Current Concepts & Controversies in Macular Degeneration

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Financial Disclosures

- Speaker for Novartis

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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

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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
- Five year risk of developing AMD is decreasing by relative 60% with each generation
  - Beaver Dam, N = 4819 / Boomers and adult children
  - Factors contributing to decline yet to be discovered
    - Cruickshanks KJ, et al JAMA Ophthalmol Nov 16, 2017

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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)

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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

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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

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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

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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

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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.

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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

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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

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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

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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

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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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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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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

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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

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Components of Ocular Supplements

- Vitamins
  - Vitamin A as beta carotene (removed after AREDS II)
  - Vitamin C
  - Vitamin E
- Minerals
  - Zinc (Dose decreased after AREDS II)
  - Copper (Cupric oxide)
  - Selenium
- Macular pigments
  - Lutein – macular carotinoid
  - Zeaxanthin – foveal carotenoid
- Bioflavenoids
  - Ginko biloba – for AMD and glaucoma (blood flow) and memory

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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

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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)

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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

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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

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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

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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%

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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

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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

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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

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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

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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

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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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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 !**

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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

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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

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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

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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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FAF Imaging Systems

- **Autofluorescent Fundus Camera:** Canon CX-1
  - Single Image in real time
  - Higher Flash
    - 50-100 wps (color) vs. 250-300wps (FAF)
  - 30-45deg FOV
  - Exciter: 530-580nm, Barrier: 640nm
- Optos Daytona
- Heidelberg OCT
- FAF Systems
  - No Standardization
    - Different protocols (RE correction, axial position). Different filters (may record different **dominant fluorophore** excitation).

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Optos California Imaging Device

- Newest Optomap imaging device
- New hardware and software technology
- Designed for those needing multiple imaging modalities
  - Ultra-wide field imaging up to 200 degrees
  - Indo-cyanine green angiography
  - Color, red-free, autofluorescence photography
  - Fluorescein angiography
  - Auto-montage of 95% of retina
  - Images presented in ProView - solves the problem of representing 3D structure of eye in a 2D image

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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

- 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

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Pipeline for Dry AMD

- Decrease oxidative stress
  - AREDS 2 — Antioxidant — NEI — completed
- 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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Investigational Therapy for Dry AMD

- Lampalizumab for geographic atrophy
  - CHROMA, SPECTRI
    - 936 patients, pivitol trial
    - Injections every 2 or 4 weeks
  - Aimed at unmet medical need for treating dry AMD (GA)
  - Phase 3
  - Genentech
- Oracea for geographic atrophy
  - TOGA
- Oral minocycline for geographic atrophy

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Investigational Therapy for Dry AMD

- Bioelctrical stimulation for dry AMD treatment – very low current similar to natural currents in body
- Metformin for minimization of geographic atrophy progression in AMD
  - METforMIN
  - Study for advanced dry AMD in non-diabetics
- Intravitreal aflibercept injection vs sham as prophylaxis against conversion to neovascular AMD
  - PRO-CON
- Intravitreal Zimura (anti-C5 aptamer) in GA w dry AMD

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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

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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

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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

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Triamcinolone acetonide

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

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rhuFabV2

- recombinantly produced
- humanized
- Fab fragment
- Mouse Monoclonal Ab vs VEGF
- V2 – Version 2 Affinity Matured

Generic name = "Ranibizumab"

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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

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Avastin for EVERYTHING Systemic

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

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Avastin for EVERYTHING ocular

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

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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

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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

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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

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Medicare Payments for Eye Care - 2015

Service	MDs	ODs
Eye exams	$2.2B	$0.9B
Tests	$1.0B	$0.2B
Surgery	$2.3B	$0
Supplies	$3.0B	$0
Total	$8.5B	$1.1B

- Elephant in the room is the costs of drugs
  - Just 2 anti-VEGF drugs (Lucentis & Eyelea) represent 93% of ophthalmic supplies
- 2.96 mil intravitreal injections, 5.25 m OCTs (retina)

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Real World Data on Anti-VEGF on IOP

- Review of data from the IRIS Registry (Intelligent Research In Sight) - 23,262 patients
- 2-3% of all 3 anti-VEGF agents injected cause an IOP rise of >6mm to a new IOP measurement of >21mm
- When given over 25 times, bevacizumab caused this pressure rise in an even higher percentage of patients, up to 9.5%
  - Ranibizumab and aflibercept did not have a similar effect
- Mechanism unknown but transient IOP rise after injections chronically damage TM, vs mechanical blockage with protein and silicone microdroplets

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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

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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

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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,

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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

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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

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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

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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

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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

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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

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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

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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

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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

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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

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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

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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

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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"

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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)

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Investigational Therapy for Wet AMD

- Sustained Released Drugs
  - LADDER – study of 220 patients
  - Using refillable implant w drug reservoir
  - Lasting 4-6 months; reduces treatment burden
  - Lucentis steady dose
  - Reduces possibility of under treatment
  - Offers opportunity to deliver other ocular drugs
  - Phase 2
  - Genentech

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Investigational Therapy for Wet AMD

- CrossMab technology – allows 1 antibody molecule to bind 2 different targets
  - RG7716 bispecific Ang2 inhibitor/Anti-VEGF biologic
  - AVENUE – study of wet AMD
  - STAIRWAY – study of extended dosing in wet AMD
  - BOULEVARD – study of DME Phase 2 / Genentech/Roche
- MAKO Study – topical squalamine lactate 0.2% bid with monthly Ranibizumab (combination) injections vs placebo
- DAWN Study – topical dorzolamide-timolol in combination with anti-VEGF injections for wet AMD

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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

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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

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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

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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

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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)

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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

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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

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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

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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

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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

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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?

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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

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Thank you

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