A Comparison of Home and Conventional Optical Coherence Tomography Technology: Results of the EVOKON Study

ABSTRACT

Purpose:

The existing treatment guidelines for many macular diseases stress the conduct of frequent monitoring using optical coherence tomography (OCT). However, the burden of persistent disease control leads to low rates of therapy adherence in real life. OCT home monitoring, using a novel off-axis full-field OCT approach, is potentially inexpensive and involves the use of a self-operable device. In this pilot study, we assessed the sensitivity and specificity of patients self-operating an OCT device to drive an anti-vascular endothelial growth factor (VEGF) treatment decision using a clinical prototype (Home-OCT).

Methods:

A total of 47 patients with different macular diseases, most commonly including diseases such as age-related macular degeneration (89%) and diabetic macular edema (3%), were recruited in a cross-sectional study. Study participants participated in a short training course on device usage and then performed multiple self-scans with the Home-OCT device. For comparison, scans using a standard clinical spectral-domain OCT system were also taken.

Results:

Following the brief training session, the study participants could successfully acquire images that were clinically gradable for 85% of the included eyes without further assistance. The sensitivity and specificity values for an anti-VEGF treatment decision were 0.94 and 0.95.

Conclusions:

Home-OCT was used successfully for retinal self-examination; it demonstrated good sensitivity and specificity values for making anti-VEGF treatment decisions.

DECLARATIONS

Funding: This work was supported by the German Federal Ministry of Education and Research (BMBF) (grant no. 13N13766).

Ethics approval: The study was approved by the Ethics Committee of the Medical Faculty of the Christian Albrechts University in Kiel, Germany.

Consent to participate: All patients signed an informed consent form prior to entering the trial.

The EVOKON trial was registered in the German Trial Register under the number DRKS00013755 on March 14, 2018.

INTRODUCTION

Optical coherence tomography (OCT) is considered to be the current standard retinal imaging modality. Given its noninvasive, fast, and easy application, OCT imaging can be repeated infinitely and often. Moreover, OCT imaging boasts high resolution and good contrast of the retinal layers, making it the most sensitive means of detecting disease activity in many retinal diseases (1) and outperforming the consideration of subjective visual function deterioration (2,3).

The three most common retinal diseases—age-related macular degeneration (AMD), diabetic macular edema (DME), and retinal vein occlusion (RVO)—can be effectively treated with intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) antibodies (4–6). These treatments must be repeated frequently because of recurring disease activity (7). However, it has been shown that the treatment interval can be individualized with the help of frequent OCT imaging, enabling these patients to still attain outcomes comparable to those of patients on a fixed monthly dosing schedule (8). The introduction of OCT-guided therapy in this context has since become the worldwide standard of care and has saved billions of dollars (9).

Since frequent OCT imaging is a key driving factor in attaining the best treatment results (10), frequent office visits are required. The development of home-based OCT diagnostics could reduce the number of required office visits, lower the disease burden, improve rates of therapy adherence, and possibly enhance the overall treatment outcome. However, current clinical OCT technology is not suited for use in the home because the systems are too expensive, too large, and do not allow for the performance of a self-examination by the patient.

Therefore, we herein propose a novel, compact, and low-cost OCT system (Home-OCT). This device is based on a novel full-field OCT (11) technology that was designed to reduce device complexity, lessen component costs, and facilitate patient self-examination. The proposed device sequentially acquires single-shot en-face images of the retina; with this approach, in about one second, a whole volume scan of the central retina can be acquired.

Here, we present the clinical data collected using the first Home-OCT prototype, which was built as a table-top device that allows the patients to perform retinal self-scans without assistance by medical personnel. We determined the percentage of patients who could complete the procedure and the accuracy of potential treatment decisions made using information gleaned from the acquired images.

MATERIALS AND METHODS

Technical description of the Home-OCT prototype

The prototype of our Home-OCT system relies on the principles of off-axis full-field time-domain OCT, which is described in detail by Sudkamp et al. (11). In short, this design adopts an extended-illumination approach of the retina by generating a parallel beam from a superluminescent diode with an 841-nm central wavelength and a 26-nm spectral bandwidth. The retina is imaged using a CMOS camera, where it interferes with light from a slightly tilted reference beam. Because of the short coherence length of the light source, only light from a certain depth forms an interference pattern; this interference pattern is then converted into an en-face image of the retina at that distinctive depth. Through stepwise alterations of the length of the reference arm, the complete retina volume is imaged within a time frame of about one second. This eliminates the necessity of

conducting lateral scanning and of involving other expensive components such as spectrometers or tunable light sources. The system is characterized by its technical simplicity and cost efficiency. Figure 1 shows the clinical prototype used in this study.

In contrast with current OCT systems, the investigated Home-OCT device enables the conduct of unassisted OCT self-examinations. To achieve correct alignment, the patient must position the fixation target at the center of the illuminated part of the retina, which appears to the patient as a red circular area. This creates a “keyhole” effect and automatically guides the patient into the correct position. Notably, scanning OCT systems would require additional optics to achieve a similar effect supporting self-alignment, which would further increase the overall cost, device size, and complexity.

The investigated Home-OCT prototype records a densely sampled volumetric retina scan of 3.0 × 1.8 mm with an axial resolution of 12 µm and a lateral resolution of approximately 8 µm depending on the size of the pupil of the eye.

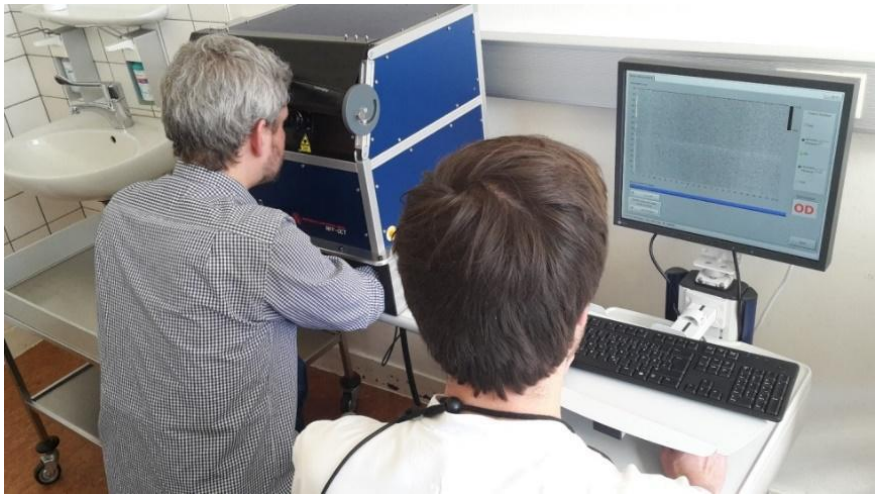

Figure 1: The clinical Home-OCT prototype used for data acquisition within the study.

Study protocol

In a prospective clinical study (registered as DRKS00013755 in the German Clinical Trials Register; European Database on Medical Devices no. CIV-17-12-022384), 47 patients with retinal diseases were recruited to complete a retinal self-scan using the OCT prototype in addition to their routine clinical examination. This study was conducted in accordance with the German Medical Devices Act and the Declaration of Helsinki. Inclusion criteria (older than 18 years with a need to undergo macular examination, including OCT imaging) were deliberately kept broad in this pilot trial. However, we mainly recruited consecutive AMD patients to test the device in the intended target group. One eye per patient was selected as the study eye; however, if both eyes fulfilled the inclusion criteria, then both eyes were evaluated in this paper. The main exclusion criteria were pregnancy, significant opacities in the optical media, and ametropia of greater than 3 diopters. We further excluded patients with visual acuity of less than 0.1 in the study eye or obvious difficulty with achieving steady head positioning. No further preselection of patients (such as fixation testing or geographic atrophy assessment) was undertaken so as to minimize the inclusion bias.

After giving informed consent, the included patients underwent the assessment of best-corrected visual acuity (BCVA) and intraocular pressure (IOP) and a complete examination of the anterior eye segment. The patients were then introduced to the usage of the Home-OCT system completed by

way of an oral introduction provided by the examiner, which lasted approximately for 5 minutes. No further training documents or videos were shown.

To make use of the system, the patient had to look into the eyepiece mounted on the device. An adjustable headrest could be adopted for comfortable head positioning during and between measurements. Within the eyepiece, a small, green fixation target was presented to guide the patient's eye into correct alignment. Diopter adjustment, if necessary, was performed in postprocessing after data acquisition. Once the patients had properly adjusted themselves, they initiated the measurement by pushing a handheld trigger button. During the measurement process, the patients could observe the green fixation target superimposed onto the red illumination of the retina by the superluminescent diode. The patients had to keep the fixation target centered on the illumination via small head movements.

Within one measurement cycle of 60 seconds, the device first performed one overview scan to locate the exact position of the retinal pigment epithelium (RPE) and then performed five consecutive detailed volume scans of the retina that lasted 1.3 seconds each. Throughout the study protocol, the patient performed several of these measurement cycles. The study protocol included both training cycles and evaluation cycles; however, only the latter were used for analysis.

The first measurement cycle, M0 (training cycle), was used as an introduction to the technology and was performed under supervision of the attending physician. During this period, the physician guided the patient into achieving the correct head positioning. The M0 measurement could be repeated ad libitum until both the patient and examiner felt certain that the former was sufficiently experienced with the operation of the device. Subsequently, the patient performed two entire measurement cycles (M1 and M2) without medical assistance, which were included into the statistical analysis, regardless of quality or performance, and could not be repeated. Ultimately, only these completely unassisted measurements were evaluated. All measurements were collected without prior installment of mydriatic eye drops.

After finishing the Home-OCT measurements, all patients underwent a detailed scan (6- × 6-mm volume scan with 49 adjacent B-scans, without enhanced depth imaging) performed by a reference OCT system (Heidelberg Spectralis HRA + OCT2; Heidelberg Engineering, Heidelberg, Germany), color fundus photography (Zeiss FF450 plus; Carl Zeiss AG, Oberkochen, Germany), and a complete binocular funduscopic examination.

Image rating

The acquired images were processed by the software package implemented in MatLab (Mathworks, Natick, MA, USA). All images were then rated for image quality in a standardized manner. A scoring system was devised that rated image-acquisition artifacts as per five defined criteria: motion artifacts, saturation artifacts, vignetting, blurring, and signal strength of the neuroretina. For each criterion, a score of zero (no artifacts) to three (heavy artifacts) points was assigned. Based on these artifacts and not considering the presence of disease-specific biomarkers, we ranked all images to select the best three images for each eye. All images where any criterion was awarded three points (heavy artifacts) or where more than three criteria were awarded two points (medium artifacts) were assigned an overall classification of unsuccessful.

Image grading

The best up to three successful images per eye were graded in a reading center for OCT images (Macula Monitor Münster, Augenzentrum am St. Franziskus-Hospital, Münster, Germany) considering various biomarkers as well as an indication for an anti-VEGF treatment decision. Data were graded by two junior graders. For instances of deviation between the two graders, a final decision was rendered by an additional senior grader. If there were less than three successful measurements available for one eye, the accordingly reduced number was graded. Data for the Home-OCT and the SD-OCT devices were graded independently (blinded). For the biomarkers drusen, intraretinal fluid (IRF), subretinal fluid (SRF), pigment epithelium depletion (PED), and retinal thickening, a binary yes/no decision indicating whether they are visible in the images or not was made. The anti-VEGF treatment indication was performed as a clinical treatment decision based on the visible biomarkers and the diagnosis visible in the OCT images. For this grading scheme, a yes/no/uncertain decision was made based only on the single Home-OCT or SD-OCT measurement, respectively.

Analysis of the sensitivity and specificity

For the calculation of the sensitivity and specificity, only the measurement with the best technical rating for each eye was used. In the calculation of the sensitivity and specificity for the anti-VEGF treatment decision, eyes with an “uncertain” treatment decision in the gold-standard SD-OCT images were excluded from the analysis. Meanwhile, eyes with an “uncertain” treatment decision per the Home-OCT system were treated as “yes” (treatment indicated), because in an at-home setting, an uncertain treatment decision should result in an additional investigation using the clinical gold-standard modality. Because the clinical anti-VEGF treatment decision was influenced by some uncertainties in the diagnosis derived from the OCT images, we make a second hypothetical anti-VEGF treatment decision, which was based only on the biomarkers IRF and SRF—specifically, if any IRF or SRF was present in the OCT images, then treatment would be indicated regardless of the diagnosis.

Data for the various biomarkers were already in a binary yes/no form and no adjustments had to be made. For all data, confidence intervals were calculated using the Clopper–Pearson interval. Any correlation between the two eyes of one patient was neglected.

RESULTS

Study population

In total, 88 study eyes of 47 patients were included in this study. Among these eyes, 89% had AMD, 3% had DME, 3% had other retinal diseases, and 5% were healthy. Additionally, 52% of the patients were female and 48% were male and the mean age of the patients was 77 years old. Also, the mean BCVA of the eyes was 0.64. Data on age and BCVA, spherical error, and condition of the anterior eye can be found in Figure 2. No adverse events were recorded during the study.

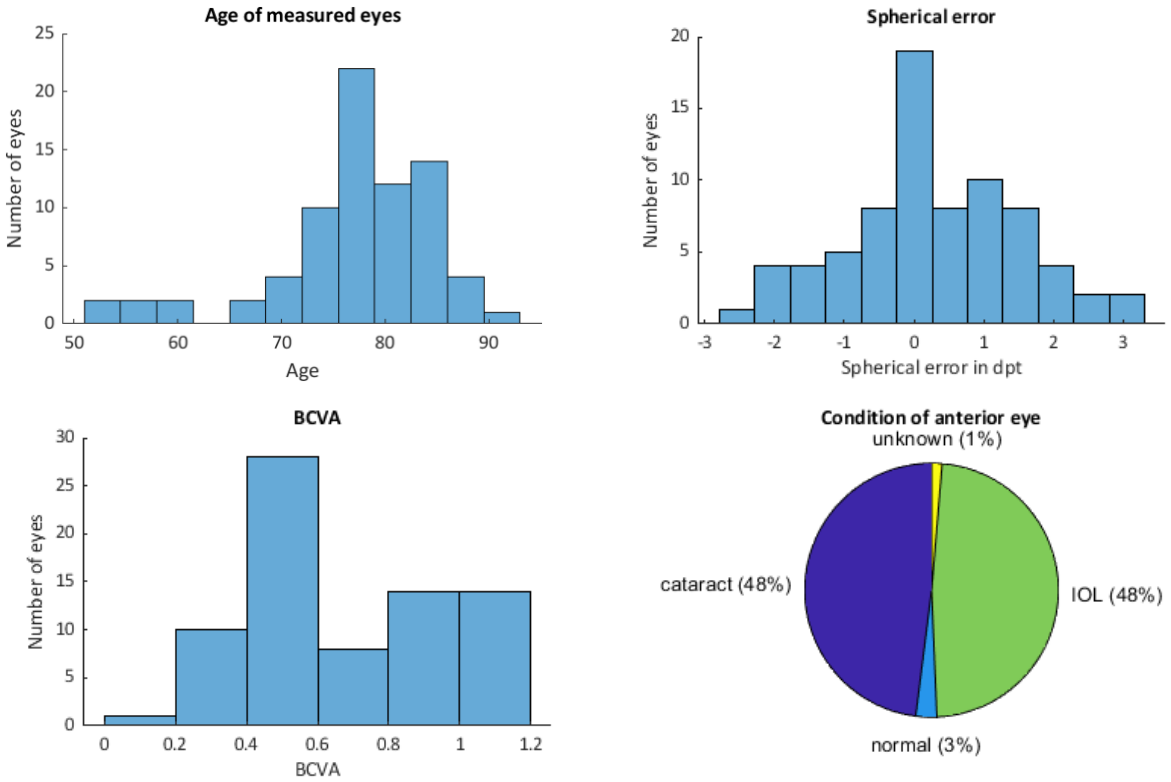

Figure 2: Age, shperical error, BCVA and anterior condition of the analyzed eyes.

Success rate in image self-acquisition

Overall, 88 out of 94 eyes (94%) were analyzed. Four of the remaining eyes did not meet the inclusion criteria, while for the final two eyes, no SD-OCT images were acquired.

For 76 out of the 88 eyes, patients could successfully acquire at least one scan that met the rating criteria based on image artifacts as described in the Materials and Methods section of this paper. Data from one eye were determined to be not clinically interpretable by the reading center, resulting in a final success rate of 75 out of 88 eyes (85%) measured. The main reason for the data not being interpretable was motion artifacts.

Image quality

Figure 3 shows representative SD-OCT and Home-OCT images acquired during the study. Despite the higher degree of background noise apparent among the Home-OCT images, the retinal layers were well-defined in most cases. Also, the most prominent biomarkers for AMD could be observed as follows: SRF (Figure 3, eyes 1 and 2), IRF (Figure 3, eyes 3 and 4), and PED (Figure 3, eye 1). Due to vast light scattering of the RPE, visibility below the RPE into the choroid was limited as compared with in SD-OCT images so that, apart from Bruch's membrane, no further details were distinguishable there. Also, some motion artifacts were visible as horizontal dark lines below the RPE in eyes 1 and 3 (Figure 3).

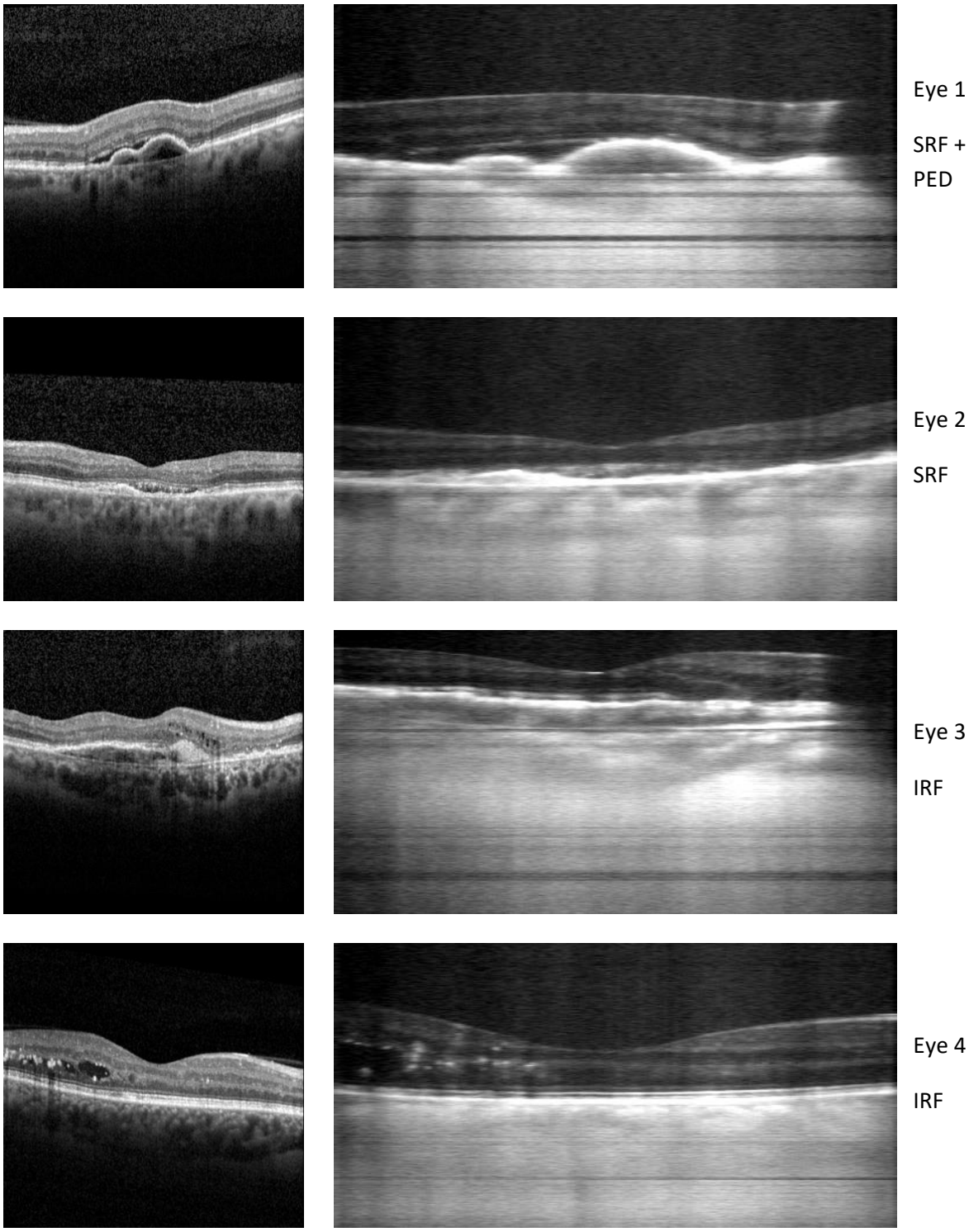

Figure 3: Exemplary Spectralis (left) and Home-OCT (right) images from different eyes acquired during the study. SRF can be found in eyes 1 and 2, IRF can be seen in eyes 3 and 4, and PED can be observed in eye 1, respectively.

Sensitivity and specificity for the anti-VEGF treatment decision and different biomarkers

For the calculation of the sensitivity and specificity for the anti-VEGF treatment decision, four eyes given an “uncertain” treatment decision according to the gold-standard SD-OCT images were excluded from the analysis. When treating “uncertain” treatment decisions as “yes” decisions as

described in the Materials and Methods sections, a sensitivity of 0.94 (confidence interval: 0.80–0.99) and a specificity of 0.95 (confidence interval: 0.82–0.99) regarding the clinical anti-VEGF treatment decision were calculated. For the sensitivity and specificity, data from all 75 eyes were used. The sensitivity for the presence of IRF was calculated to be 0.63 (0.35–0.85), with a specificity of 0.95 (0.86–0.99). For SRF, a sensitivity of 0.90 (0.73–0.98) and specificity of 0.98 (0.89–1.00) were determined. Drusen were correctly detected in all cases with a sensitivity of 1 (0.95–1.00) and specificity of 1 (0.40–1.00), while PED was detected with a sensitivity of 0.77 (0.59–0.89) and a specificity of 0.95 (0.85–0.99). For the hypothetical anti-VEGF treatment decision (the presence of any IRF or SRF regardless of the diagnosis), a sensitivity of 0.92 (0.79–0.98) and a specificity of 0.97 (0.86–1.00) were obtained.

Reproducibility

For three eyes, only one successful Home-OCT measurement was available and, for 15 eyes, only two successful Home-OCT measurements were available. For the 72 eyes with at least two available Home-OCT measurements, the anti-VEGF treatment decision between the two technically best-rated measurements matched in 70 cases (97%). For the 60 eyes with at least three successful measurements, all three measurements agreed in 59 cases (98%).

DISCUSSION

We conducted this study to assess both the success rate of a self-operable OCT device in the target population and to investigate the diagnostic accuracy of this new technology in a clinical setting. The image resolution was close to that of the reference OCT but had a worse signal-to-noise ratio and different image artifacts. Notably, however, the reduced image quality was a consequence of the low-cost full-field OCT concept; since the device is not intended for regular ophthalmic diagnosis but only for monitoring disease activity, this reduced image quality is acceptable as long as morphological changes can be detected with sufficient sensitivity and specificity. In the case of disease activity, such a device would refer the patient to their doctor to undergo a confirmatory OCT scan using more advanced technology and possibly an immediate intravitreal injection in the case of confirmed activity.

Visibility of biomarkers and the sensitivity and specificity

In our study, we could detect all common biomarkers of disease activity in AMD, including SRF and IRF. SRF is easily detectable since both the adjacent RPE and ellipsoid zone are hyper-reflective. In contrast, IRF does not have hyper-reflective borders and is therefore more challenging to detect. This discrepancy is also visible in the sensitivity outcomes for the two biomarkers of 0.90 for SRF and 0.63 for IRF, respectively. The specificity for both, however, was comparably high at 0.98 for SRF and 0.95 for IRF. Meanwhile, the sensitivity values for the clinical anti-VEGF treatment decision (0.94) and the hypothetical anti-VEGF treatment decision (0.92) were also comparably higher, while the specificity (0.95 and 0.97) appeared at a similar or slightly increased level. This could be explained by the correlation between the occurrence of SRF and IRF. The reproducibility of 97% for the grading of multiple images of the same eye in the anti-VEGF treatment decision-making process indicates good confidence in the treatment decision that was ultimately made.

As all graders had limited experience with grading the Home-OCT images with their specific artifacts, the sensitivity and specificity values might improve with further training. Also, as data were acquired

at a single time point, no previous measurements were available for comparison, which complicates efforts to discriminate between artifacts and the presence of biomarkers. In the intended future use-case, patients would frequently measure their retina, which eases image grading, as changes in the retina would be graded alongside the absolute presence of biomarkers in this study. Also, the image quality of future generations of the Home-OCT device is expected to be improved.

Device ergonomics and success rate

Because of the requirements for self-alignment and the necessity of keeping physically still during measurements, Home-OCT requires more cognitive, visual, and musculoskeletal function than clinical OCT systems. Therefore, we excluded patients who would obviously not meet these requirements and these individuals would similarly likely not be eligible candidates for future home monitoring. However, we did not conduct extensive preselection of the patients, including assessments such as fixation testing, but instead included a broad real-life cross-section of AMD patients.

Keeping these facts in mind, 85% of the included eyes were successfully imaged and culminated in clinically gradable images. The keyhole alignment method proved to be very reliable even in patients with low BCVA but limits device application to only among patients with some residual visual function; especially in cases of geographic atrophy, the usability of the tested system may therefore be limited. In some patients, variations in the fixation target, such as a circle or star, could possibly further reduce the problem.

We consider the reported success rate encouraging for a pivotal trial. We believe the attainment of a similar success rate in a later real-world home-care scenario would be satisfactory. The success rate might also further improve as the device was only used once during a single visit and, thus, the number of patients training with the device was very limited relative to what would be regular use. Furthermore, in-laboratory testing with a handheld device showed that, because of the improved patient interface, less motion artifacts occurred as compared with when using the table-top device, despite the former being handheld and therefore potentially subject to motion artifacts.

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