AMD; What is Next?

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Excellence in Optometric Education

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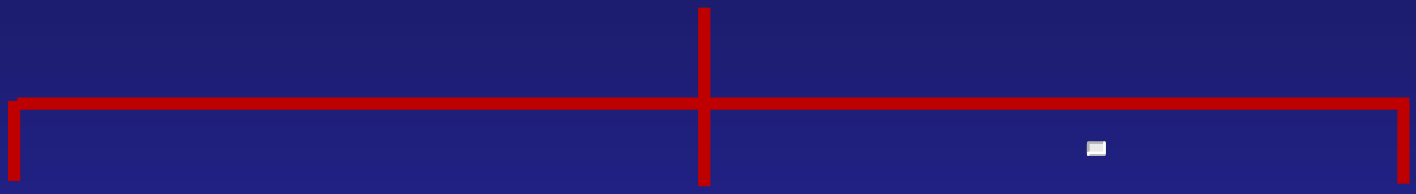
Theories on Aging and Eye Disease

- 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

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***

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 & 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.

Macula Risk NXG

- Includes 7 new AMD markers
  - Cholesterol metabolic markers
    - CETP, LPL, LIPC, ABCA1
  - CF1
  - C2
  - C2FB
  - Tissue inhibitor metalloproteinase gene (TIMP3)
  - Collagen type 8 alpha I gene (COL8A1)
    - Extracellular matrix
- Additional non-genetic risk factors
  - Age, smoking history, BMI, status of AMD in both eyes

Macula Risk NXG

- Improved 5, 10 year risk estimates
- Higher predictive power of 89.5%
- Sensitivity & specificity of >80%
- 92% of CNV patients maintain near normal vision in 2nd eye
  - Compared to 35-47% of 1st eye CNV patients
- kathy.rymer@macularisk.com, 314 288 6255

Multivitamins in Prevention of CVD in Men

- Physicians' Health Study II JAMA Nov7 2012 Vol 308 No 17
  - MV most common supplement in USA
  - Randomized, controlled trial of US male physicians
  - N=14,641
  - 50 year average age
  - Results – daily MV did NOT reduce major cardiovascular events of stroke, MI, CVD mortality after decade of follow up

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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

- 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 _____?

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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 caroteniod

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
- I-Sense OcuShield (Akorn)
- Maximize
- EyePromise (ZeaVision)
- Macutrition (Advanced Vision Research)

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) (pschyophysical)
  - (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%
- Ophthal 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

- 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

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

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

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

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?

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

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

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

JAM

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

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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

JAM

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

JAM

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

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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

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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

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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

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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
  - 200Ascans x 200 Bscans (6x6mm)
  - “Fundus Image” shows true GA
    - Often ignored
    - Not SLO or photo
    - Compilation of A scans and demonstrates integrity of RPE

Pipeline for Dry AMD

- Decrease oxidative stress
  - AREDS 2 — Antioxidant — NEI — Phase 3
- Visual cycle modulators
  - Fenretinide — Retinol analogue — Sirion — Phase 2
  - ACU4429 — non-retinoid — Acuela — Phase 2
- Neuroprotectants
  - NT-501 — ECT/CNTF — Neurotech — Phase 3
  - Brimonidine — a-2 adrenergic — Allergan — Phase 2
    - implant
  - Tandospirone — 5HT1A agonist — Alcon — Phase 2
    - Seratonin inhibitor

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Pipeline for Dry AMD

- Drugs Reduce toxic by-products
  - Copaxone — Suppress T-cells — Kaplan — Phase 2
  - RN6G — Amyloid antibody — Pfizer — Phase 2
- Drugs suppress inflammation
  - Iluvien — Fluocinolone — Alimera — Phase 3
  - POT-4 — CompastatinC3 — Alcon — Phase 3
    - Intravitreal slow release
  - Eculizumab — C5 — Phase 2
    - Approved for paroxismal nocturnal hemoglobinuria

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Fundus Photography
92250

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

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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)

JAM

Fluorescein Angiography 92235
Indocyanine-Green 92240

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

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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

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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

- ANCHOR Study (Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in ARMD. N Engl J Med 2006;355
- 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

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 Systemic

- Colorectal CA
- Metastatic breast CA
- Metastatic renal CA
- Lung CA
- Exploring uses in
  - prostate,
  - pancreatic,
  - liver and others

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

Prophylactic Ranibizumab for Wet AMD

- PREVENT - Clinical Trial exploring whether quarterly injections of ranibizumab would prevent eyes with dry macular degeneration from progressing to wet macular degeneration

Silence Reduces Risk of Infections

- Wills Eye Hospital study of intravitreal injections
- 126,587 IVI, retrospective case series of endophthalmitis after anti-VEGF agents
  - 48 cases / 17 culture positive
- 47,773 talking
  - 27 cases / 9 culture positive high in oral pathogens
- 78,814 no-talking
  - 21 cases / 8 culture positive
- No talking policy during IVI affective in reducing risk of infection, including oral pathogen associated cases

JAM

X-82 / Tyrogenex

- ORAL
- Effect – Anti VEGF & Anti PDGF
- Dose – daily, PO
- Indication – neovascular “wet’ macular degeneration
- Studies looking at daily oral dosing with as needed aflibercept

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

Regorafenib / Bayer

- TOPICAL
- Effect – Anti VEGF-A, targets receptor tyrosine kinase so inhibition is after VEGF binds to receptor
- Indication – neovascular “wet’ macular degeneration
- Benefit – no injections, less cost,

PAN-90806 / PanOptica

- TOPICAL
- Effect – Anti VEGF-A, targets receptor tyrosine kinase so inhibition is after VEGF binds to receptor
- Indications
  - Neovascular macular degeneration
  - Proliferative diabetic retinopathy
- Current studies have 2 arms
  - Drops alone for AMD
  - Ranibizumab once followed by 12 weeks of topical eyedrops

JAM

DME – RISE & RIDE Studies

- Unequivalently demonstrated importance of VEGF monotherapy
- Both found resistant patient populations with chronic DME
  - Increase inflammatory cytokine in aqueous (Austria)
  - Increased inflammatory cytokines in vitreous (Japan)
- Conclusion
  - Non-chronic DME (<3yrs) = anti-VEGF Rx
    - OCT is a barometer for VEGF levels
  - Chronic DME (>3yrs) = anti-inflammatory Rx
    - OCT is not helpful for inflammation
  - Modest macular thickening (20-30%) laser is equivalent to anti-VEGF

DME - FLAME Studies

- Iluvien (Fluocinolone)/ Alimera
- Non-bioerodable micro-implant 0.2ug
- Slow release 3 yrs
- Fullfills unmet need in chronic, severe, blinding DME

Iluvien Implant (Alimera)

- Fluocinolone 0.19% injectable implant (intravitreal)
- 3.5mm long x 0.37mm diameter
- Treatment of Diabetic macular edema (DME) in patients previously treated with corticosteroids, that did not have increased IOP
- Single implant delivers steroid for 36 months
- AE
  - cataracts (82%, sham 50%),
  - Increased IOP (34%, Sham 10%)

DME Cost Comparison

- Drug / Cost / No. treatments / 3 yr Total Cost / FDA status
- Iluvien / $8,800 / 1 / $8906 / Approved
- Eyelea / $1,850 / 22 / $43K / Approved
- Lucentis / $1,170 / 22-36 / $28-$45K / Approved
- Ozurdex / $1,333 / 5-12 / $7-17K / Approved
- Avastin / $50 / 22-36 / $3-6K / Unapproved

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

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
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Medicare Approvals -Bevacizumab

- Diabetic macular edema (DME)
- Venous tributary occlusion (BRVO, CRVO)
- Exudative macular degeneration (AMD, wet)
- Rubeosis iridis (NVI)
- 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 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

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 Concepts – PDGF Drugs

- Platelet-derived growth factor – cytokine involved in recruitment of pericytes
  - Envelope vessels protecting from anti-VEGF drugs, even producing more VEGF
  - Cells signal in cross talk (VEGF – PDGF)
  - Treatment only works on pericytes so cant be monotherapy for CNV
- Fovista (Ophthotec Corp/Princeton NJ)
  - Anti-PDGF aptamer used in combination with ranibizumab
  - Inhibits pericyte recruitment & strip pericytes from CV complex, regression of CNVM, no negative affects on host non cardiovascular vessels

Burden of VEGF Treatments

- ANCHOR/MARINA – in general no regression of CNV
  - 20%/15% of CNV grew
  - 2/3rds fail to achieve significant gains (>3 lines)
  - Vision improves in first 2-3 months, stabilizes at 4 months then plateaus with continued therapy (protocol)
- APPEAR/EXCITE/SAILOR/HARBOR - best outcomes with strict monthly injections
- CATT/HORIZON – demonstrated rapid vision worsening in decreased dosing frequency
  - CMS claims data average number of injection in US is <6

Investigational Therapy for Wet AMD

- Finding Better Anti-VEGF agents
  - ESBA (Alcon) – humanized single chain antibody fragment and pan-VEGF inhibitor
  - OSPREY – phase 2 trial of ESBA & aflibercept
  - DARPin (Allergan) – designed from natural ankyrin repeat proteins
    - Small molecule designed to bind to any receptor
    - Function is cell signaling and receptor binding
    - REACH study in phase 2
- Exploring combination therapies – platelet derived growth factor, Fovista (Ophthotech) combined wit anti-VEGF agents demonstrates 62% additional benefits

Investigational Therapy for Wet AMD

- Finding Better Anti-VEGF agents
- DARPin abicipar pego in wet AMD (Allergan)
  - Small molecule size, high binding affinity and high specificity with long half life
  - Long acting antagonist of VEGF
  - 6-8 weeks between injections vs 4 in Lucentis
- REACH study successfully completed phase 2
  - Abicipar - Results equal to or greater than ranibizumab (Lucentis) with less injections, no serious AEs
- SEQUOIA and CEDAR trials (N=900 each) comparing abicipar to Lucentis

Investigational Therapy for Wet AMD

- Finding Better Anti-VEGF agents
- DARPin abicipar pego in wet AMD
  - Small molecule size, high binding affinity and high specificity with long half life
  - Long acting antagonist of VEGF
- Multi-VEGF/PDGF DARPin
  - Combination of DARPin abicipar & DARPin PDGF
  - Creates multi-specific therapy targets
  - Pre-clinical studies

Investigational Therapy for Wet AMD

- Finding Better Anti-VEGF Delivery Systems – 3 ways
  - Gene therapy
    - Genzyme - viral vector given intravitreally to deliver tyrosine kinase inhibitor sFLT-1, a chimeric protein that binds to VEGF
    - AvalancheBiotech – subretinal injection following vitrectomy of tyrosine kinase, phase 2
      - Viral vector pipeline to inhibit VEGF
      - Replace missing proteins in retinal disease
    - Applied Genetic Technologies – Adeno-virus vector for RP, retinoschisis, phase 2
    - Spark Therapeutics – SPK-RPE65 – long lasting gene replacement in ANY inherited disease

Investigational Therapy for Wet AMD

- Finding Better Anti-VEGF Delivery systems – 3 ways
  - Gene therapy
    - Genzyme - viral vector given intravitreally to deliver tyrosine kinase inhibitor sFLT-1, a chimeric protein that binds to VEGF
    - Avalanche – subretinal injection following vitrectomy of tyrosine kinase, phase 2
  - Encapsulated cell technology (ECT/ Neurotech)
    - Neurotech – protein factory implanted in the posterior segment, phase 3
    - Part drug / part device
    - Novel VEGF receptor protein produced by recombinant RPE cells encapsulated in semipermeable membrane
    - “Bakes the bread daily”

Investigational Therapy for Wet AMD

- Sustained Released Drugs
  - GrayBug (GB-102)
    - Small molecule compound already approved for cancer delivery
    - VEGF & PDGF into biodegradable carrier
    - Releases drug for 4-6 months
  - Aerie/GrayBug (AR-13154)
    - Better results than aflibercept
    - Inhibits 3 different molecules
      - PDGF,
      - Rho kinase (ROCK) &
      - Janus kinase 2 (JAK2)

New Routes to the Retina

- Aerpie (AKB-9778)
  - 1st in class drug
  - ***Systemic*** treatment for diabetic macular edema (DME)
    - In combination with ranibizumab
  - Self injected subcutaneously BID
  - Inhibits human protin tyrosine phosphatase B
  - Downregulates Tie2 receptor in retinal cells
  - Also decreases diabetic retinopathy severity scale
    - May initiate clinical trials for diabetic retinopathy indication

Anti-HTN Drugs Associated with AMD

- Researchers at University of Wisconsin
  - Cohort of NEI's Beaver Damn study of 5000 residents aged 43-86
  - Use of any vasodilators was associated with 72%greater risk of developing early stage AMD
  - Use of oral beta blockers was associated with 71% increase in risk of neovascular AMD
  - Klein et al Vasodilators, blood pressure lowering medications and AMD, Beaver Damn Study April 11, 2014 on line Ophthal

Gene Therapy Turning Foes into Friends

- 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 (infects dividing & non-dividing cells)
  - Can integrate into host chromosomes in cytoplasm

Gene Therapy Turning Foes into Friends

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

Gene Therapy Turning Foes into Friends

- RNA interference (gene silencing) – switching off genes that encode defective proteins
  - Works best in partitioned organs (eye, lungs, CNS)
  - Inhibits genes qhich 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 disgards 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

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

Unanswered Questions

- Will complement inhibition work in AMD?
- Will C3 or C5 be the answer?
- Systemic, topical, intravitreal injection be the best route?
- Will Radiation with VEGF be better?
- Will VEGF & PDGF be better?
- Will DARPin proteins change the game?
- Will treating high risk drusen with these drugs help?
- Does rheotherapy need to be reconsidered given the focus on complement??
- Will prophylaxis be a better approach?

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!
- Unmet need is treatment for DRY

JAM

Thank you

Missouri Eye Associates

McGreal Educational Institute

Excellence in Optometric Education