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Rod-mediated dark adaptation as a suitable outcome for early and intermediate age-related macular degeneration

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Age-related macular degeneration (AMD) is a leading cause of irreversible central vision loss in older persons worldwide, resulting from loss of photoreceptors, retinal pigment epithelium (RPE), and choriocapillaris endothelium in the setting of characteristic extracellular deposits between visual cells and their blood supply. A major barrier to new treatments targeting progression of early AMD to advanced disease is the lack of valid functional endpoints. Photopic visual acuity is useful in clinical trials of agents targeting neovascularization, yet acuity decreases only minimally or not at all during milder disease. Visual function testing is important for assessing treatment outcomes, because patients gauge treatment success by quality of vision and visual task performance in everyday life, and because disease pathogenesis can be informed by testing specific neurophysiologic processes in the precisely layered retina.

Chen et al[1] provide important new information strengthening the suitability of rod-mediated dark adaptation (RMDA) as an early-to-intermediate AMD outcome measure. Results substantiate prior evidence that intermediate AMD eyes both progressed and exhibited further delay in RMDA over two years[2] and extend the earlier study by demonstrating that RMDA slowing over four years was worse in eyes with severest disease at baseline and at the four-year follow-up. Eyes developing subretinal drusenoid deposits (SDD, originally called reticular pseudodrusen[3]) during follow-up had more precipitous RMDA slowing than eyes lacking these lesions. RMDA deterioration is associated with patient reported difficulties with driving, mobility, and performing tasks under extreme or dim lighting[4–6] as well as emotional distress. Findings collectively document the fundamental responsiveness of RMDA to the natural history of early and intermediate AMD. As the authors discuss[1], good test-retest repeatability is already established for RMDA. What barriers remain to using RMDA as a functional endpoint in AMD trials? The test protocol used in this study[1] and others[7] is 20 minutes in duration, which some might consider long, but it is similar or in some cases even shorter than that for microperimetry. Microperimetry uses an extensive test target grid and requires pre-adaptation to the background light level. Personnel administering the test require appropriate training and certification, as in any test used in trials.

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In human macula, rods outnumber cones.[8] The 6-mm diameter central area (as defined by neurobiology and by the Early Treatment of Diabetic Retinopathy Study grid) contains a cone-dominated fovea surrounded by an annulus of rod-dominated perifovea. In aging, rods in central macula die before cones, and the longest-lasting photoreceptors in advanced AMD are cones. Thus, tests of rod- as well as cone-mediated vision are warranted in assessing macular health, and dynamic measures like RMDA are particularly informative. We previously showed that delayed RMDA in older adults in normal macular health is a risk factor for incipient AMD.[7] RMDA assesses the efficiency of replenishing retinoids (vitamin A derivatives) to rod outer segments, as established by landmark quantitative modeling by T. Lamb and E.N. Pugh, incorporating fundus reflectometry, visual cycle biochemistry, and clinical observations of sensitivity recovery after bleaching light in outer retinal disease. Delayed RMDA indicates dysregulation at one or more of several discrete steps, including: extravasation and uptake of circulating vitamin A complexes through choriocapillaris endothelium; diffusion across or binding to Bruch's membrane; RPE uptake of retinoids; isomerization and/or oxidation of retinol; intracellular transport across RPE; trafficking through the interphotoreceptor matrix; and uptake/loading of 11-cis retinal onto opsin.

To these known contributors to RMDA dynamics, based on Chen et al.'s findings[1] we now also add SDD, which are solid space-filling extracellular deposits between the RPE and photoreceptors revealed by OCT-based imaging within the last decade.[3] SDD are critically positioned to impact photoreceptor health as well as retinoid transfer, because lesions directly contact the affected cells.

Chen et al's results have several levels of significance. For AMD outcome measures, rod-mediated functions continue to merit attention, especially if compared with cone-mediated vision, which also receives retinoids through the Müller glia. For human retinal neurobiology, better understanding of rod-mediated visual neurophysiology will spur new tests of central vision beyond photopic acuity and contrast sensitivity. For AMD pathobiology, SDD's devastating impact on vision is now solidified, adding to strong association with progression to neovascularization and atrophy[3]. Thus, new data from Chen et al, with previous work, helps motivate research on night vision and SDD pathobiology for AMD progress.

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Conflict of Interest statement:

Christine A. Curcio receives research funding from Hoffman LaRoche and Heidelberg Engineering. Cynthia Owsley is a patent holder on an apparatus used to measure dark adaptation and a consultant for Johnson & Johnson Vision and Biophytis.

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