intraretinal cystic changes, and subretinal hyperreflective deposits.[4]

There were no comparative data referring to the baseline renal function, the level of endogenous and exogenous corticosteroids, the personality type of the patients, and the testing of patients with regard to *Helicobacter pylori* infection in patients of the study groups.

The authors of this study found that a thick baseline choroid (>515 μm) was the only predictive factor associated with treatment response in the multivariate analysis. Importantly, using the enhanced depth imaging OCT model the choroidal thickness measurements can be limited in cases of severe subretinal detachment, where the underlying chorioscleral interface may become obscured, resulting in a selection bias toward eyes with less severe disease. Moreover, eyes with a thinner choroid at baseline may not undergo additional thinning owing to a "floor effect."[5]

Altogether, the validation, extrapolation, and generalizability of the authors' conclusions can be made only by statistical analyses including all the missing baseline potential predictive factors mentioned by us in addition to the baseline characteristics already assessed in this study, which serve as potential prognosticators influencing functional and anatomic improvements.

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FUNDING/SUPPORT: NO FUNDING OR GRANT SUPPORT. Financial Disclosures: The following authors have no financial disclosures: Dan Călugăru and Mihai Călugăru. The authors attest that they meet the current ICMJE criteria for authorship.

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Serum Angiotensin-Converting Enzyme Has a High Negative Predictive Value in the Investigation for Systemic Sarcoidosis

EDITOR:

NIEDERER AND ASSOCIATES[1] CONCLUDED THAT ADDITIONAL screening tests for sarcoidosis-associated uveitis are not necessary in patients with normal serum angiotensin-converting enzyme (ACE), though the authors subsequently add that further testing in patients with ACE within the normal limits might be of value only when clinical suspicion is high. We would like to discuss some aspects regarding the interpretation of their results, specifically the high negative predictive value (NPV) of serum ACE, by comparison to our previous work on the same subject.

Firstly, the pretest probability (often the prevalence of the specific disease) is important in the interpretation of predictive values. Sarcoidosis has a prevalence ranging from 10% to 15% in the uveitis population (see also Supplementary Table 1).[2] The lower NPVs in previous studies can be due to testing in a population with higher sarcoidosis prevalence (eg, pretest probability) (see Supplementary Table 2). Secondly, the cut-off value that is chosen for the test may change the NPV. In Niederer's study, the cut-off was lower compared to ours, creating a higher sensitivity (while the prevalence of sarcoidosis in the population remains stable), raising the NPV (Supplementary Tables 1 and 2). Another important aspect is the influence of race on ACE levels. Previous research has shown that in the sarcoidosis-associated uveitis population, mean ACE values are higher for African Americans compared to whites.[3] In a uveitis population with higher proportion of black patients the sensitivity will be higher, increasing the NPV.

In conclusion, the prevalence of sarcoidosis in the population, the cut-off value for ACE, and the proportion of black patients in the specific population influence the diagnostic value of ACE. In populations with a higher prevalence of sarcoidosis and lower proportion of black patients and in centers using a higher cut-off, the NPV will be lower. In these settings, further screening tests in patients with normal results of ACE remain useful.

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FUNDING/SUPPORT: FAHRIYE GROEN-HAKAN WAS IN PART financially supported by AbbVie, the Netherlands. The sponsor had no role in the content of this letter. Financial Disclosures: The following authors have no financial disclosures: Fahriye Groen-Hakan and Laura Eurelings. The authors attest that they meet the current ICMJE criteria for authorship.

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Serum Angiotensin-Converting Enzyme Has a High Negative Predictive Value in the Investigation for Systemic Sarcoidosis

REPLY

WE THANK DR GROEN AND DR EURELINGS FOR THEIR INTEREST in our recent publication[1] and for the opportunity to discuss screening investigations for systemic sarcoidosis in further detail.

Undifferentiated uveitis is a common presentation to general ophthalmology clinics, and screening for systemic disease is of value to help refine treatment strategies, to give prognostic information to the patient, and to identify and manage any systemic complications. In screening for sarcoidosis, the most valuable assessment is the history and clinical examination. However, investigations also play a role, in particular serum angiotensin-converting enzyme (ACE), lymphocyte count, lung imaging (chest radiograph and/or computed tomography chest), and biopsy.[2,3]

We agree that sensitivity and specificity will vary depending on the cut-off used. AUC provides a useful comparison in test results where a range of cut-offs have been used. We reported positive and negative predictive value, along with the prevalence of sarcoidosis in our population, as these are commonly understood values used by clinicians. Positive and negative predictive value are influenced by the prevalence of disease within the population, and thus a more accurate portrayal would be to report positive and negative likelihood ratios to compare pretest and posttest likelihood of sarcoidosis.[4] For our sample, a negative serum ACE gives a likelihood ratio of 0.24, meaning that, for a given pretest likelihood, the chance of having sarcoidosis decreased by around a quarter in the presence of a negative serum ACE. For those with a low pretest likelihood, this would obviate further testing. In contrast, an elevated serum ACE has a likelihood ratio of 7.81, meaning that the chance that this subject has sarcoidosis is almost 8 times higher than the pretest likelihood.

For those with a high pretest likelihood of sarcoidosis, we recommend further testing as directed by the clinical history and examination.

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CONFLICT OF INTEREST DISCLOSURES: SEE THE ORIGINAL article for any disclosures of the authors.

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