Topography (HRT, Spectralis)
  - Carl Zeiss / Optical Coherence Tomography (GDX, Stratus, Cirrus)
  - Optovue / (RTVue, iVue)
  - Marco / Retinal Thickness Analyzer (RTA)
- Requires Interpretation & report
- Fee  $42.24
Scanning Computerized Ophthalmic Diagnostic Imaging - 92134

- 190.6, 190.8 Malignant neoplasm choroid
- 224.6, 224.8 Benign neoplasm choroid or other sites
- 360.11 Sympathetic uveitis
- 360.21 Progressive high (degenerative) myopia
- 360.30-360.34 Hypotony, flat chamber
- 361.00-361.07 Retinal detachments
- 361.10 Retinoschisis
- 361.2 Serous retinal detachment
- 361.81 Traction detachment
- 362.01-362.06 Diabetic retinopathy, background to severe NPD
- 362.07 Diabetic macular edema
- 362.10-362.18 BDR, retinal vasculitis
- 362.31-362.32 Central or branch retinal artery occlusion
- 362.35-362.37 Central or branch retinal vein occlusion
- 362.40-362.43 Retinal layer separation, hemor detach RPE
- 362.50-362.77 Macular degeneration, retinal dystrophies involving Bruch's membrane
- 362.81 Retinal hemorrhage
- 362.82 Retinal exudates and deposits
- 362.83 Retinal edema

Scanning Computerized Ophthalmic Diagnostic Imaging - 92134

- 363.00-363.08 Focal chorioretnitis
- 363.10-363.15 Disseminated chorioretnitis
- 363.20-363.35 Chorioretinitis unspecified
- 363.43 Angioid streaks
- 363.61 Choroidal hemorrhage
- 363.63 Choroidal rupture
- 363.70-363.72 Choroidal detachments
- 376.00-376.9 Acute inflammations of orbit
- 379.11-379.19 Scleral ectasia and other scleral disorders
- 379.21-379.29 Vitreous degenerations & other disor of vitreous
- 921.3 Contusion of eyeball
Conclusion
Cirrus HD-OCT

Clinical efficiency
- Small footprint and 90 degree orientation
- Mouse driven alignment
- Auto patient recall
- Repeat scan function
- Precise registration for clinical confidence
- Advanced optics for scanning of patients with cataracts or pupils as small as 2.5mm

Spectralis™ HRA+OCT Advantages
- **Eye Tracking** – Every cross section is captured simultaneous to a fundus image
- **6 modes** – Multiple perspectives of the anatomy from multiple wavelengths
- **40k Hz scanning** – High speed helps overcome eye movement artifact and increases patient comfort
- **TruTrack™** – Image alignment compares reference location at baseline to follow-up
- **Heidelberg Noise Reduction technology** – Overcomes the limits of “resolution”

The Future of OCT
- RTVue Fourier Domain OCT overcomes limitations of Time Domain OCT (Stratus)
  - Better resolution (5 micron vs 10)
  - Faster scan speeds (26,000 A scans / sec vs 400)
  - 3-D data sets (won’t miss pathology)
  - Large data maps (less interpolation)
  - Progression capabilities
  - Layer by layer assessment
  - Versatility (Anterior Chamber Imaging)
Spectral-Domain OCT
- 26,000 A-scans/sec
- 5 micron resolution

Scans
- Retina – 6x6mm thickness map, 5 line raster over-sampled & averaged, and Cross Line
- Glaucoma – ONH scan (w/o Optic Disk metrics)
- Cornea – 6x6mm Pachymetry Map with averaged horizontal line scan, and Angle scan
- Follow-up scans with Change Analysis

2006 New CPT Codes
- Pegaptanib for AMD
  - 67028 Intravitreal injection - $196.58
  - J2503 Macugen - $1054.70
- Verteporfin for AMD
  - 67221 infusion of photodynamic agent - $301.46
  - J3396 Visudyne - $1400
- Bevacizumab for AMD
  - 67028 Intravitreal injection - $196.58
  - J9035 Avastin

Pharmacologic Management of CNVMs
- MARINA Study (Minimally Classic/Occult Trial of Anti-VEGF Antibody Ranizumab in Treatment of ARMD. N Engl J Med 2006;355
- N 716 injected w Lucentis (0.3mg or 0.5mg) or sham
- VA improved by 15 or more letters in 24.8% of 0.3mg grp, 33.8% of 0.5mg grp, compared to 5% of sham grp
- At 2 yrs 6.6 letter gain w Tx vs 14.9 letters lost w/o Tx
Pharmacologic Management of CNVMs
- N 423 injected w Lucentis (0.3mg or 0.5mg) or with photodynamic Therapy using Visudyn
- VA improved by 15 or more letters (moderate gain)
  - 35.7% of the 0.3mg grp
  - 40.3% of the 0.6mg grp
  - 5.6% of the Visudyn grp
- Average VA gain was 11.3 letters vs. 9.5 letters lost w Visudyn at 1 yr
- 31% had VA of 20/40 or better vs 3% w Visudyn

Photodynamic Therapy (PDT)
- Goal is chemical obliteration of CNVM without damage to overlying retina
- Photosensitizing agents – tin ethyletiopurpurin 1mg/kg
  - Photosensitivity of skin & eyes for 1-2 days
- Laser - 689nm of 50 J/cm2 at 600 mW for 83 seconds
- Retreatments are 91% at 3 months and 64% at 24 months
- TAP Results
  - VA stable or improved 61% vs 46% placebo
  - 16% improved 1-2 lines vs 7% placebo

Triamcinolone acetonide
- Principle effects:
  - Stabilizes blood-retinal barrier
  - Resorption of exudation
  - Downregulation of inflammatory stimuli
- Secondary effect:
  - Anti-angiogenesis
### Macugen

- Selective vascular endothelial growth factor antagonist
  - VEGF induces angiogenesis
  - Increases vascular permeability and inflammation
  - Breaks blood retina barrier

- Growth Factors Associated with CNV
  - VEGF –A, VEGF-B, VEGF-C, VEGF-D
  - Placenta Growth factor PIGF
  - Platelet derived growth factor
  - Angiopoetins

<table>
<thead>
<tr>
<th>Pegaptanib sodium for injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single dose, pre-filled syringe, 3.47 mg/ml, glass vial</td>
</tr>
<tr>
<td>Administration – 27g needle intravitreal injection</td>
</tr>
<tr>
<td>Indication – neovascular “wet” macular degeneration</td>
</tr>
<tr>
<td>Contraindications – ocular infection</td>
</tr>
<tr>
<td>Warnings – risk of endophthalmitis, increased IOP</td>
</tr>
<tr>
<td>Dose – once every 6 weeks for one-two years</td>
</tr>
<tr>
<td>Macugen treated patients continue to lose vision but at a slower rate than sham</td>
</tr>
</tbody>
</table>

### rhuFabV2

- Recombinantly produced
- Humanized
- Fab fragment
- Mouse Monoclonal
  - Ab vs VEGF
- V2 – Version 2
  - Affinity Matured

Generic name = “Ranibizumab”
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

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

Avastin for EVERYTHING Systemic
- Colorectal CA
- Metastatic breast CA
- Metastatic renal CA
- Lung CA
- Exploring uses in
  - prostate,
  - pancreatic,
  - liver and others
Avastin for EVERYTHING ocular

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

Avastin for EVERYTHING

- Lucentis for DME
  - 3-year study
  - Double masked & fully enrolled
  - Results in 2 years
- DaVinci Study
  - Phase II
  - VEGF TRAP in DME
  - Causes “regression” of retinopathy not “contraction”

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
- Benefits - half the number of injections, less cost
**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 Medicare Approvals - Bevacizumab**

- 362.07 Diabetic macular edema
- 362.36 Venous tributary occlusion
- 362.55 Exudative macular degeneration
- 364.42 Rubeosis iridis
- 365.63 Glaucoma associated with vascular disorders

**Non-Pharmacologic Management CNVMs**

- Br J Ophthalmol 2006; 0:1-3
- Regular exercise reduced the risk of developing ARM by as much as 70%
- Independent of BMI and other confounders, study provides evidence that regular physical activity such as walking might protect against AMD
- Physical activity known to reduce systemic inflammation and endothelial dysfunction
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

New Wet AMD Clinical Trials
- HARBOR Trial
  - High Affinity VEGF Trap
    - 200 fold higher affinity than Lucentis
    - Lasts 72 days vs 38 days
    - All human amino acids
    - Penetrates all layers
    - Specially purified & formulated
  - Phase II – 1.5 years for results
  - Compares dose forms
    - 0.5mg
    - 2.0mg
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

- 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

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

- 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 bevasizumab
- A significant unmet need for more potent, longer lasting or complementary mechanism of action
Antti-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 1st year
  - Nationwide outcomes must be worst than we want to admit!

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

- 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 pericycte recruitment, strip pericyctes from NV complex without negatively affecting host non-cardiovascular vessels, causing both inhibition & regression of NV complex
Eye is desirable for research since Blood-retina barrier affords relative immune privilege

Human alteration of virus nucleic acid can modify destructive DNA and genes, and insertion of desired genes can transform malevolent microorganism into compliant partners

Adeno-associated viruses (AAV) – preferred vector
- Wild type not implicated in disease
- Broad host range (infected dividing & non-dividing cells)
- Can integrate into host chromosomes in cytoplasm

Single gene transfection (gene delivery)
- Over 25 genetic conditions of retina
- Leber’s congenital amaurosis - caused by RPE65 gene mutation
  - Moorefield Eye Hospital started studies in 2007
- AMD – AAVs delivery to VEGF receptor flt-1
  - Cuts number of endothelial cell nuclei in retina by half

RNA interference (gene silencing) – switching off genes that encode defective proteins
- Works best in partitioned organs (eye, lungs, CNS)
- Inhibits genes which encode for endothelial growth factor
- Uses dsRNA of carrier viruses, cut by Dicer enzyme into 20-23 piece nucleotide called siRNA
- Protein called RNA-induced Silencing Complex (RISC) unzips the siRNA, removes and discards targeted strand, degrades the mRNA indicated on the siRNA so it no longer replicates

RNAi can suppress any gene, but some diseases are caused by multiple genes (ie. RP- 30 genes)
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

- 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

- 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.

Unanswered Questions

- Will complement inhibition work in AMD?
- Will C3 or C5 be the answer?
- Systemic topical, intravitreal injection be the best route?
- Will VEGF Trap be better than Avastin?
- Will Radiation with VEGF be better?
- Will treating high risk drusen with these drugs help?
- Does rheotherapy need to be reconsidered given the focus on complement?
Real World Observations

- Failures are failures of convenience & finances
- True failures = visual loss
  - ANCHOR & MARINA: Only 10% lost VA, 70% improve
- Never give up when fluid returns on OCT
- Follow monthly/OCT/Treat as needed
- Loss of Vision is from ATROPHY
- GA grows 1.25mm/year
- Can stop NV but not disease process
- We currently convert wet AMD back to Dry AMD!

Thank you
Missouri Eye Associates
McGreal Educational Institute

Excellence in Optometric Education