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REPLY: We thank Sacconi et al for their interest in our publication.[1] In 2016, Querques et al[2] termed hyporeflective spaces in the choroid of patients with geographic atrophy secondary to age-related macular degeneration using OCT choroidal caverns. Our 2018 publication included 2 studies. First, in 41 eyes of 28 patients from 2 retina clinics (New York and Milan), we defined multimodal imaging of eyes with caverns, expanding the original OCT description to include posterior hyperreflective tails and localization to healthy eyes and disease entities beyond geographic atrophy. Second, in a large series of donor eyes, we reinvestigated the 1966 pathology report of Friedman and Smith,[3] who described lipid globules (extracellular depots of lipid) without signs of inflammation in autopsy eyes thought to be normal. On the basis of demographics, tissue localization, prevalence, size, and optical properties, we hypothesized that lipid globules were candidate histologic correlates for caverns. Sacconi et al raise 2 issues that we address herein.

First is the angiographic characteristics of caverns, which drive a line of reasoning about cavern appearance in myopia and other conditions. Sacconi et al rightfully state that indocyanine green angiography (ICGA) involving a hydrophilic dye should not stain caverns, which should be hydrophobic if the globule hypothesis is correct. To support this idea, they cite a recent independent study by Sakurada et al[4] as demonstrating late hyperfluorescence of caverns in ICGA. We interpret the findings of Sakurada et al[4] differently. These authors investigated the presence, distribution, and size of caverns in 21 eyes of 11 patients with choroidal vascular hyperpermeability (CVH) as visualized with ICGA in patients with several pachychoroid disease spectrum disorders. Choroidal caverns were indeed identified by Sakurada et al[4] in areas of CVH, but the caverns themselves were not hyperfluorescent. In fact, the larger caverns were hypofluorescent relative to the surrounding tissue, as seen with a cavern superior to the optic nerve in Fig 2A of their publication.[4] Also, because areas of CVH are much larger than caverns, most of the hyperfluorescent CVH cannot be attributed to the caverns themselves. In late phase ICGA images, diffuse staining of choroidal tissue surrounding small, nonfluorescent caverns makes it difficult to detect caverns. Nevertheless, sometimes caverns can be localized to small areas of relative hypofluorescence, just like the hypofluorescent silhouettes of pachyvessels seen after most of the indocyanine green dye has cleared from the systemic circulation.

Second, Sacconi et al state that our conclusion was speculative owing to the lack of direct clinicopathologic correlation of the study eyes. We agree that clinicopathologic correlation will provide the most direct evidence linking caverns and globules. Because we found en face OCT to be the most efficient way to identify caverns in vivo, premortem OCT angiography imaging, which can yield clear en face reconstructions, would be ideal. For this reason, 2 of us (K.B.F. and C.A.C.) established in 2011, in collaboration with The Eye-Bank for Sight Restoration (New York), an advanced directive registry of patients of Vitreous Retina Macula Consultants of New York, where one of us (K.B.F.) practices. The patient eyes recovered to date, although limited in number, have enabled the validation of several commonly observed OCT signatures in age-related macular degeneration. We are confident that long-term commitment to encouraging patient registration and fostering regular communication among the practice, patient families, eye bank, and research laboratory will eventually yield a case that answers the important questions raised by Sacconi et al. Clinical centers elsewhere may wish to consider similar programs. We remind readers that the 139 histology study eyes in the study by Dolz-Marco et al[2] were accessioned over a 14-year course of screening undocumented donor eyes from the Alabama Eye Bank. Federal and foundation support allowed the processing, systematic review, analysis, and online posting of histologic data.

Modern multimodal imaging can be thought of as clinical microscopy. Like all good microscopy studies, a hypothesis to drive image capture can lead to new insights and hypothesis refinement for future study. We suggest that clinical observations based on multimodal imaging of well-defined patient groups will test the hypotheses posed in our publication[1] and enhance our understanding of cavern significance while new tissue resources become available.

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Re: Hwang et al.: Distinguishing highly asymmetric keratoconus eyes using combined Scheimpflug and spectral-domain OCT analysis (*Ophthalmology*. 2018;125:1862-1871)

TO THE EDITOR: We commend Hwang et al[1] for their article, and also praise the elegant commentary from Klyce on the applications of artificial intelligence (AI) to improve keratoconus screening and medical decisions in virtually every aspect of medicine. We agree that consciously integrating clinical parameters from different imaging devices using AI techniques is fundamental to augment accuracy on ectasia diagnosis. Nonetheless, we respectfully have germane remarks and suggestions.

The retrospective case-control study[1] included 30 so-called normal fellow eyes from patients presenting with very asymmetric ectasia (VAE). The fellow eyes from these patients had definitive evidence of ectatic corneal disease, whereas the eyes that entered in the study had normal corrected visual acuity and had "no definitive abnormalities on corneal imaging."[1] However, in reviewing the supplemental maps, we are concerned that the color scales and scaling are inconsistent, and that abnormal posterior elevations are noted in at least one-third of the patients (i.e., patients 3, 5, 7, 8, 9, 12, 21, 27, and 29). Interestingly, there is a significant variability on the subjective interpretations of color-coded maps, which is aggravated by changing scales.[2] Thereby, we recommend consistent scales and using objective criteria for defining normality on corneal imaging.[3] We also suggest including OCT maps in the supplemental online material.[1]

There is a minor oversight statement in the abstract that no individual metric yielded an area under the receiver operating characteristic curve (AUC) of >0.75. The data presented in Table 1 show the Belin-Ambrósio deviation value (BAD-D) was the parameter with the highest AUC of 0.754 (95% confidence interval [CI], 0.64−0.86). Nevertheless, we agree this represents a low accuracy. The relatively low cutoff value of 1.01 used in the study detected correctly 80% of the asymmetric cases, but resulted in 33.3% false positives.[1] Indeed, these data support the unquestionable need to improve the detection of susceptible cases for progressive iatrogenic ectasia (keratectasia). This has been a major area of interest from our group, including corneal biomechanics,[3] and also further improving algorithms based on tomographic data.[4]

In a series of 94 eyes with normal topography from patients with VAE,[3] we found a similar accuracy for the BAD-D in distinguishing VAE with normal topography cases from 1 eye randomly selected from 480 patients with normal corneas. The BAD-D had an AUC of 0.84 (95% CI, 0.79−0.88), a sensitivity of 80.43%, and a specificity of 71.61%, with 1.08 as the cut-off. Interestingly, the Pentacam random Forest index (PRFI), a novel AI-derived parameter developed in a multicenter case-control study (including the preoperative of post-LASIK ectasia),[4] had an AUC of 0.98 (95% CI, 0.96−0.99), with a sensitivity of 92.39%, a specificity of 93.86%, and 0.12 as the cut-off.

Considering the accuracy for detecting clinical ectasia cases in this study, composed of 1 eye randomly selected from 204 patients with keratoconus and by the 72 nonoperated ectatic eyes from the VAE patients,[3] the BAD-D had an AUC of 0.99 (95% CI, 0.99−1.00), a sensitivity of 98.16%, a specificity of 99.15%, with a cut-off of 1.97. The PRFI had a virtually perfect AUC of 1.0, with 0.50 as the cut-off.

Adding the PRFI data,[4] and other parameters from spectral-domain OCT, such as the pattern standard deviation of the epithelial thickness[5] may augment the scientific value of this paper.

We are afraid that, considering the low number of cases in the study and the relative limitation of logistic regression analysis, there is not enough strength to determine the relevance from any parameter when more advanced AI functions are to be used. This is the case of posterior corneal surface metrics, which indeed entered in the random forest algorithm of the PRFI.[4]

Nevertheless, our main concern is the lack of cross-validation for the logistic regression,[1] leading to a fatal risk of overfitting. In