Developing Treatments for Age-Related Macular Degeneration – A Workshop

Functional Endpoints

David Birch and Karl Csaky

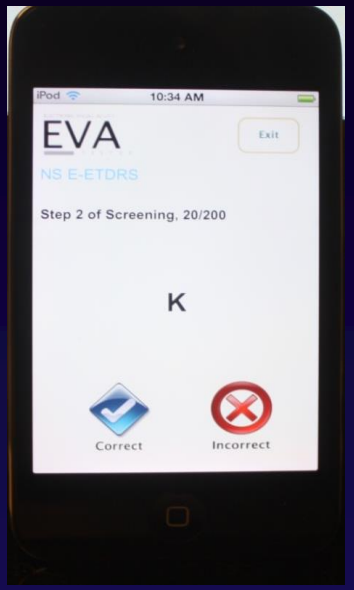
Best-corrected Visual Acuity (BCVA)

- Gold standard
- Related to success in daily activities such as driving and reading
- Long tradition of research
- ETDRS protocol
- Primary outcome measure for most clinical trials in ophthalmology

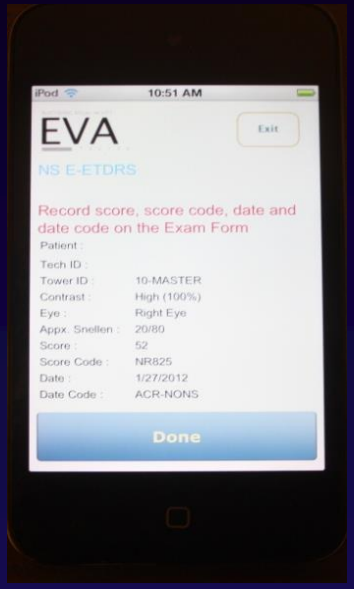
E-ETDRS

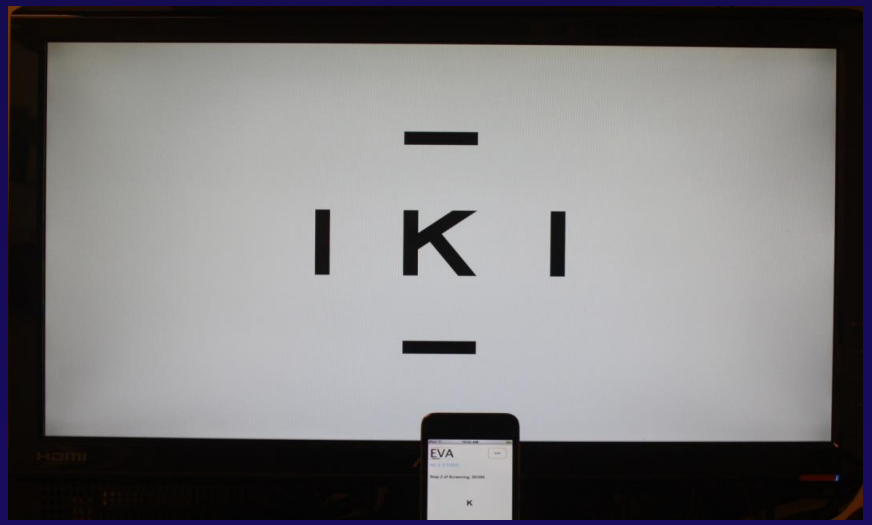
iTouch Screen (choose test)

iTouch Screen (during test)



iTouch Screen (test results)

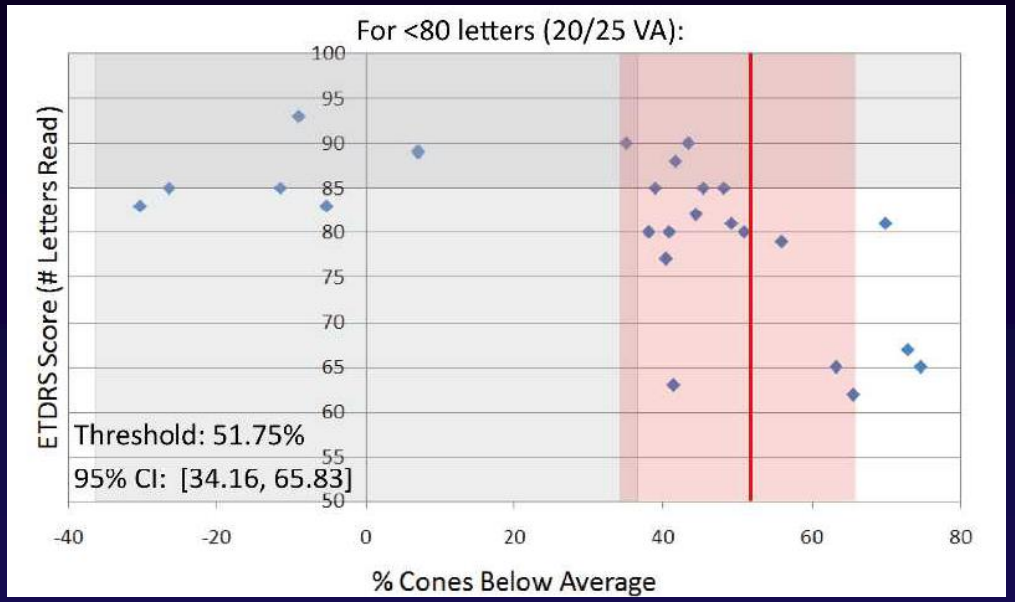




Acuity has become synonymous for “vision”, but…….

Best-corrected Visual Acuity (BCVA)

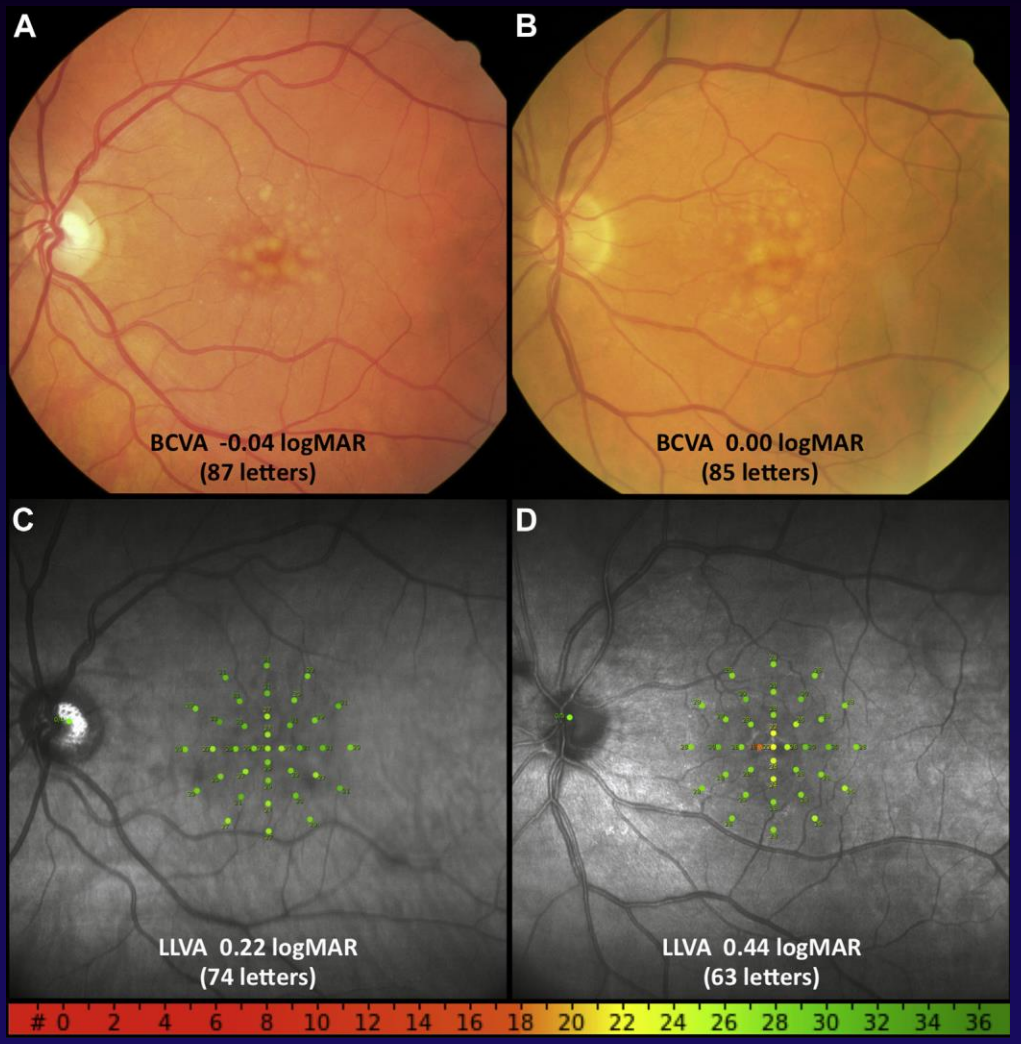
- Depends on a few dozen cones in the foveola
- Shallow relationship between change in VA and changes in quality of life (VFQ-25) unless > 3 line decreases in better eye are included
- Simulations – 88% of sampling elements must be subtracted before affecting high-frequency grating acuity (Geller et al, 1992)



- AOSLO - Visual acuity is preserved despite cone density measures that are 52% below normal (Ratman et al, IOVS 2013)

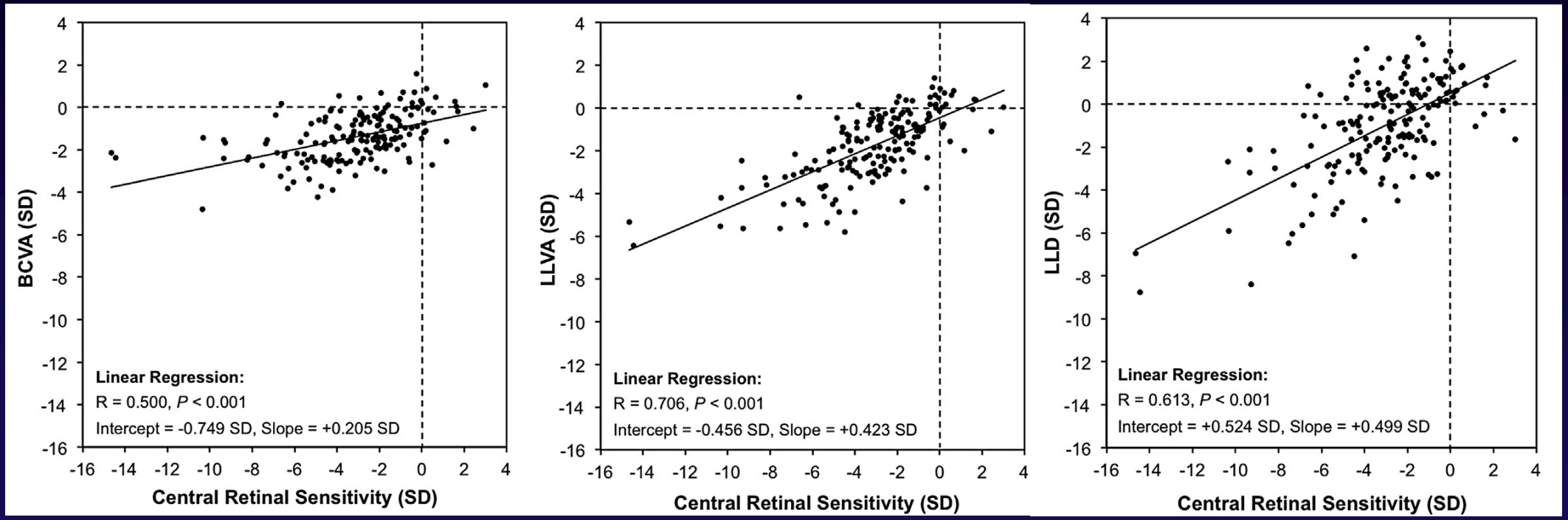
Low-Luminance Visual Acuity (LLVA)

- 2.0 log neutral density filter (Sunness et al, 2008)
- Low luminance deficit (LLD) = BCVA - LLVA
- LLD often greater than normal in intermediate and advanced AMD
- LLD is strong predictor of subsequent loss (Sunness et al, 2008)
- LLD and foveal thresholds closely related



- (Wu et al, Ophthalmol, 2014)

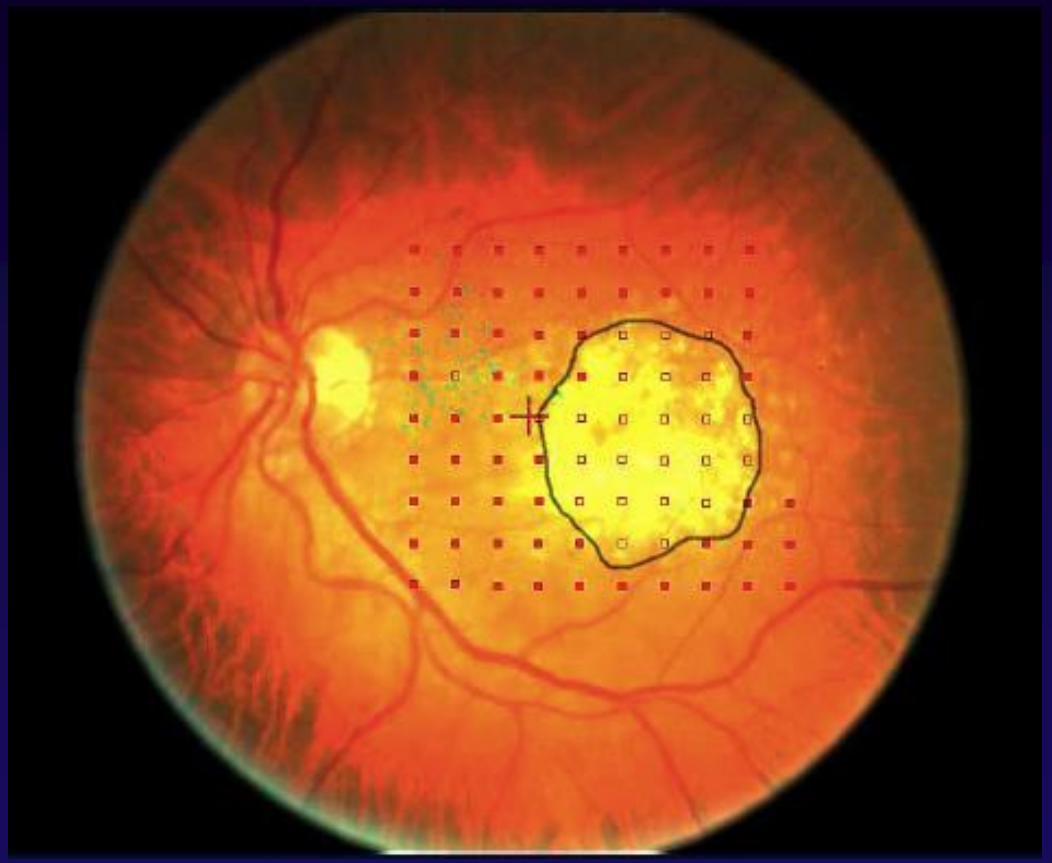
Visual Acuity in AMD



- Deficits on BCVA and LLVA are correlated with deficits in central retinal sensitivity (Wu et al, Ophthalmol, 2014)
- However, microperimetry deficits are greater

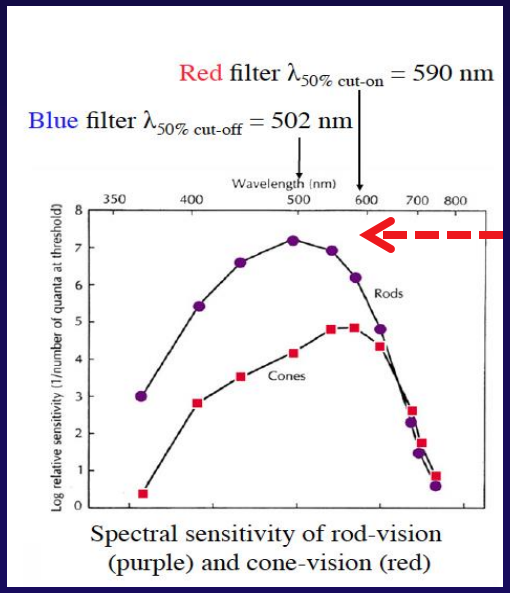
Mesopic microperimetry in GA

- Rodenstock SLO (Sunness et al, 1999)
- Nidek MP-1 or MAIA
- The area of GA is essentially identical with the area of dense scotoma
- Additional cone perimetry unnecessary?

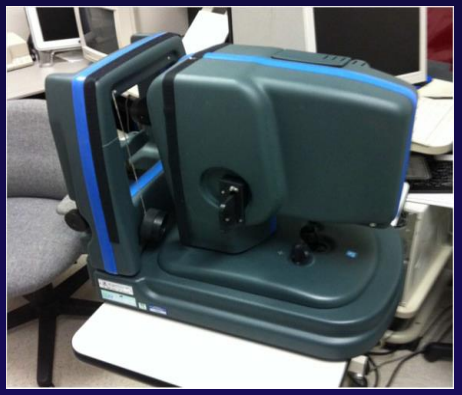


Scotopic microperimetry

- Rod photoreceptors are more sensitive to short-wave (blue) stimuli
- Rod photoreceptors span 50 dB range of sensitivity



Rod Sensitivity



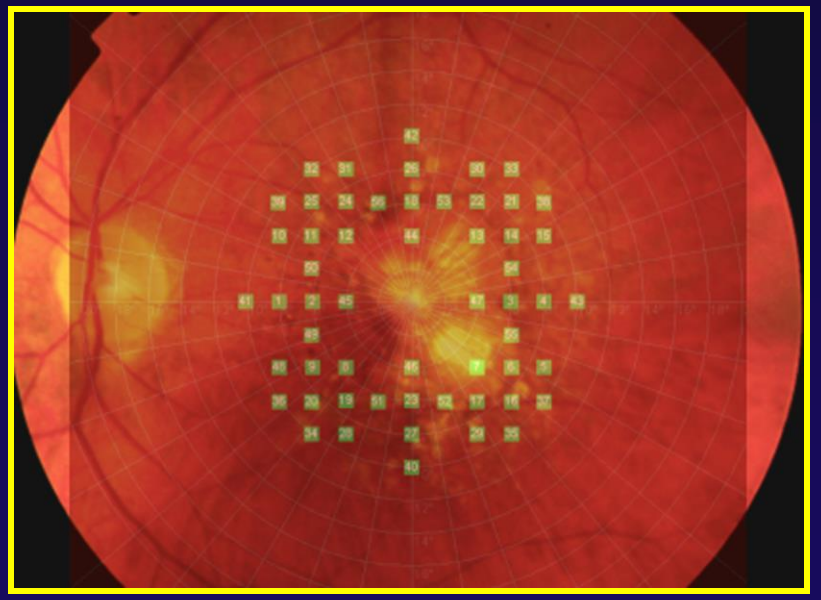
- 2-color microperimetry units can directly quantify rod function

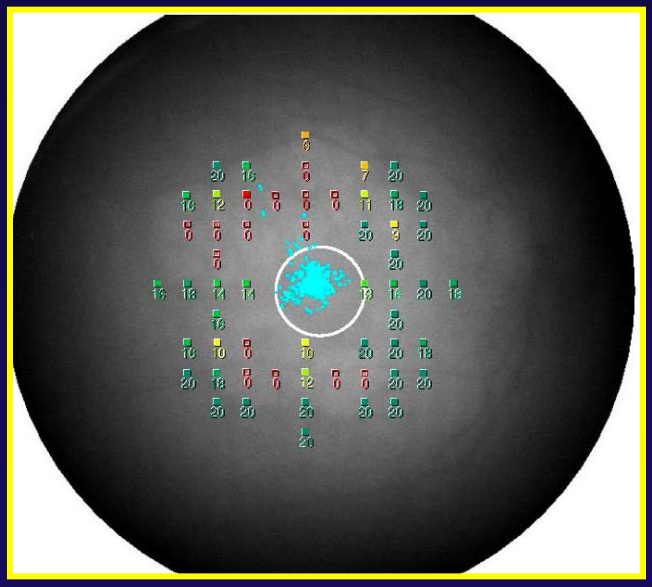
- 30 minutes of dark adaptation – 15 minutes of testing

Scotopic microperimetry

Clinical trial protocol

- assay 56 spots in the perifoveal area
- patient must have adequate fixation / assessed during test
- same locations on the retina are measured between study visits
- rod sensitivity measured over a 50 dB range





Sample Test

Test-retest variability

Group	Mean diff	LOA-	LOA+
All	-1.74	-10.6	+7.2
Normal	-2.33	-10.1	+5.4
Early AMD	-2.49	-11.5	+6.6
Intermediate AMD	-0.50	-9.6	+8.6
GA	-1.33	-10.5	+7.8
4-14dB	-0.69	-7.9	+6.6
14-24dB	-0.28	-8.8	+8.2
24-34dB	-1.49	-9.2	+6.5
34-44dB	-1.72	-7.3	+3.8

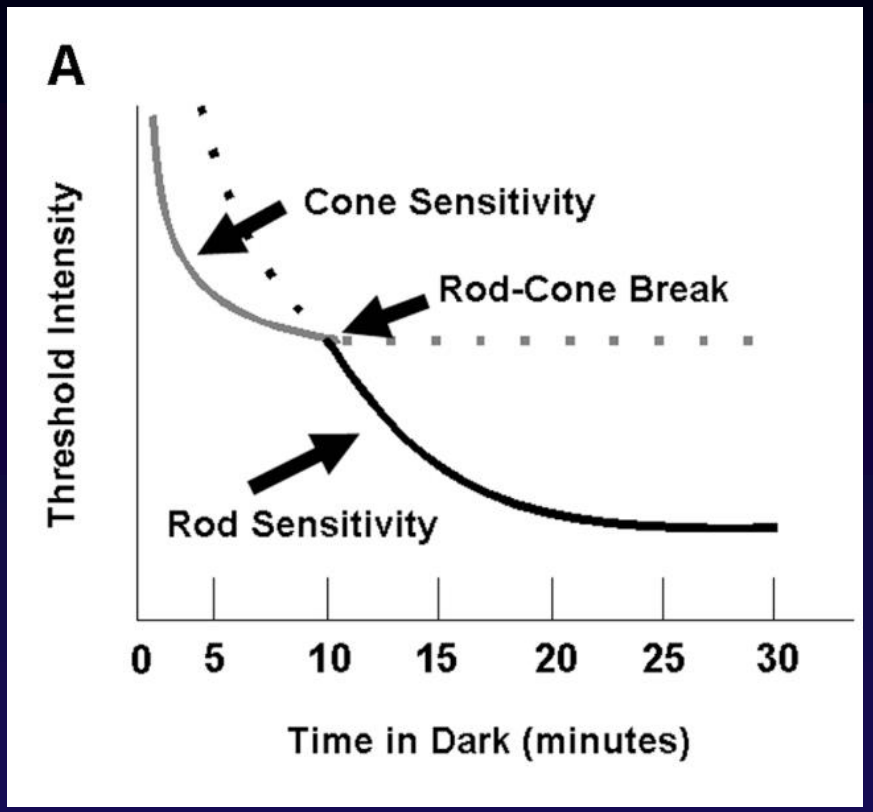
Csaky et al., ARVO, 2012

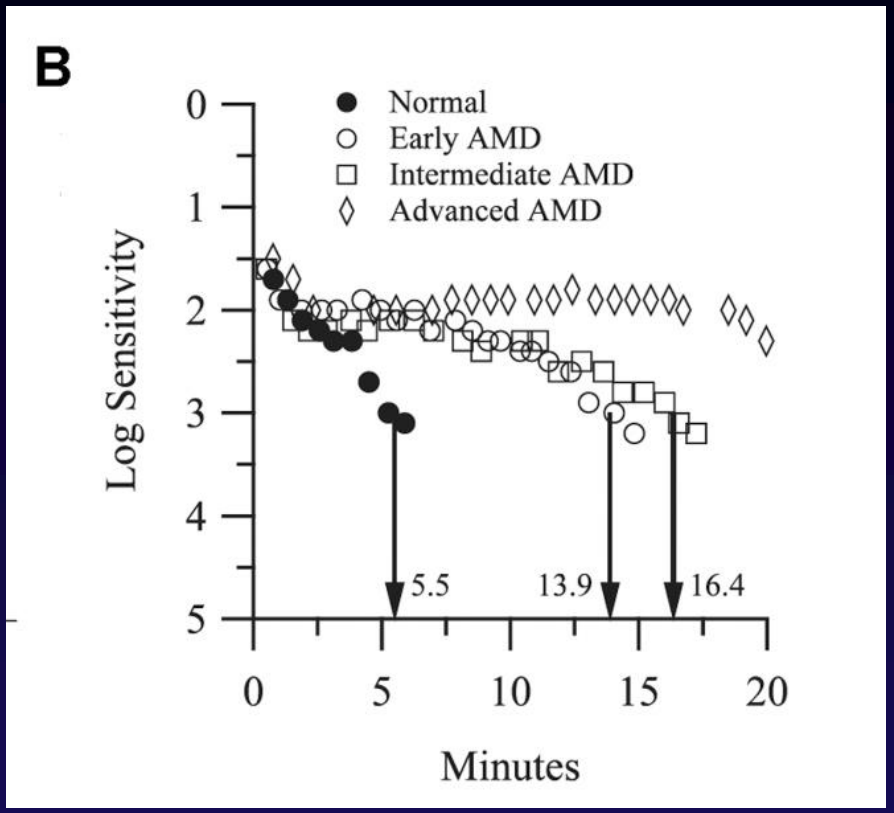
Mean Scotopic Sensitivities in a Clinical Trial

Group	Mean Scotopic Sensitivities ± SD	p Values
Normal Aging Changes	34.1 ± 2.0	NS
Early AMD	33.0 ± 2.6	NS
Intermediate AMD	32.1 ± 3.6	NS
Advanced AMD (GA)	25.6 ± 6.1	P<0.001

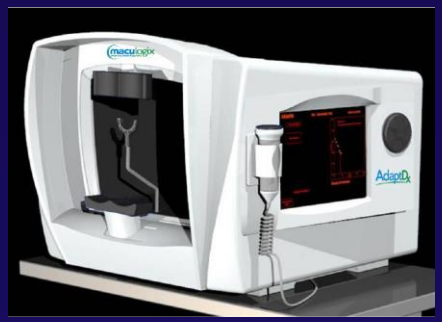
Spot size V Protocol – Detects significant differences in non-GA perifoveal rod sensitivities between advanced and other AMD groups (Csaky et al., ARVO, 2012)

Dark adaptation kinetics





- AdaptDx, MacuLogix, Inc



- Clinical trial protocol in place
- Increased delay in DA with progressively worse AMD (Jackson et al., IOVS, 2014)

Prevalence of Smartphones

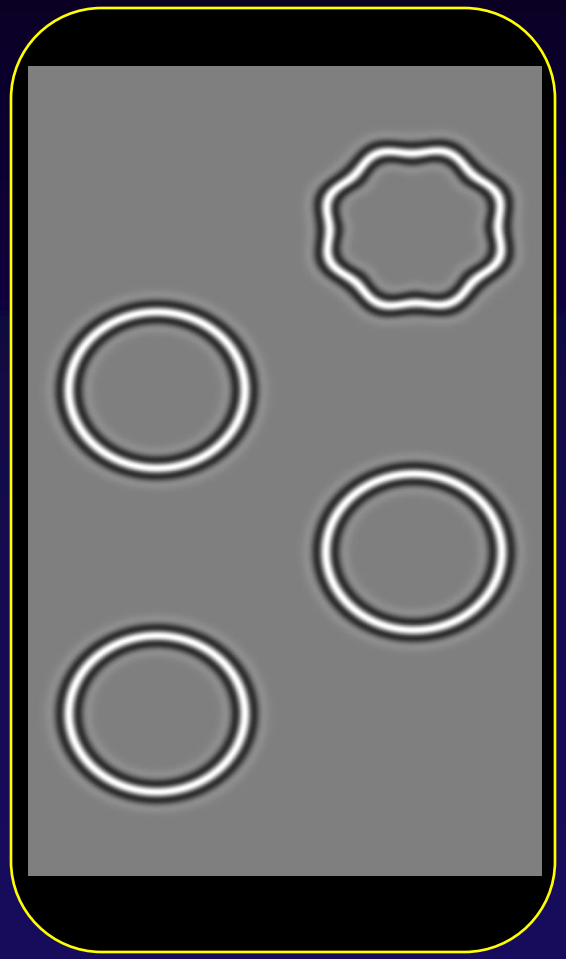
- As of January 2014, the estimated smartphone users worldwide was 1.4 billion. This number will increase to 2.7 billion by the end of 2018
- Over 160 million people in the US are smartphone users in 2014.
- Among US smartphone users:
  - 49% of US adults aged 50-64 years
  - 19% of US adults 65 years and older

SightBook™

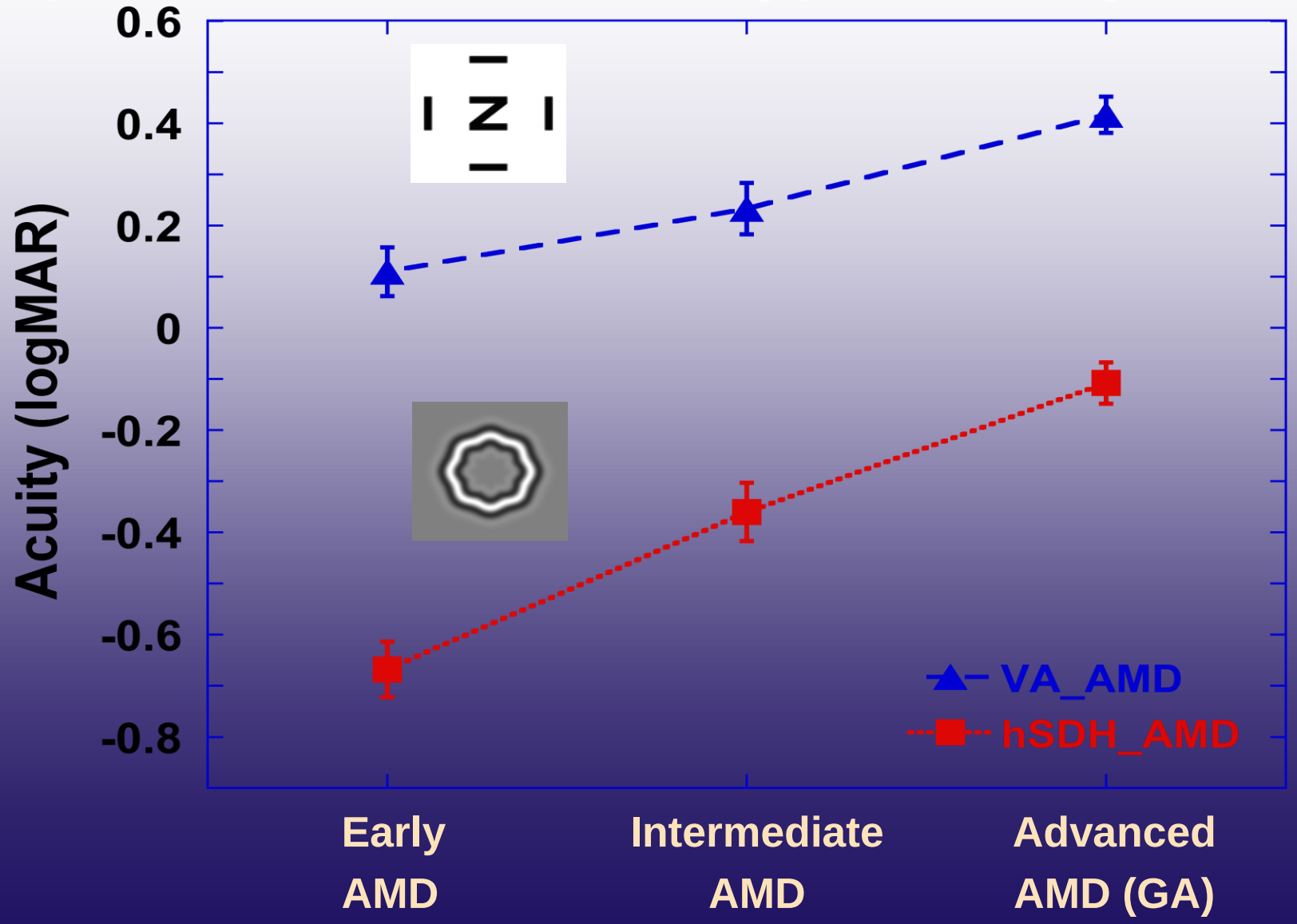
- Used to collect patient visual acuity data

myVisionTrack®

- Uses smooth and distorted circular contour patterns as stimulus
- The circles are laid out at random and the user must differentiate
- 4 - 6 minute test performed twice weekly or at physician’s discretion
- Results are stored on a cloud database for prescribing physician access



Shape discrimination hyperacuity in AMD



Wang et al, IOVS, 2013

Functional endpoints

Clinical trial protocols

- Best-Corrected Visual Acuity
- Low-Luminance Visual Acuity
- Mesopic Microperimetry
- Scotopic Microperimery
- Dark adaptation kinetics
- Shape discrimination

Potential tests

- Contrast sensitivity
  - Pelli-Robson chart
  - Mars CS test
- Color vision
- Foveal flicker sensitivity
- Photostress test
- Preferential hyperacuity perimetry
  - Amsler grid
  - ForeseeHome