**Title:** Repeatability and Reliability of Flood-Illuminated Adaptive Optics Automated Cone Measurements in Patients with *Retinitis pigmentosa*

**Authors:** Michael J. Gale, BA1, Gareth A. Harman, BS1, Jimmy Chen, BS1, Mark E. Pennesi, MD, PhD1

**Affiliations:**

1Casey Eye Institute, Oregon Health & Science University, 3375 SW Terwilliger Blvd, Portland, OR 97239

**Correspondence:**

Mark Pennesi, MD, PhD

3375 SW Terwilliger Blvd, Portland, OR 97239

Tel: 503-494-8386, Fax: 503-418-2218

pennesim@ohsu.edu

**Abstract**

**Purpose:**

To determine the intersession repeatability of photoreceptor cone measurements via AO imaging in subjects with RP, in order to better differentiate between random variation due to imaging inaccuracies versus pathology-driven change.

**Methods:**

A series of 25 4°x4° macular AO images was acquired three times on the same day in 10 subjects with RP. Each set of 3 corresponding images were registered in I2K Retina and cone photoreceptors were identified using a custom-built MATLAB cone counting algorithm. Nine equally spaced 100μm x 100μm regions of interest (ROIs) were selected for each imaging set, with the central ROI determined from an overlay of the three registered images. A subset of subjectively “poor” and “good” quality images were selected by three independent graders based on the ability to clearly visualize a hexagonal cone mosaic. The repeatability and reliability of the images were evaluated using three main metrics: cone density, cone location similarity, and cone spacing. The images were also compared to age matched normal subjects.

**Results:**

Automated cone counts and absolute cone density values were lower in subjects with RP compared to normals, but similar to density values reported in prior studies (reference? Or listed in future discussion?). The repeatability of cone density metrics were similar between these two groups. Cone location similarity and cone spacing via standard deviation of nearest neighbor distance both demonstrated a statistically significant difference when comparing good-quality images to poor-quality images, regardless of whether the images were acquired in subjects with RP or normals.

**Conclusions:**

Misidentification of cones is a major limitation of automated cone counting algorithms in subjects with RP, especially when attempting to evaluate cone density over large retinal areas. Cone location similarity and cone spacing metrics could be used to help determine image quality and thus increase confidence in automated cone counts in patients with RP.

**Introduction:**

Flood-illuminated adaptive optics (AO) is a high-resolution retinal imaging technique that uses infrared light and finely tuned deformable mirrors to continuously sample imaging waveform distortions in order to counteract the inherent optical aberrations of the human eye. AO has been used to study the cone mosaic in numerous retinal conditions including acquired and inherited retinal disorders, and color deficiencies.1-7 However, the majority of these studies assess a single imaging session for each subject and thus do not provide data about the repeatability or reliability of cone identification via AO imaging. Intersession repeatability of cone density via flood-illuminated AO has been shown to be reliable in healthy subjects8 and while this provides an important reference database, it does not describe the repeatability of AO imaging for individuals with *retinitis pigmentosa* (RP). Qualitative patterns and findings on flood-illuminated AO imaging have been described in subjects with RP9, but there have not been any intersession quantitative studies to date. Recently, there have been studies investigating the repeatability of cone photoreceptor imaging via adaptive optics scanning laser ophthalmoscopes (AO-SLO) in subjects with no pathology as well as various retinal genetic diseases10-15. However, these devices are relatively expensive compared to the rtx1 flood-illuminated AO camera, and are not commercially available. Given that repeatability studies have yet to be performed via flood-illuminated AO in subjects with RP, establishing the reliability in this population may help to improve clinical management through more accurate prognosis, disease monitoring, and assessment of future therapeutic interventions. As AO technology improves, it may provide the ability to track not only global trends in retinal degeneration, but also monitor the health of individual cones in a longitudinal manner. Therefore, the goal of our study is to evaluate the repeatability and reliability of flood-illuminated AO images obtained in patients with RP via intersession cone analysis.

**Methods:**

**Patients:**

This study adhered to the tenets of the Declaration of Helsinki and was approved by the Oregon Health & Sciences University IRB. Prior to enrollment, all patients signed an informed consent after the nature and possible consequences of the study were explained. Ten patients with a clinical diagnosis of RP ranging in age from 22-57 years were recruited for this study (Table 1) and were compared to 11 normal patients from a previous study9 with similar characteristics. Exclusion criteria included patients with significant opacification of the ocular media, subjects with uncontrolled nystagmus, head movement that prevented target fixation, visual acuity of less than 20/50, history of cataract surgery, cystoid macular edema or advanced RP. In summary, we selected for patients with good fixation, media clarity, visual acuity and diverse genetic mutations.

**Image Acquisition:**

Both eyes were dilated with 1% phenylephrine and 2.5% tropicamide prior to each imaging session. For each session, a series of 25 4°x4° images was acquired covering a 12°x12° field of the central macula in both eyes (Figure 1A). Three imaging sessions were performed on each patient on the same clinic visit day, in order to minimize the potential for retinal change due to pathological progression. Retinal eccentricities were determined based on Euclidian distance from the fovea (Figure 1B). After image acquisition, each set of 3 images at each corresponding location were registered with an affine transformation in i2K Retina (DualAlign LLC, Clifton Park, NY, USA) to create a stack (Figure 1C). Images were subsequently pre-filtered, and cone photoreceptors were identified using a custom-built MATLAB cone counting algorithm (MathWorks, Natick, MA, USA) as previously described.8 In short, pre-filtering was accomplished by background subtraction using a moving 11-by-11 moving average filter, and the MATLAB algorithm was used to detect cones by thresholding intensity values of local maxima. Binary cone detection maps were then generated for each image and used to create Voronoi diagrams representing cone density maps. Age-matched normals images from a prior AO repeatability study8 were used for comparison with the RP subjects from this study.

Regions of interest (ROIs) were used to determine cone density variation in images across the three sessions for each fixation point. A grid of nine 100um x 100um ROIs were selected for each imaging set, with the central ROI positioned at the center of the padded stack overlay and the ROIs equally spaced .5 degrees from each other (Figure 1C). ROIs that did not completely lie within the boundary of the three registered images were excluded from analysis (Figure 1D). There were 4,500 total ROIs (10 subjects, 25 image stacks per eye, 9 ROIs per location), out of which 33 ROIs were excluded, all from the same subject. For data analysis, ROIs were grouped based on the Euclidian distance from the fovea of the central ROI at each imaging location. This created five different foveal eccentricity groups, as shown in Figure 1B.

A subset of ROIs ranging from 2 to 4 degrees retinal eccentricity were evaluated for further subgroup analysis based on subjective image quality, which was determined by the ability to clearly visualize a hexagonal cone mosaic. These ROIs avoided regions with major blood vessels, but there were no other exclusion criteria. Three independent graders reviewed a set of training images to establish “good”, “intermediate” and “poor” image quality. Following training, each grader independently reviewed the images and assigned one of the three grades. Images for which there was consensus of “good” and “poor” were included for analysis. When there was disagreement on an image grade, the graders collectively reviewed the image and a group decision was reached. Due to a low number of images graded as “intermediate” and a wide variation in image appearance resulting in reduced inter-grader agreement, this group was not included in the final analysis.

**Cone Density Statistical Methods:**

From each ROI that was included in analysis, average cone density, coefficient of variation, coefficient of repeatability, and repeatability were calculated. Cone densities for each ROI across all 3 sessions were found from the corresponding Voronoi maps and used to calculate average cone density. Coefficient of repeatability was found using an adaptation of the method described by Garrioch et. al15. Within-subject standard deviation of cone density across all sessions for a given ROI was found and converted to coefficient of repeatability using , where SD = standard deviation, n = number of subjects, and m = number of observations for each subject. Using the previous measurements, repeatability was computed as. Repeatability explains the variability in cone density attributable to the methods involved in image acquisition. Here, it is reported in terms of its raw value as well as a percentage of the mean cone density in the given region. In addition, 95% confidence intervals are reported for average cone density, coefficient of variation, coefficient of repeatability, repeatability, and percent repeatability.

**Cone Location Similarity:**

To our knowledge, cone location similarity (CLS) is a new metric which we developed for this paper by registering the binary cone detection maps for each image stack. With our imaging system, average cone width appeared as between four and six pixels (3.13 and 4.69 microns respectively); if any three identified cone locations were within 5 pixels (3.91 microns) of each other across all three imaging sessions, this was considered to be a shared cone location. A visual representation of this process is shown in Figure 2. We considered adjusting for axial length, as this can affect the imaged cone sizes. However, given the inherent heterogeneity in cone luminance and reflectivity, as well as the physiological variation in cone size across retinal eccentricities, we found that axial length adjustments did not significantly impact our CLS measurements. In the final analysis, absolute number of cones and percent shared cones were used to evaluate image reliability between the “poor” and “good” quality image sets.

**Cone Spacing:**

Cone spacing metrics were performed using two-dimensional binary cone identification maps from the “poor” and “good” image sets. Cone spacing was analyzed using nearest-neighbor distance (NND) based on center-to-center spacing of adjacent cones, which is one of the techniques that has been explored and validated by prior studies 4, 10, 16-17. We also explored the standard deviation of NND across these “poor” and “good” 100x100μm ROIs as method to evaluate and compare cone mosaic uniformity.

**Results:**

The repeatability and reliability of adaptive optics images in patients with RP were evaluated using three main metrics: cone density, cone location similarity and cone spacing.

**Cone Density**

The average cone density, average coefficient of variation (CoV) of cone density, repeatability, and percent repeatability are reported in Table 2. Average cone density was inversely correlated to the distance from the fovea and ranged from 16,784 cones/mm2 at 0 degrees to 12,895 cones/mm2 at 5.66 degrees, which are significantly lower than those described in normal subjects using similar methods8. Average CoV between imaging sessions in subjects with RP range from 522 cones/mm2 to 597 cones/mm2 (3.93% to 4.25%), which is similar to findings in normal subjects8. Repeatability ranges from 2,464 cones/mm2 to 3,593 cones/mm2 and percent repeatability ranges from 14.74% to 16.38%, which are all similar to values observed in normal subjects8.

**Cone Location Similarity**

The cone location similarity (CLS) between imaging sessions varied greatly across sub-analysis groups (Table 3). Normals “good” subjects demonstrated an average CLS of 80.54%, while normals “poor” had an average CLS of 40.47%. RP “good” subjects showed an averaged CLS of 76.85%, and RP “poor” had an average CLS of 39.57%. There was a statistically significant difference between the average CLS percentage of the “good”-quality groups versus the “poor”-quality groups (p < 0.01).

**Cone Spacing**

Average cone spacing values for each sub-analysis group ranged from 5.17μm to 5.73μm (Table 3), and did not show any statistically significant difference. The average standard deviation (SD) of cone spacing values for each sub-analysis group were 1.02mm for normals “good”, 1.45mm for normals “poor”, 0.87 for RP “good” and 1.52mm for RP “poor” (Table 3, Figure 3). When comparing sub-analysis groups via one-way ANOVA all groups had a statistically significant difference except for normals “poor” vs RP “poor” (Table 4).

**Discussion:**

Accurate quantitative analysis of cone changes in patients with RP may prove to be a valuable clinical tool by helping to augment the qualitative interpretation of disease progression in clinical patients and therapeutic trials. However, this is a difficult task, as the repeatability of flood-illuminated AO imaging in this patient population is limited by a variety of confounding factors. Our study attempts to quantify the changes in cone density across multiple imaging sessions in order to better delineate between random variations and true pathology-driven loss of cone photoreceptors. Additionally, we explored cone spacing and cone location similarity image analysis techniques and their potential use as objective metrics for image quality assessment.

One of the major challenges in imaging patients with RP is determining objective image quality. Good-quality images with a clearly visible, uniform hexagonal cone mosaic are fairly easy to identify. However, when an image shows blurred or hazy photoreceptors, it is often very difficult to determine whether impaired cone visualization is due to retinal disease affecting reflectance, camera imaging artifact, or some combination thereof. An experienced AO image grader can usually provide accurate and repeatable interpretations of image quality, but this requires a significant amount of subjective interpretation and contextual awareness. Automated cone detection algorithms have been shown to perform very well in high quality images, but they can often misidentify retinal debris and imaging noise as true photoreceptors18. Because automated cone detection is necessary for practical applications of flood-illuminated AO imaging systems, it is crucial to be able to differentiate between a good-quality image and a poor-quality image, in order to achieve confidence in the validity of identified cones. While there have been recent advances in cone detection algorithms and improvements on traditional techniques19-21, this still remains an area of adaptive optics research that requires significant attention.

**Cone Density**

As expected, average cone density was reduced in a topographic fashion in patients with RP when compared to healthy subjects8. Our automated cone density profiles and values are similar to those reported in prior studies evaluating both scanning laser ophthalmoscope (SLO) and flood-illuminated adaptive optics images in subjects with RP22-24. Interestingly, the automated cone density repeatability metrics such as CoV, repeatability and percent repeatability of cone density were similar between patients with RP and normal subjects. However, these findings must be interpreted with caution. The high repeatability in RP patients, in spite of poor image quality, likely results from inherent inaccuracies in the automated cone-identification algorithm especially in areas of poor image quality. These algorithms identify cellular debris and imaging noise as photoreceptors in an inaccurate, but consistent manner. Due to the non-specificity of cone density detection algorithms in differentiating between true and false cones, we evaluated two additional photoreceptor identification metrics to try and improve the accuracy of cone identification.

**Cone Location Similarity**

In the highly organized, wave-guiding structure of a healthy cone photoreceptor mosaic, the location of identified cones should not change from one imaging session to the next. Many prior studies have demonstrated that cones may vary in degree of reflectivity signal due to a variety of factors. Physiological diurnal variations and outer-segment renewal have been shown to affect cone reflectivity25-28. The Stiles-Crawford effect and cone alignment changes can alter incident light angles and create heterogeneity in cone imaging29-32. Although the cone reflectivity profiles are influenced by these factors, the retinal location and spatial orientation has been shown to remain constant33-34. However, there is often more reflectivity variability and artifact in the diseased or dying retina18. This can result in similar intersession cone density values via misidentification of image noise as cones, but the specific cone locations are inconsistent.

While there are some promising novel methods for cone identification20-21, these techniques are not able to take image quality into consideration when performing cone counting, which generates uncertainty in the validity of the identified cones. We subjectively judged a subset of images as “good” or “poor”, and then decided to create and investigate a metric of spatial organization repeatability, called cone location similarity (CLS), to assess how it correlates to image quality. Figure 2 illustrates that intersession CLS is greatly improved in “good” quality images compared to “poor” quality images. Given these findings, CLS may be a very specific metric for grading image quality and helping to differentiate between true photoreceptor signals and imaging noise when utilizing an automated cone-identification algorithm. However, the major limitation with this analysis technique is that it requires repeat images from the same retinal location, which is often not feasible in the clinical setting.

**Cone Spacing**

Another potential AO image analysis tool is standard deviation of cone spacing via NND. In a healthy cone mosaic, the photoreceptors are arranged in a hexagonal matrix for optimal packing efficiency. This creates theoretically uniform cone spacing at a given foveal eccentricity, with increasing inter-photoreceptor distances as foveal eccentricity increases. Therefore, in a healthy photoreceptor mosaic, the standard deviation of cone spacing values should approach zero at a given eccentricity. Additionally, prior studies have shown that AO image cone spacing metrics can be used to differentiate healthy retina from retinal pathology at a given foveal eccentricity, based on an increase in Euclidian distance between neighboring cones due to photoreceptor loss as a result of the disease process4,10. However, these studies only evaluated relatively high-quality images with a clearly visible cone mosaic. In a poor-quality image with artifact and noise, the absolute number of cones identified may remain constant across imaging sessions, but the cone location distribution, and thus inter-cone spacing, is often non-uniform. As shown in Table 3, even though the average distance between cones may be similar between good and poor-quality images, the standard deviation (SD) of cone spacing values can help to further determine image quality. Good-quality images with a clearly visualized cone mosaic have a significantly lower SD of cone spacing when compared to poor-quality images, indicating that this may be another useful metric for determination of image quality.

**Limitations/Future Work**

The biggest limitations to this study are the manner in which we selected patients and the relatively small number of patients imaged. Selective criteria were used to screen for patients with mild to moderate RP, so there were no cases of severe or advanced RP included. However, there was no post-imaging exclusion of patients with lower quality images, so our findings portray an accurate representation of the recruited patient population. Future studies should investigate the feasibility and repeatability of flood-illuminated AO imaging in patients with advanced RP. Additionally, further investigation into standard deviation of cone spacing and cone location similarity as parameters for determining image quality and differentiating healthy retina from areas of pathology is warranted. After adjustment for normal changes in cone density and spacing at various foveal eccentricities, it may be possible to discriminate between organized, healthy cone mosaics and the more random reflectivity patterns and spacing seen in diseased retina. This could also help to provide more information about regional changes throughout the retina and better delineate areas of pathological progression. Furthermore, it may lead to the development of an objective algorithm for assessing image quality and automated cone identification reliability without the need for subjective assessment by an experienced grader.

**Conclusions:**

We found that automated cone density repeatability metrics are similar for subjects with RP compared to normal subjects. However, our confidence in the validity of these cone counts depends on image quality, which is highly variable when imaging the diseased retina via flood-illuminated adaptive optics. While human graders can easily determine image quality via subjective assessment, there is not currently a reliable automated computer algorithm for judging image quality of AO images. We investigated two new metrics as a way to grade image quality: intersession cone location similarity and standard deviation of nearest neighbor distance. By selecting subsets of

**References:**

1. Baraas RC, Carroll J, Gunther KL, et al. Adaptive optics retinal imaging reveals S-cone dystrophy in tritan color-vision deficiency. *Journal of the Optical Society of America. A, Optics, image science, and vision.* May 2007;24(5):1438- 1447.

2. Carroll J, Neitz M, Hofer H, Neitz J, Williams DR. Functional photoreceptor loss revealed with adaptive optics: an alternate cause of color blindness. *Proceedings of the National Academy of Sciences of the United States of America.* Jun 1 2004;101(22):8461-8466.

3. Dees EW, Dubra A, Baraas RC. Variability in parafoveal cone mosaic in normal trichromatic individuals. *Biomedical optics express.* 2011;2(5):1351- 1358.

4. Duncan JL, Zhang Y, Gandhi J, et al. High-resolution imaging with adaptive optics in patients with inherited retinal degeneration. *Investigative ophthalmology & visual science.* Jul 2007;48(7):3283-3291.

5. Hofer H, Singer B, Williams DR. Different sensations from cones with the same photopigment. *Journal of vision.* 2005;5(5):444-454.

6. Roorda A, Williams DR. The arrangement of the three cone classes in the living human eye. *Nature.* Feb 11 1999;397(6719):520-522.

7. Wolfing JI, Chung M, Carroll J, Roorda A, Williams DR. High-resolution retinal imaging of cone-rod dystrophy. *Ophthalmology.* Jun 2006;113(6):1019-1011.

8. Feng S, Gale MJ, Fay JD, Faridi A, Titus HE, Garg AK, Michaels KV, Erker LR, Peters D, Smith TB, Pennesi ME. Repeatability of a Standardized Protocol Using Flood Illuminated Adaptive Optics in the Clinical Setting. Invest Ophthalmol Vis Sci. 2015 Sep 01.

9. Gale MJ, Feng S, Titus HE, Smith TB, Pennesi ME. Interpretation of Flood-Illuminated Adaptive Optics in Subjects with *Retinitis pigmentosa.* Chapter 39, Retinal Degenerative Diseases. Springer International Publishing, Switzerland 2016.

10. Zayit-Soudry S, Sippl-Swezey N, Porco TC, et al. Repeatability of cone spacing measures in eyes with inherited retinal degenerations. Invest Ophthalmol Vis Sci. 2015; 56: 6179–6189.

11. Liu BS, Tarima S, Visotcky A, et al. The reliability of parafoveal cone density measurements. Br J Ophthalmol. 2014; 98: 1126–1131.

12. Abozaid MA, Langlo CS, Dubis AM, Michaelides M, Tarima S, Carroll J. Reliability and Repeatability of Cone Density Measurements in Patients with Congenital Achromatopsia. Adv Exp Med Biol. 2016; 854:277-83.

13. Sun LW, Johnson RD, Langlo CS, Cooper RF, Razeen MM, Russillo MC, Dubra A, Connor TB Jr, Han DP, Pennesi ME, et al. Assessing Photoreceptor Structure in Retinitis Pigmentosa and Usher Syndrome. Invest Ophthalmol Vis Sci. 2016 May 1; 57(6):2428-42.

14. Tanna P, Kasilian M, Strauss R, Tee J, Kalitzeos A, Tarima S, Visotcky A, Dubra A, Carroll J, Michaelides M. Reliability and Repeatability of Cone Density Measurements in Patients with Stargardt Disease and RPGR-Associated Retinopathy. Invest Ophthalmol Vis Sci. 2017 Jul 1; 58(9):3608-3615.

15. Garrioch R., Langlo C., Dubis AM, Cooper RF, Dubra A, Carroll J. Repeatability of in vivo parafoveal cone density and spacing measurements. Optom Vis Sci. 2012 May;89(5):632-43.

16. Giannini D, Lombardo G, Mariotti L, Devaney N, Serrao S, Lombardo M. Reliability and Agreement Between Metrics of Cone Spacing in Adaptive Optics Images of the Human Retinal Photoreceptor Mosaic. Investigative Ophthalmology & Visual Science June 2017, Vol.58, 3127-3137.

17. Muthiah MN, Gias C, Chen FK, Zhong J, McClelland Z, Sallo FB, Peto T, Coffey PJ, da Cruz L. Cone photoreceptor definition on adaptive optics retinal imaging. Br J Ophthalmol. 2014 Aug;98(8):1073-9.

18. Gale MJ, Feng S, Titus HE, Smith TB, Pennesi ME. Interpretation of Flood-Illuminated Adaptive Optics in Subjects with Retinitis pigmentosa. Advances in Experimental Medicine and Biology (vol. 854). Springer New York LLC. 2016 Oct 1.

19. Li KY, Roorda A. Automated identification of cone photoreceptors in adaptive optics retinal images. J Opt Soc AM A Opt Image Sci Vis. 2007 May;24(5):1358-63.

20. Cunefare D, Fang L, Cooper RF, Dubra A, Carroll J, Farsiu S. Open source software for automatic detection of cone photoreceptors in adaptive opticsophthalmoscopy using convolutional neural networks. Sci Rep. 2017 Jul 26;7(1):6620.

21. Liu J, Jung H, Dubra A, Tam J. Automated photoreceptor cell identification on nonconfocal adaptive optics images using multiscale circular voting. Invest Ophthalmol Vis Sci. 2017 Sep 1;58(11):4477-4489.

22. Makiyama Y, Ooto S, Hangai N, Takayama K, Uji A, Oishi A, Ogino K, Nakagawa S, Yoshimura N. Macular Cone Abnormalities in Retinitis Pigmentosa with Preserved Central Vision Using Adaptive Optics Scanning Laser Ophthalmoscopy. PLoS One. 2013; 8(11): e79447.

23. Sun LW, Johnson RD, Langlo CS, Cooper RF, Razeen MM, Russillo MC, Dubra A, Connor TB, Han DP, Pennesi ME, Kay CN, Weinberg DV, Stepien KE, Carroll J. Assessing Photoreceptor Structure in Retinitis Pigmentosa and Usher Syndrome. Invest Ophthalmol Vis Sci. 2016 May; 57(6): 2428–2442.

24.Tojo N, Nakamura T, Fuchizawa C, Oiwake T, Hayashi A. Adaptive optics fundus images of cone photoreceptors in the macula of patients with retinitis pigmentosa. Clin Ophthalmol. 2013; 7: 203–210.

25. Pallikaris A, Williams DR, Hofer H. The reflectance of single cones in the living human eye. Invest. Ophthalmol. Vis. Sci. 2003, 44, 4580–4592.

26. Jonnal R, Besecker J, Derby J, Kocaoglu O, Cense B, Gao W, Wang Q, Miller D. Imaging outer segment renewal in living human cone photoreceptors. Opt. Express 2010. 18, 5257–5270.

27. Cooper RF, Dubis AM, Pavaskar A, Rha J, Dubra A, Carroll J. Spatial and temporal variation of rod photoreceptor reflectance in the human retina. Biomed. Opt. Express 2011, 2, 2577–2589.

28. Pircher M, Kroisamer J, Felberer F, Sattmann H, Götzinger E, Hitzenberger C. Temporal changes of human cone photoreceptors observed in vivo with SLO/OCT. Biomed. Opt. Express 2011, 2, 100–112.

29. Roorda A, Williams DR. Optical fiber properties of individual human cones. J. Vis., 2002. 2, 404–412.

30. Gao W, Cense B, Zhang Y, Jonnal RS, Miller DT. Measuring retinal contributions to the optical Stiles-Crawford effect with optical coherence tomography. Opt. Express, 2008. 16, 6486–6501.

31. Miloudi C, Rossant F, Bloch I, Chaumette C, Leseigneur A, Sahel JA, Meimon S, Mrejen S, Paques M. The Negative Cone Mosaic: A New Manifestation of the Optical Stiles-Crawford Effect in Normal Eyes. Invest Ophthalmol Vis Sci. 2015 Nov;56(12):7043-50

32. Morris HJ, Blanco L, Codona JL, Li SL, Choi SS, Doble N. Directionality of individual cone photoreceptors in the parafoveal region. Vision Res. 2015 Dec;117:67-80

33. Mariotti L, Devaney N, Lombardo G, Lombardo M. Understanding the changes of cone reflectance in adaptive optics flood illumination retinal images over three years. Biomed Opt Express. 2016 Jul 1; 7(7): 2807–2822.

34. Godara P, Cooper RF, Sergouniotis PI, Diederichs MA, Streb MR, Genead MA, McAnany JJ, Webster AR, Moore AT, Dubis AM, Neitz M, Dubra A, Stone EM, Fishman GA, Han DP, Michaelides M, Carroll J. Assessing retinal structure in complete congenital stationary night blindness and oguchi disease. Am. J. Ophthalmol. 2012, 154, 987–1001.