Repeatability and Reproducibility of Corneal Epithelial Thickness Mapping With Spectral-Domain Optical Coherence Tomography in Normal and Diseased Cornea Eyes

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• PURPOSE: To evaluate the performance of the epithelial thickness mapping (ETM) of the iVue spectral-domain optical coherence tomography (SD-OCT) device (Optovue Inc, Fremont, California, USA) in normal and diseased cornea eyes.

• DESIGN: Reliability and validity analysis.

• METHODS: Sixty eyes of 60 subjects were recruited for the study, which included normal subjects (n = 12) and patients with corneal diseases (12 patients each: dry eye syndrome [DES], contact lens wear, post–laser refractive surgery, and keratoconus). Three repeated scans were acquired on 3 iVue SD-OCTs with device-designated operators from consented subjects. Each subject was scanned on each device. Repeatability (based on random error of repeated scans) and reproducibility (including the random error and the instrument/operator variability) were assessed based on spatial zones derived from a 6-mm-diameter corneal ETM centered on the pupil and compared between the groups.

• RESULTS: Fifty-nine eyes qualified for final analysis. Seventy-one of 598 acquired scans (11.9%) were excluded owing to scan quality concerns. The percentage of disqualified scans was similar across normal (10.7%) and diseased eyes (12.1%). Of 527 qualified scans, 40 (7.6%) scans required manual edits of the segmentation lines. Repeatability and reproducibility results were similar, indicating minimal device/operator variability for both groups. Repeatability and reproducibility were similar in all subgroups of cornea patients, excluding the DES group, for which reproducibility was significantly lower (range 3.2%–5.5% for DES patients and 1.1%–2.9% for normal subjects).

• CONCLUSIONS: The iVue SD-OCT provides good corneal ETM repeatability and reproducibility in normal and diseased cornea eyes through all map zones. (Am J Ophthalmol 2019;197:88–97. © 2018 Elsevier Inc. All rights reserved.)

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HEALTHY CORNEAL EPITHELIUM IS ESSENTIAL FOR maintaining optical clarity and visual acuity. Corneal epithelial thickness (ET) can be affected by various conditions and pathologies, including dry eye syndrome (DES), contact lens (CL) warpage, laser refractive surgery (LRS), and keratoconus (KCN).[1–5] The analysis of ET and stromal thickness in the presence of such diseases holds a key role in their early diagnosis and evaluation.[1,4,6,7] Moreover, epithelial remodeling with consequent epithelial thickness alterations as a compensatory mechanism for corneal curvature irregularities may lead to underestimation of stromal thinning if not accounted for.[4,6] Many devices have therefore attempted to accurately measure corneal ET, including confocal microscopy[2,8,9] and high-frequency scanning ultrasound biomicroscopy (HF-UBM).[7,10–13] Spectral-domain/Fourier-domain optical coherence tomography (SD-OCT), a noninvasive imaging device, holds the advantages of providing significantly faster, more reliable, and better-quality cross-sectional images of the anterior segment of the eye in comparison to the time-domain OCT.[1,14,15] It may therefore be the most advantageous of the current technologies at hand for ET measurement. The repeatability and reproducibility of the SD-OCT in the measurement of ET were previously investigated in different devices, with contradicting results.[16,17] The RTVue SD-OCT device (Optovue, Inc, Fremont, California, USA) has been used routinely in clinical practice for imaging the cornea and other anterior segment structures. It has shown excellent repeatability of corneal ET measurements in normal eyes[18] as well as in KCN eyes,[1,4,19] post–laser-assisted in situ keratomileusis (LASIK) eyes,[3] and dry eye patients[5] using different versions of the RTVue epithelial software for scan processing. It was also previously shown by Schallhorn and associates that it allowed for distinction between contact lens warpage and ectasia in 21 eyes with KCN, by correlating the area of focal epithelial thinning to topographic corneal steepening.[4]

The iVue SD-OCT epithelial thickness mapping (ETM) software is the first U.S. Food and Drug Administration (FDA) software approved for ET measurement. The purpose of this clinical study was to evaluate the repeatability

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and reproducibility of this novel software for corneal mapping in normal and corneal patient eyes.

METHODS

• **PATIENTS:** This reliability and validity analysis adhered to the tenets of the Declaration of Helsinki and the Health Insurance Portability and Accountability Act, and all study methods were approved by the institutional review boards at the University of California, San Diego. Informed consent was obtained from all participants. The study was conducted at 1 study site. All subjects were 18 years old or older and were able to complete the required examinations.

Twelve normal subjects were recruited from the patient pool of the Shiley Eye Institute (SEI). Subjects were excluded from this group in the presence of a history of LRS or previous cataract surgery, history of soft or hard contact lens wear in the 3 months prior to the recruitment date, clinical diagnosis of blepharitis, history or current diagnosis of DES, history or current diagnosis of a corneal pathology, or inability to complete SD-OCT scans. The enrollment of the normal subjects aimed at covering a wide age range and included 3 subjects over age 55 and 3 subjects under age 35.

Forty-eight additional patients were recruited from the patient pool in the SEI cornea clinic and were included if they had a history or current diagnosis of either (1) clinically diagnosed DES with no prior refractive surgery, or (2) history of consistent soft or hard contact lens wear for refractive error correction, without complications, immediately prior to the study and without history of LRS or DES, or (3) at least 1 month post LRS without complications, or (4) KCN in the study eye. Patients were excluded from the patient group if they were unable to complete the SD-OCT scans. Dry eye patients and KCN patients were enrolled to cover the mild-to-severe stages of the diseases. For the DES group, an assessment of the relationship between variability of measurements and the severity of the disease was also performed.

One eye per study subject was included in the study. If both eyes qualified for the study, either the right eye or the left eye was chosen, based on randomization or guided by an attempt to fulfill subgroup stratification targets.

• **OPTICAL COHERENCE TOMOGRAPHY:** The iVue SD-OCT device (Optovue, Inc, Fremont, California, USA) with the corneal adaptor module (CAM) was used. The device has a speed of 26 000 A-scans per second, depth resolution of 5.0 μm, and a scan beam wavelength of 840 nm (± 10 nm). The CAM lens used in the study provides a transverse resolution of 15 μm.

iVue Software for Epithelial Thickness Mapping. As previously described with the RTVue SD-OCT,[1] the pachymetry scan of the iVue device provides a color-coded pachymetry map of the central 6 mm along with zonal (regional) thickness parameters and summary statistics derived from various regions of the pachymetry map (Figure 1). The pachymetry scan pattern consists of 1 set of 8 meridian scans, and each of the meridian scans (ie, B-scans) is 6 mm in scan length and consists of 1024 axial-scans (A-scans), with alignment centered on the pupil for scan acquisition. The iVue ETM scan (ie, modified pachymetry scan) consists of the same 8 meridians, distributed in the same orientation pattern as that of the pachymetry scan, each meridian with the same scan length and A-scan density (6 mm in scan length and 1024 A-scans per meridian); however, unlike the pachymetry scan, each meridian of the ETM is repeated 4 times in rapid succession. These 4 B-scan images are registered and averaged to produce an averaged B-scan image with reduced speckle noise, as illustrated in Figure 2 (Top and Middle). The alignment on the eye for scan acquisition is also the same as the previous pachymetry scan, centering on the pupil. The scan acquisition time of the ETM scan is less than 1.25 seconds.

The software performs automatic segmentation for each of the 8 averaged meridian images to detect the following 3 boundaries (Figure 2, Bottom): 2 boundaries, as in the previous software (ie, the corneal anterior surface boundary and the corneal posterior surface boundary), and the corneal epithelial posterior boundary, which is new in this modification. The pachymetry is measured based on the distance from the corneal anterior surface boundary (Figure 2, Bottom, segmentation line 1) to the corneal posterior surface boundary (Figure 2, Bottom, segmentation line 3); the epithelial thickness is measured based on the distance from the anterior corneal surface boundary (Figure 2, Bottom, segmentation line 1) to the epithelial posterior boundary (Figure 2, Bottom, segmentation line 2). With the epithelial posterior boundary available, corneal stromal thickness may also be provided based on distance from this boundary to the corneal posterior surface boundary (Figure 2, Bottom, from segmentation line 2 to segmentation line 3). All distance measurements are along a straight line perpendicular to the anterior corneal surface.

An example of the report screens for the modified pachymetry scan with iVue SD-OCT is shown in Figure 3.

Optical Coherence Tomography/measurements. Three SD-OCT instruments with the iVue ETM software modification were installed at the SEI for study data collection. Each iVue instrument was paired with designated operators and each of them operated 1 designated iVue instrument. Each study subject was imaged with all 3 iVue and operator pairs, and at least 3 ETM scans were acquired within each pair. The operator realigned the instrument on the study eye for each scan acquisition. All scans from a given study subject were

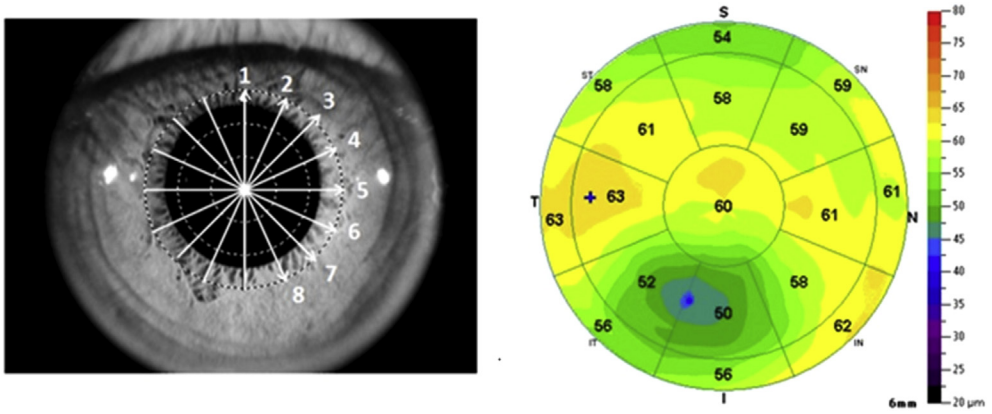


FIGURE 1. Pachymetry scan pattern centered on pupil (Left) and thickness map derived from automated segmentation of epithelium (Right).

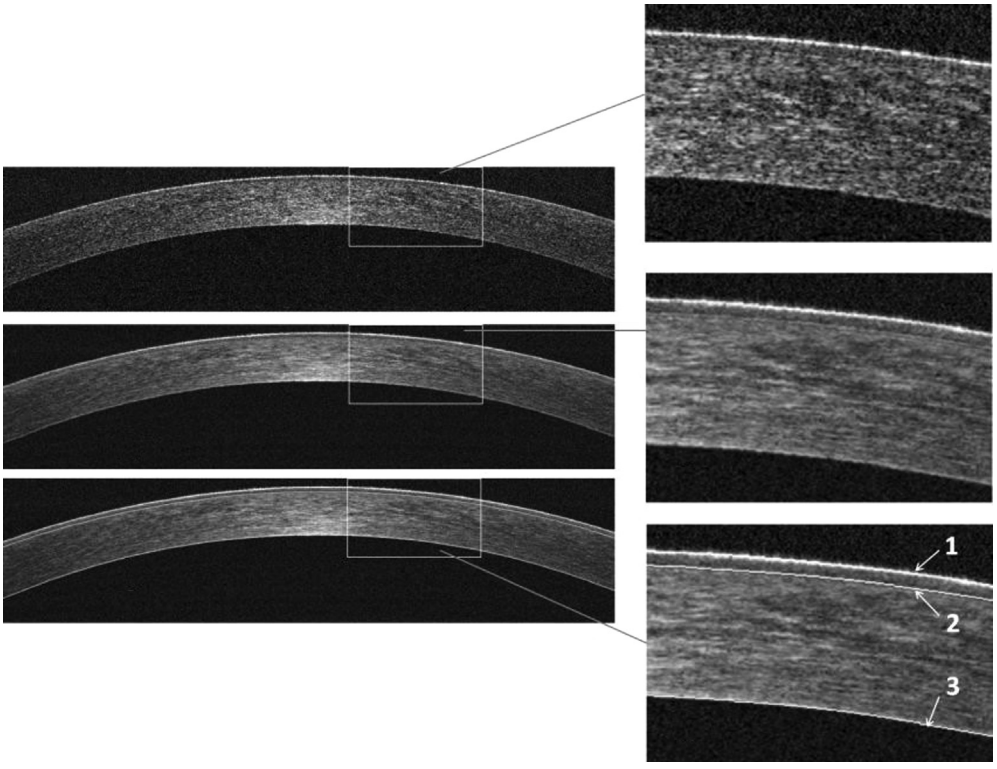


FIGURE 2. Illustration of speckle noise reduction through B-scan averaging and the 3 boundaries automatically segmented in the epithelial thickness mapping scan. (Top) Single-frame B-scan image of a meridian scan without averaging. (Middle) Averaged image of the same meridian. (Bottom) Segmentation lines corresponding to the corneal anterior surface boundary ("1"), the corneal epithelial posterior boundary ("2"), and the corneal posterior surface boundary ("3").

acquired on a single visit. All scans were acquired with alignment of the eye centered on the pupil. Subjects were repositioned by the operator after each scan to ensure realignment of the instrument on the test eye. Each patient was instructed to blink prior to each scan acquisition.

Contact lenses were removed prior to OCT scan acquisition, either the night before or on the day of the study visit, at any time prior to the OCT scan acquisition. If an operator raised a quality concern during scan acquisition, such as eye blink, scan out of range, or obvious misalignment on the pupil, he or she could take up to 2 additional

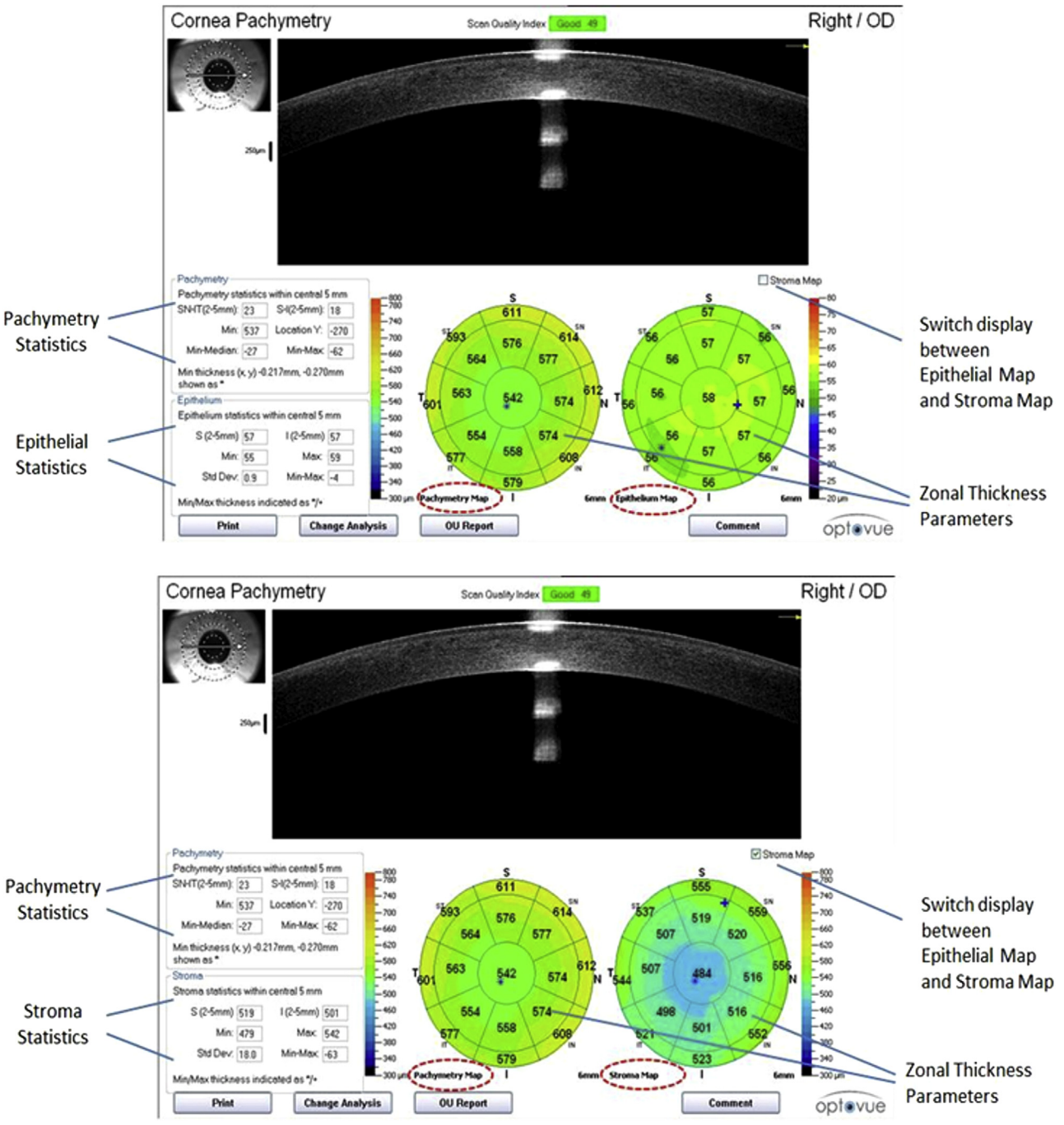
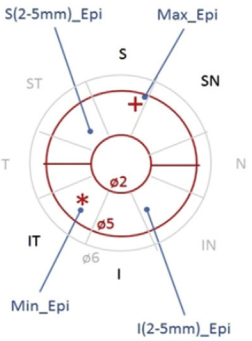


FIGURE 3. An example of report screen for the iVue epithelial thickness mapping scan (ie, modified pachymetry scan). A toggle button is provided to switch display between the epithelial map and the stromal map. Summary statistics based on the thickness maps are displayed on the left side of the screen. Zonal thickness parameters are overlaid on top of the thickness maps. (Top) Report screen showing side-by-side the pachymetry map and the corneal epithelial map with map labels at the adjacent lower left corner (red dotted lines). (Bottom) Report screen showing side-by-side the pachymetry map and the corneal stroma map with map labels at the adjacent lower left corner (red dotted lines).

scans. Up to 5 scans could be acquired per instrument per study eye. Following the completion of scan acquisition, study site operators reviewed scan quality and selected the first 3 scans with sufficient image quality per instrument as the study scans. For each selected study scan, the operator also reviewed the corneal maps for obvious segmentation error and manually corrected it. In order to confirm the segmentation error, B-scans were reviewed with and without segmentation lines using a toggle feature to confirm the error. Segmentation edit tools were used to



	Mean (µm)±SD					Repeatability SD (µm)				
	DES	CL	post LRS	KCN	Normal	DES	CL	post LRS	KCN	Normal
S*(2-5mm	50.0±5.5	51.4±3.4	52.9±4.5	52.7±4.5	52.0±2.8	2.0	1.1	0.8	1.3	1.2
I**(2-5mm	52.7±4.4	52.1±3.2	56.1±3.7	48.1±4.6‡	54.0±3.9	2.4‡	0.8	0.8	1.1	1.0
Min	46.3±4.6‡	48.7±3.2	49.4±4	41.0±6.1‡	49.6±2.6	2.1‡	1.0	1.2	1.9	1.2
Max	56.3±6.5	54.3±3.2	59.2±4.1	59.1±3.4‡	56.0±3.8	2.3	1.3	1.0	1.6	1.2
Min-Max	-9.9	-5.6	-9.8	-18.1‡	-6.4	2.1	1.2	1.2	2.3	1.2

FIGURE 4. (Left) Diagram showing the regions (outlined in red) for summary statistics calculations for the iVue epithelial thickness mapping scan (ie, modified pachymetry scan) and parameter naming convention. I = inferior; IN = inferonasal; IT = inferotemporal; N = nasal; S = superior; SN = superonasal; ST = superotemporal; T = temporal. Epithelial parameters are calculated from the central 5-mm diameter of the corresponding maps. (Right) Data for mean epithelial thickness and repeatability of epithelial thickness measurements by summary statistics in normal and cornea patient eyes. *S = Superior values were measured at the superior hemicircular region of the central 5 mm. **I = Inferior values were measured at the inferior hemicircular region of the central 5 mm. ‡Statistically different from normal ($P < .05$). DES n = 98 scans; CL n = 108 scans; post LRS n = 107 scans; KCN n = 106 scans; normal n = 108 scans. CL = contact lens; CoV = coefficient of variance; DES = dry eye syndrome; post LRS = post–laser refractive surgery; SD = standard deviation.

perform manual correction and then the epithelial map was reprocessed. The rate of scans requiring manual correction among the qualified scans was reported.

• **DATA ANALYSIS:** Repeatability was assessed based on variability of repeated same eye scans, excluding the scans with failed image quality. The reproducibility was assessed based on repeatability and the combined instrument/operator effect. Repeatability and reproducibility were assessed for all zonal thickness parameters and the summary statistics parameters were displayed on screen for the pachymetry, epithelial thickness, and stromal thickness.

Regional Thickness Parameters. The regional thickness parameters are the average thickness values computed from the corresponding region of the map and displayed as overlay on the thickness map. As shown in Figure 1, each map was divided first into 3 concentric rings (2 mm, 2-5 mm, and 5-6 mm in diameter) and then further divided into 8 sectors (temporal, superotemporal, superior, superonasal, nasal, inferonasal, inferior, inferotemporal), with the exception of the innermost 2-mm region. Therefore, 51 zonal parameters (17 zonal parameters for each of the 3 thickness maps) were included in the repeatability and reproducibility evaluation of the epithelial, stromal, and corneal thickness maps.

Statistical Parameters. In addition to the zonal thickness parameters displayed on the thickness maps, there are summary statistics parameters derived from the thickness maps. The parameter names describe the statistical calculations from predefined map regions, as shown in Figure 4 (Left).

• **STATISTICAL ANALYSIS:** Study data were batch exported using the XML export feature, which generates a file containing measurements for all zonal parameters and summary parameters, as previously described. The scan list was merged with the scan quality review list for designation of data for exclusion as well as identification of scans that were manually edited. A final scan list consisting of up to 3 qualified scans per eye was sent to statistical analysis. All analysis was performed using the SAS statistical software system (version 9.1; SAS Institute Inc, Cary, North Carolina, USA). The repeatability and reproducibility analysis was based on all qualified scans, including the scans that required manual segmentation correction. The analysis was performed for each study group separately. Based on the crossed study design, the total variance was decomposed into 3 parts: a variance component attributable to operator + device, a component derived from between-subject variability, and a residual variance component attributable to random error. The primary measure of repeatability was defined as the square root of the residual variance, and that pertaining to reproducibility was defined as the square root of the sum of the residual variance and the variance component caused by operator + device. A regular 2-way cross-ANOVA model was used to estimate these components. The precision results were reported for all study parameters and for each study group, respectively, as follows: mean of the group, standard deviation of the group, repeatability standard deviation (SD), reproducibility SD, coefficient of variation (CoV, in %) based on reproducibility (reproducibility SD/mean × 100), and 95% limits of reproducibility (2.8 × reproducibility SD). In addition to the 2 primary study groups, the repeatability and reproducibility results were also provided

TABLE. Epithelial Thickness Repeatability and Reproducibility in Normal and Corneal Diseased Eyes

	Repeatability			Reproducibility					
	SD (μm)			SD (μm)			CoV (%)		
Zone	2 mm	2-5 mm	5-6 mm	2 mm	2-5 mm	5-6 mm	2 mm	2-5 mm	5-6 mm
Normal group									
Mean	0.9	1.1	1.2	0.9	1.1	1.2	1.8	2.1	2.4
Min		0.9	1.0		0.9	1.0		1.6	1.8
Max		1.3	1.4		1.3	1.5		2.5	2.9
Cornea patient group									
Mean	1.2	1.4	1.7	1.2	1.4	1.7	2.4	2.7	3.3
Min		1.3	1.5		1.4	1.6		2.6	2.9
Max		1.5	1.9		1.5	1.9		2.8	3.6

CoV = coefficient of variance; Max = maximum; Min = minimum; SD = standard deviation.

Repeatability and reproducibility results for normal and cornea patient eyes summarized for central 2 mm, 2-5 mm paracentral (numerical average of 8 sectors), and 5-6 mm peripheral (numerical average of 8 sectors) zones. Values for repeatability and reproducibility are very similar, given a negligible instrument/operator effect.

for the subgroups within the corneal patient group. A *t* test was used to assess whether the values from each subgroup were significantly different from the values of the normal group.

For assessing the relationship between variability of measurements and the severity of DES, the SD of the epithelial thickness scans in each sector from each individual subject was also calculated. The tear break-up time (TBUT) and Ocular Surface Disease Index (OSDI) based on the OSDI questionnaire (score 0-100)[20] were correlated to the SD in the DES group, using the Pearson correlation coefficient.

RESULTS

SIXTY SUBJECTS WERE CONSENTED FOR THE STUDY (12 normal, 12 CL wearers, 12 DES patients, 12 post-LRS, and 12 KCN). One subject from the DES group was excluded from the analysis owing to corneal comorbidities. A total of 25 (42%) male subjects and 34 (58%) female subjects completed the study. The ethnicity of most of the participants was white (63.3%), followed by African American, Hispanic, and Asian at 16.7%, 13.3%, and 6.7% respectively. Age distribution was similar in both groups, with an average of 42 ± 15.7 years in the normal group (range, 18-63 years), and 45 ± 16.9 years in the cornea patient group (range, 18-79 years). Within the latter group, patients in the CL and KCN groups were aged 38 ± 10.8 years (range, 20-58 years) and 39 ± 14.7 years (range, 19-63 years) respectively, younger than the DES and post-LRS patients, aged 57 ± 18.8 years (range, 30-79 years) and 50 ± 18.7 years (range, 30-78 years), respectively. Among the 59 qualified eyes, 29 were right eyes and 30 were left eyes.

• **SCAN QUALITY:** A total of 598 scans were acquired for the 59 qualified eyes across the 3 devices. Among the scans, 71 (11.9%) were excluded from further analysis owing to concerns of poor quality, including blinks resulting in blank OCT images, cropped OCT images (bottom or top), or scans not well centered on the pupil. For the normal group, a 10.7% scan attrition rate was calculated, in comparison to 12.1% for the corneal patient group. Of 527 qualified scans, there were 40 scans (7.6%) with segmentation errors that were manually edited. A similar distribution of manual edits across all instruments and study groups was noted. Edited scans were included in the data analysis for assessment of the repeatability and reproducibility.

• **REPEATABILITY AND REPRODUCIBILITY:** Repeatability and reproducibility results for normal and corneal patient eyes are summarized for central and peripheral zones in the Table. Summary statistics calculations of ET by regions, including mean ET and repeatability SD, are presented in the table in Figure 4. The CoV values (%) were low in all patient subgroups, for both pachymetry (Figure 5, Top) and ET (Figure 5, Bottom). CoV value results were also low for stromal thickness, with a range of 0.4%–0.9% for central and paracentral zones and 0.7%–1.4% for peripheral zones in the normal group, and 0.7%–1.1% for central and paracentral zones and 1.0%–1.7% for peripheral zones in the corneal patient group.

• **CHARACTERIZATION AND RESULTS BY STUDY GROUP:** *Dry Eye Group.* Ninety-eight scans of 11 dry eye patients were included in the study. The severity of DES for each study subject was documented using the OSDI score with a scale from 0 to 100 (mild to severe) and documentation of TBUT. The average OSDI score was 48.8 ± 21.5 (range, 14.6–83.3) and the average TBUT was 7 ± 3 seconds

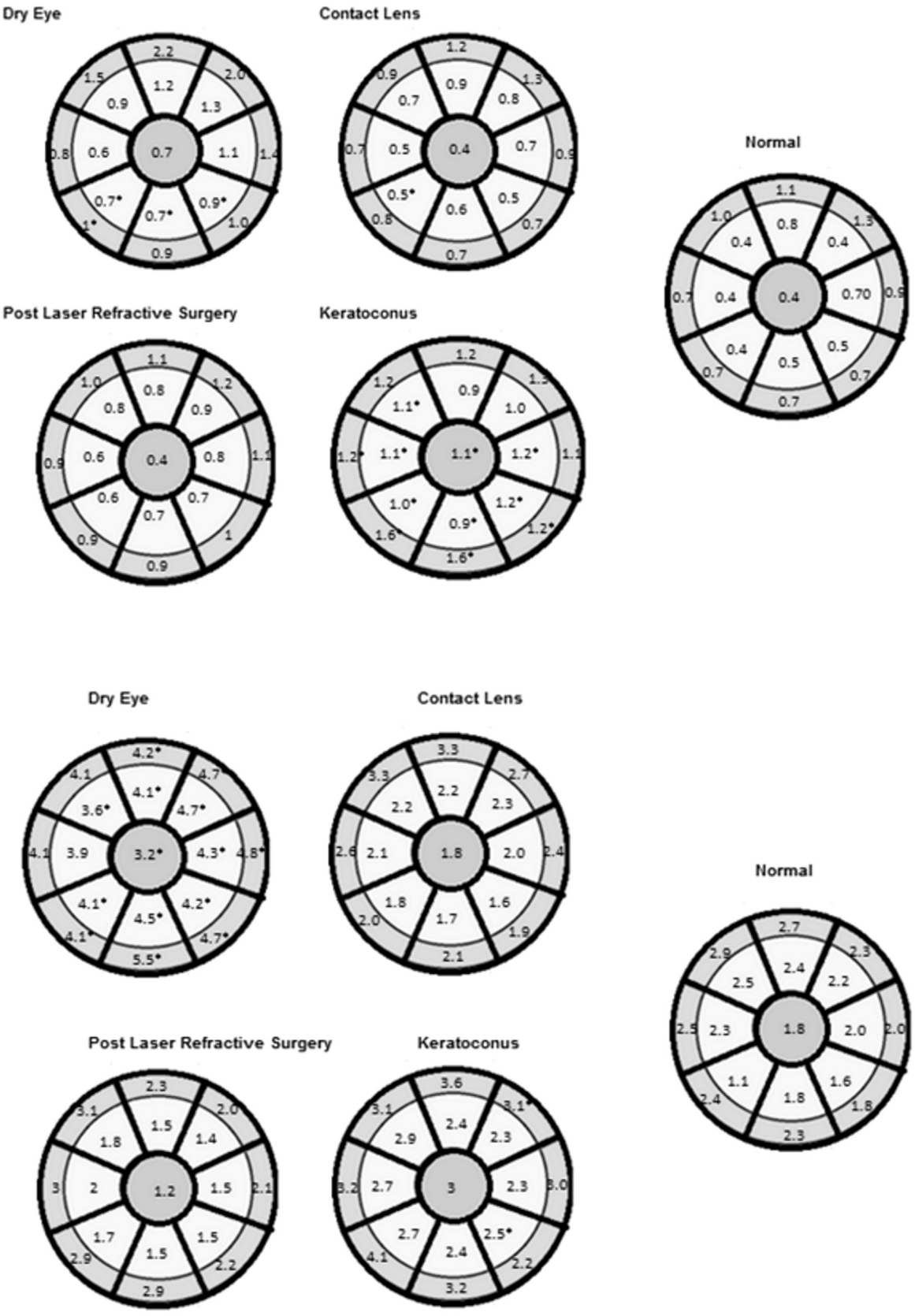


FIGURE 5. The coefficients of variance (%) are presented for all patient subgroups for both pachymetry (Top) and epithelial thickness (Bottom). * signifies statistically significant difference ($P < .05$) in comparison to normal subjects.

(range, 1-10 seconds). The mean central epithelial thickness was similar in both groups (normal eyes ET: 52.9 ± 3.4 μm, dry eyes ET: 51.7 ± 3.4 μm, $P = .395$). Reproducibility of 15 of the 17 ET measurements was significantly better in the normal group compared to the dry eye group (Figure 5, Bottom). The variability of the maximal ET (representing the maximum thickness value within 5 mm diameter of a map area) measured in the dry eye group was positively correlated with a high OSDI score ($P = .02$). In addition, the variability of the thickness measured at the superotemporal 2.5 mm of the cornea was positively correlated with a higher TBUT ($P = .008$).

Contact Lens Group. Consistent CL wear was defined as 8 or more hours per day for at least 3 months prior to enrollment. Within the CL group, average duration of use was 11 ± 6.3 years (range, 2-20 years), for an average of 12 ± 3.6 hours per day (range, 8-18 hours per day). The mean central epithelial thickness was similar in both groups (normal eyes ET: 52.9 ± 3.4 μm, contact lens ET: 51.0 ± 3.6 μm, $P = .190$). Only the reproducibility of the inferotemporal 2-5 mm pachymetry measurement (1/17, Figure 5, Top) was significantly different in the CL group compared to the normal group ($P = .02$). None of the 17 ETM zones significantly differed in reproducibility in the CL group compared to the normal group (Figure 5, Bottom).

Post–Laser Refractive Surgery Group. Nine out of 12 (75%) patients in this group had a LASIK procedure and 3/12 (25%) had a photorefractive keratectomy (PRK) procedure done. Ten out of 12 (83.3%) of the patients had a myopic vision correction. One patient had hyperopic correction and 1 patient had an astigmatic correction. Most patients (11/12, 91.7%) had the procedure done 1 year or more prior to study enrollment. The mean central epithelial thickness was similar in both groups (normal eyes ET: 52.9 ± 3.4 μm, post-LRS eyes ET: 54.0 ± 4.6 μm, $P = .576$). None of the 17 ETM or pachymetry zones significantly differed in reproducibility in the post-LRS group compared to the normal group (Figure 5, Top and Bottom).

Keratoconus Group. All subjects in this group had a clinical diagnosis of KCN supported by characteristic topographic patterns. Clinical signs were evident on slit-lamp examination in 7 of 12 patients (58.3%). A retinoscope reflex was suggestive for KCN in 2 patients (16.7%). Most patients (66.7%) were diagnosed with moderate KCN, while 2 patients (16.7%) had mild KCN and 2 patients (16.7%) had severe KCN. Mean steep K was 48.1 ± 3.9 diopters (range, 42.1-54 diopters), and delta K, representing the difference between steep K and flat K, was 2.4 ± 1.1 diopters (range, 0.6–4.3 diopters) in the KCN group. None of the study eyes underwent previous collagen cross-linking treatment. One study eye had a previous Intacs implant and 1 study eye had a previous penetrating keratoplasty 5 years prior to the study. While reproducibility of the ETM only differed from the normal group in 2 of 17 of the map zones, in 10 of 17 of the pachymetry measurements the reproducibility was significantly lower in the KCN group (Figure 5, Top and Bottom). While all the mean pachymetry values differed between the KCN group and the normal group, only 4 of 17 areas of the ETM differed (central 2 mm, inferior 2-5 mm, inferotemporal 2-5 mm, superotemporal 5-6 mm). A statistically significant difference in the epithelial thickness between normal and KCN eyes was also noted by summary statistics, comparing the inferior, min, max, and negative min-max ratio, as seen in Figure 4. The mean central thickness value (48.6 ± 4.8 μm) was significantly lower in the KCN group in comparison to the normal group ($P = .019$).

DISCUSSION

PREVIOUS STUDIES IMPLEMENTED DIFFERENT investigator-modified software or indirect measurements of corneal epithelium to diagnose epithelial changes in various pathologies.[1–4,21–23] This prompted the use of a reliable, repeatable, and standardized software designated for the direct evaluation of ET using the SD-OCT. Our study shows good repeatability and reproducibility of the ET with the iVue ETM scan across several common corneal pathologies as well as in normal patient eyes. Given the 4 rapid repeats of each meridian with the iVue SD-OCT, motion artifacts and speckle noise are diminished, speed of acquisition increases, and better image quality is registered. More potential advantages of this software include automatic segmentation for the posterior boundary of the epithelial layer, solving the controversial use of the Bowman layer as an interface marker.[1]

For the dry eye patients, our results imply that despite good overall repeatability and reproducibility in all corneal mapping zones, making it a reliable tool for the evaluation and follow-up of dry eye patients with this technology, there is a significant difference in this group's consistency of measurements in comparison to normal subjects. Specifically, coefficient of variance was 3.2%–5.5% in the dry eye patients and only 1.1%–2.9% in normal subjects. Moreover, our results suggest a possible correlation between the severity of dry eye disease as measured by TBUT and OSDI and the variability of ET measurements, most likely owing to more fluctuations in epithelial remodeling in this group. Increased variability of measurements in an established dry eye patient may therefore have a valuable clinical role in suggesting exacerbation of a previously stable disease, which calls for a study to evaluate this correlation in a larger cohort of patients. Interestingly, in contrast

to Kanellopoulos and associates, who found epithelial thickening in dry eye patients,[5] and El-Fayoumi and associates, who reported epithelial thinning in a group of dry eye patients secondary to rheumatoid arthritis,[24] our measurements did not show statistically significant ET differences in any zone in comparison to normal eyes. A possible explanation for the difference in results between our study and these 2 studies are the demographic differences between the populations studied, including age differences. Our study represents subjects almost a decade older than those in both aforementioned studies and includes both male and female patients. In addition, it should be noted that in all 3 studies, dry eye diagnosis was done at the discretion of the clinician and lacked objective measures for diagnosis or precise tear film evaluation.

The use of SD-OCT for ETM in evaluation of patients with abnormal topography was shown to be helpful in differentiation KCN from CL warpage.[4] Our study shows high repeatability and reproducibility and less than 3% segmentation error rate in active CL wearers (both rigid and soft) in whom CL were removed less than 24 hours prior examination.

For post-LRS patients, previous studies found the central epithelium to be thickened after myopic ablation, with corresponding stromal thickening peripherally. These changes were suggested to occur early after surgery, with stabilization 3 months postoperatively.[25] The corneal epithelial profile described after hyperopic ablation was the opposite, with epithelial thickening occurring in the periphery.[6,7,12] One explanation for the lack of significance between our LRS group and normal subjects is that our study included a variety of postmyopic and hyperopic LRS patients, including patients post–surface ablation; hence our results are more variable. Future applications of corneal epithelial measurements in these patients are numerous and include the potential diagnosis of progressive ectasia, profiling patients prior to enhancements and promoting understanding of wound-healing mechanisms.[26] Measuring epithelial thickness prior to refractive surgery may also assist the surgeon in planning a safe treatment for each cornea, taking into consideration a safe residual epithelial thickness as an indicator for postoperative keratometry.[26,27] Therefore, the iVue SD-OCT reliable and repeatable measurements, as shown in this patient group, holds the promise that it may serve as a useful tool in the preoperative and postoperative assessment of these patients.

As mentioned previously, the use of the RTVue SD-OCT for ETM was previously investigated and shown to be reliable for KCN patients.[1,4,19] Our study shows that pachymetry, stromal, and EMT results were repeatable and reproducible for the entire spectrum of severity in the iVue SD-OCT. Consistent with the results of Haque and associates[22] and Reinsten and associates,[7] a significant central and inferior thinning was noted in the KCN group, with a significantly lower minimum corneal epithelial thickness ($P = .0003$) and more negative min-max ratio ($P = .00002$). Peripheral superotemporal thickening in KCN eyes was also significantly greater in comparison to normal eyes ($P = .03$). The scans of the KCN eyes showed the highest percentage of manual edits (17.9%) owing to segmentation error, as was previously described with the RTVue OCT[1]; however, repeatability and reproducibility remained high for the ETM in this group.

The limitations of our study include the focus we had on measuring the central 6 mm of the cornea, making extrapolation of the data to peripheral corneal diseases impractical. Another limitation is the small number of eyes in each corneal pathology group; the small number of post-PRK eyes makes it harder to deduce clinical conclusions for the applicability of the device in this subgroup of patients, and having a small number of eyes in each subgroup analysis makes the clinical conclusions less generalizable. Nevertheless, our study was initially designed as a precision study and its sample size was selected accordingly. The importance of this study is therefore in presenting a reliable ready-made software with the ability to show repeatable and reproducible measurements for ET measurements across different corneal pathologies.

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