

Automated Detection of the Stromal Demarcation Line Using Optical Coherence Tomography in Keratoconus Eyes After Corneal Cross-linking



SHADY T. AWWAD, MAAMOUN ABDUL FATTAH, MANAL SHOKR, AND AHMAD R. DHAINI

- **PURPOSE:** To evaluate the role of a novel automated detection software as compared to human operators in assessing the presence and depth of stromal demarcation line on optical coherence tomography (OCT) in keratoconus eyes post cross-linking.
- **DESIGN:** Reliability analysis study.
- **METHODS:** Two independent operators and an automated detection software examined corneal OCTs of 25 eyes of 25 patients post corneal cross-linking using the Dresden protocol, at 3 months postoperatively. Operators evaluated the presence of the demarcation line and measured its depth by looking at OCT images (128 cuts) on 2 separate occasions 1 week apart. The automated software examined all 128 cuts of each OCT measurement.
- **RESULTS:** The mean corneal demarcation line depth was 321.54 ± 47.71 , 322.86 ± 45.77 , and $309.21 \pm 40.98 \mu\text{m}$, as computed by the automated detection software and the human operators, respectively. The intra-class correlation coefficients (ICC) between the automated detection software and Observers #1 and #2 were 0.884 and 0.847, respectively ($P < .001$). The ICC for interoperator reproducibility was 0.890, and for intraoperator repeatability for Operator #1 and Observer #2 were 0.922 and 0.925, respectively. The ICC for intersoftware repeatability was 1. Bland-Altman plots showed a good agreement between both observers and the software, with adequate 95% limits of agreement.
- **CONCLUSION:** Detection of the demarcation line by human operators is repeatable and reproducible, but it can be further optimized and standardized by an ultrafast and accurate automated software detection tool,

providing a reliable indicator for treatment success. (*Am J Ophthalmol* 2019;199:177–183. © 2018 Elsevier Inc. All rights reserved.)

CORNEAL CROSS-LINKING (CXL) USING RIBOFLAVIN and ultraviolet-A (UVA) irradiance has emerged as a safe and efficient way to stabilize disease progression in keratoconus.^{1–3} Evidence of the cross-linking effect has been shown in animal eyes based on biomechanical stress tests and histologic studies.^{4–6} In human eyes, however, such tests could not be readily performed. Pending the optimization of newer, promising tools like Brillouin microscopy, assessment of the demarcation line depth in the cornea can reflect cross-linking depth and has been suggested as an indirect measure of the success of the treatment, combined with other clinical parameters such as topographic and refractive stability. This measure, however, is to be used cautiously, as deeper cross-linking does not necessarily mean better treatment efficacy, and there is no clear evidence from the literature about the demarcation line and its direct correlation with cross-linking efficacy. With the sprawling techniques of performing corneal cross-linking, from “epithelial off,” to various transepithelial techniques and protocols with or without iontophoresis, to accelerated methods with varying energy and time, it is important to evaluate objective parameters to assess the adequacy of the cross-linking performed, and evaluating the depth of the demarcation line is 1 objective measure to consider, among others.^{7,8} Assessing the existence and depth of the demarcation line has been traditionally performed by a human operator examining optical coherence tomography (OCT) cuts, although less accurate techniques like slit-lamp assessment and Scheimpflug imaging have been described.^{9,10} This task is time consuming, especially if multiple cuts are examined, and is prone to human bias and errors, with subpar repeatability and reproducibility. Confocal microscopy (CM) might be prone to less error and has been described to have a better intra- and interoperator variability, but it is subject to availability and practicality.⁹

In this study, we compare demarcation line measurements performed by a novel OCT image analysis software to the ones made by human operators, while we further

AJO.com

Supplemental Material available at AJO.com.

Accepted for publication Nov 25, 2018.

From the Department of Ophthalmology, American University of Beirut Medical Center, Beirut, Lebanon (S.T.A., M.A.F.); and Department of Computer Science, American University of Beirut, Beirut, Lebanon (M.S., A.R.D.).

Drs Awwad and Dhaini contributed equally to this work.

Inquiries to Shady Awwad, Head, Cornea & Refractive Surgery Division, Department of Ophthalmology, American University of Beirut Medical Center, Cairo St, PO Box 110236, Beirut, Lebanon; e-mail: sawwad@gmail.com

evaluate their repeatability and reproducibility. The software has a role to establish an accurate, objective, and standardized method in evaluating demarcation line post CXL, in a repeatable and reproducible way.

METHODS

• **PATIENT SELECTION:** This study evaluated corneal OCT images performed on eyes that underwent CXL between January 1, 2014 and January 31, 2016 at the American University of Beirut Medical Center in Beirut, Lebanon. Corneal OCT was performed as part of their routine postoperative measurements protocol. All patients were between 14 and 40 years of age, having undergone corneal cross-linking for progressive keratoconus. The latter was defined as an increase in the steepest keratometric value (K_{max}) of at least 1 diopter (D) in 1 year or a mean central corneal thickness decrease of at least 5% in 6 months, all observed in 3 consecutive tomographic measurements using the Galilei Placido and dual Scheimpflug analyzer (Ziemer Group, Port, Switzerland). Exclusion criteria included active ocular pathologies, corneal thickness $<400 \mu\text{m}$ at the thinnest point, preexisting corneal opacities, prior history of keratitis, previous corneal and intraocular surgeries, and autoimmune or connective tissue diseases. This study was approved by the Institutional Review Board at the American University of Beirut and adhered to the principles of the Declaration of Helsinki.

• **SURGICAL PROCEDURE:** Corneal cross-linking was performed according to the Dresden protocol. Proparacaine hydrochloride 0.5% drops were instilled in the eye, to be treated on 2 occasions at 5-minute intervals. An eyelid speculum was inserted after the patient was positioned under the operating microscope, and the central 9-mm corneal epithelium was removed with a blunt spatula. A riboflavin 0.1%–20% dextran solution (IROC Innocross AG, Zurich, Switzerland) was instilled every 2 minutes until the riboflavin penetrated the corneal stroma (ie, approximately 30 minutes). An ultraviolet lamp (UV-X; IROC AG, Zurich, Switzerland) with a mean of 3.0 mW/cm^2 radiant energy was focused at a distance of 5 cm on the apex of the cornea for a total of 30 minutes. Riboflavin drops were applied to the cornea every 2 minutes during the total period of irradiation. After treatment, the eye was copiously irrigated with balanced salt solution, a drop of gatifloxacin 0.3% was instilled, and then a bandage soft contact lens was placed and kept for at least 4 days until complete epithelialization developed. Postoperatively, acetaminophen 500 mg every 8 hours was prescribed for pain for 3 days. Patients were instructed to instill 1 drop of gatifloxacin 0.3% 4 times daily for 2 weeks with 1 drop of tobramycin-dexamethasone 0.1% 4 times daily for 1 week. Thereafter, fluorometholone 0.1% was used 4 times daily, tapered over 6 weeks.

• **OPTICAL COHERENCE TOMOGRAPHY MEASUREMENTS AND OPERATOR ASSESSMENTS:** Corneal OCT was performed as part of the patients' routine corneal cross-linking protocol measurements, which are routinely performed preoperatively and 3 months postoperatively, with additional OCT measurements at subsequent visits. Eyes with previous corneal surgery, a history of corneal scar or keratitis, a history of autoimmune and/or connective tissue disease, a corneal thickness $<400 \mu\text{m}$ at the thinnest point, or poor OCT image quality were excluded. The Cirrus high-definition OCT (Cirrus HD-OCT; Carl Zeiss Meditec, Inc, Dublin, California, USA) was used for measurements, with the anterior segment cube 512×128 mode.¹¹ Corneal OCT measurements (120 sections of the cube 4×4 -mm videos) were independently evaluated at 3 months following CXL by 2 experienced operators (S.T.A. and M.A.A.) and a dedicated patented corneal OCT analysis software.^{12–14} The 2 human operators evaluated 120 horizontal sections of the cube 4×4 -mm videos. The operators selected the best cut where the demarcation line is most visible and then, using the built-in caliper, measured its depth in the central cross-line scans around the apex (30–90). Each operator independently repeated the measurements 1 week later. Both operators were masked to patients' names, results of each other, or the results of the previous measurements performed a week earlier. The corneal OCT image analysis software, devised in collaboration with the computer science department at the American University of Beirut, was also used to scan the 120 horizontal OCT cube sections for every patient at every time point.^{13,14} The software can automatically return the best representative cut in any selection, and the presence and depth of the demarcation line in that specific cut or any cut selected.

• **SOFTWARE ANALYSIS OF DEMARCATION LINE IN OPTICAL COHERENCE TOMOGRAPHY SECTIONS:** To obtain automated objective detection of corneal haze in the form of the demarcation line, a software solution was developed^{12–14} that employs machine learning to filter invalid OCT cuts, and performs custom image analysis techniques and makes use of methods from the image-processing library OpenCV (OpenCV version 3.1: Image processing software, December 2015, Intel Corporation, CA). The new software takes as input OCT images from the video files of the corneal OCT cube sections and provides 2 types of outputs: the first is the OCT image with visual annotations that reflect the detection and analysis of the linear corneal haze as well as the position of the demarcation line, and the second is statistics about the haze and demarcation line.

The process of detecting the demarcation line requires identifying the “brightest” curves that could potentially be the demarcation line, by computing a score $S(c)$ for every curve c , which is greater than a determined minimum score,

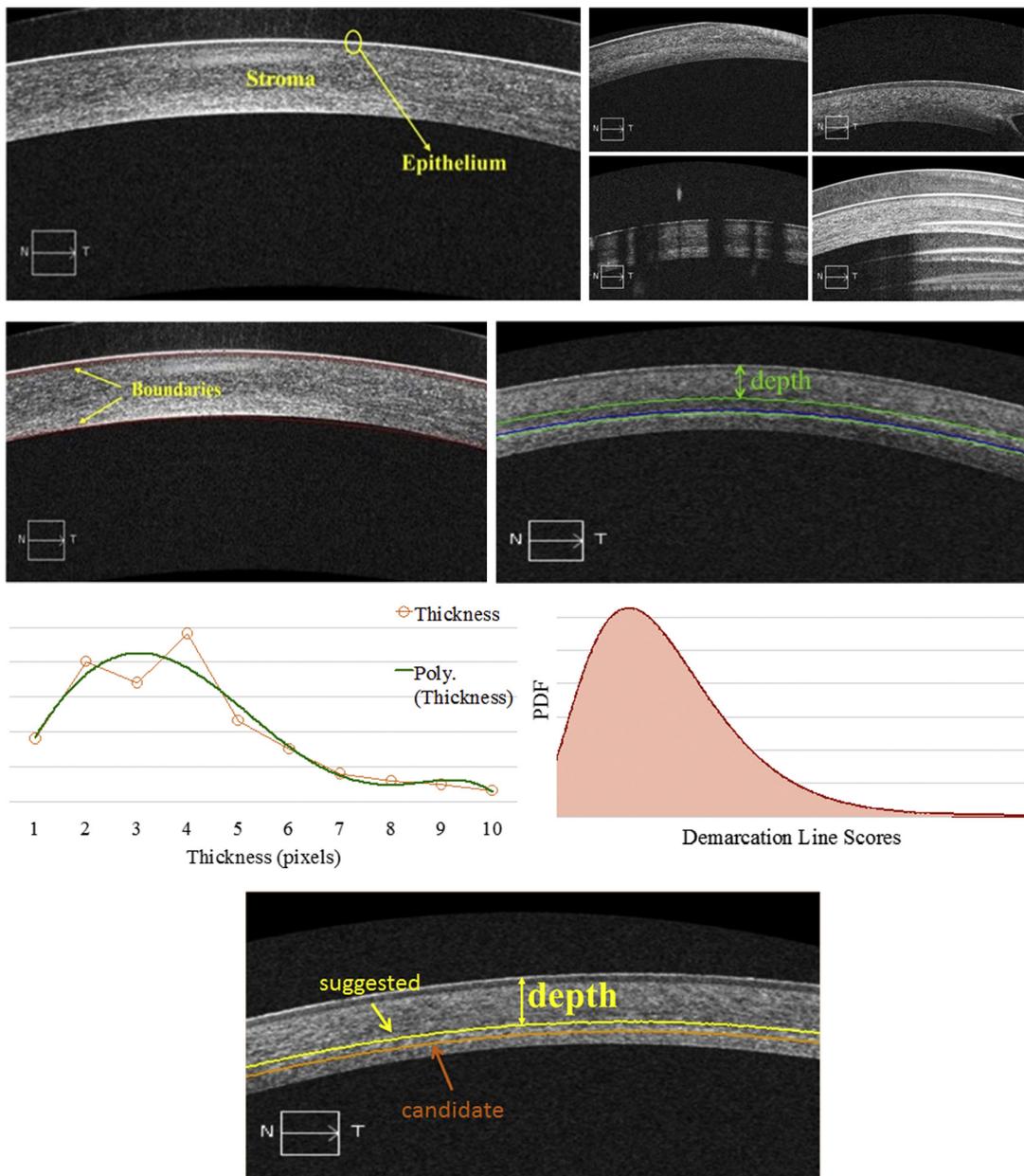


FIGURE 1. Steps of detection and analysis of demarcation line in optical coherence tomography (OCT) images. (Top left) Loading the OCT image/video into the program. (Top right) Filtering out invalid video cuts. (Middle up-left) detecting corneal boundaries and excluding the epithelium. (Middle up-right) Identifying “brighter” curves (ie, potential demarcation lines) using a score $S(c)$. (Middle down-left) Ensuring a fluctuating demarcation line within a small range is taken as 1 line. (Middle down-right) Computing the minimum required score, by observing the distribution of scores. (Bottom) Reporting the depths of the “suggested” and second-highest demarcation lines along with the corresponding cut.

denoted s ; and also observing the OCT cut in which the demarcation line appears the “clearest,” such that it consistently appears across valid cuts. To account for the fact that the demarcation line may not exist at the same depth across different cuts of the same image, a demarcation line is considered as being the same across cuts if it appears at a fluctuating depth of a certain small range obtained statistically from the available images. Subsequently, the detected

lines that get a score $S(c) > s$, are of the highest group of scores, and also are consistent are taken as potential demarcation lines. Finally, the potential line that gets the highest score is picked as *suggested* demarcation line and its corresponding cut is taken as the *best* cut; and the line with the second-highest score is reported as *candidate* line.

In summary, the detection and analysis of demarcation line in an OCT image is achieved by the automated

TABLE. Average Depth of Demarcation Line Measured by the Human Operators and the Software at 3 Months Postoperatively

	Operator #1		Operator #2		Software	P Value
	Mean 1st Measurement	Mean 2nd Measurement	Mean 1st Measurement	Mean 2nd Measurement		
Measurements (SD) μm	320.83 (44.20)	324.91 (49.06)	309.30 (43.18)	309.12 (40.23)	321.54 (47.71)	
Mean of 1st and 2nd measurements	322.86 (45.77)		309.21 (40.98)		321.54 (47.71)	.515 ^a

^aOne-way analysis of variance.

solution via the following steps: (1) loading the OCT image/video into the program (Figure 1, Top left); (2) filtering out invalid video cuts using machine learning (Figure 1, Top right); (3) detecting corneal boundaries (excluding the epithelium) for every valid cut (Figure 1, Middle up-left); (4) identifying “brighter” curves (ie, potential demarcation lines) using a score $S(c)$, which accounts for continuity and brightness, such that continuity has a higher weight (Figure 1, Middle up-right); (5) ensuring that a fluctuating demarcation line within a small range is taken as 1 line, by computing the average demarcation line thickness (Figure 1, Middle down-left); (6) computing the minimum required score, by observing the distribution of scores (Figure 1, Middle down-right); (7) picking the curves that consistently appear across valid cuts (15% was chosen based on clinical observations); (8) ranking the scores and selecting the highest group of scores using statistical fencing; and (9) reporting the depths of the “suggested” (ie, with highest score) and “candidate” (ie, second-highest) demarcation lines along with the corresponding cut (Figure 1, Bottom).

• **STATISTICAL ANALYSIS:** Statistical analysis was performed using SPSS version 22.0 (SPSS Inc, Chicago, Illinois, USA) and data management and analyses were run on Microsoft Office Excel (Microsoft Inc, Redmond, Washington, USA). Descriptive statistics were reported as means and standard deviations for continuous variables. Normality of the data distribution was assessed with the Kolmogorov-Smirnov test. One-way analysis of variance with Bonferroni correction for post hoc analysis was used to compare the baseline demarcation line depth measured by the 3 different operators. To evaluate the intraoperator repeatability and interoperator reproducibility, the intraclass correlation coefficient (ICC) was calculated from consecutive measurements obtained by the operators. Paired t test was used to compare the change in measured demarcation line depth by each operator, performed 1 week apart. Bland-Altman tests were used to evaluate the concordance over a varying range between 2 operators, with the x-axis measuring the average value between any 2 operators and the y-axis representing the difference. The 95% limits of agreement (LoA) between any 2 operators

were evaluated by the mean difference \pm 1.96 standard deviation of the difference, which defines the range within which 95% of the measurement differences between 2 operators should lie.¹⁵ A P value $<$.05 was considered to be statistically significant unless otherwise stated. The sample size calculation at 5% type 1 error was ≥ 14 . This was based on a known standard deviation of the demarcation line of 76 μm in the Dresden protocol,¹⁶ and a margin of error of 40 μm for human operators, as has been shown by Dhaini and associates using the Cirrus HD OCT.¹⁴

RESULTS

• **DEMOGRAPHICS:** The study comprised 25 consecutive eyes of 25 patients. In 1 eye the demarcation line was not detected either by the software or by any of the operators, and Operator #1 also missed an additional demarcation line. Hence 24 eyes were included in the final analysis and measurements of the demarcation line for the software and Operator #2, and 23 for Operator #1. The sample consisted of 15 male and 10 female subjects, with a mean age of 23.2 ± 6.4 years. Five eyes (20.0%) had grade 1 keratoconus according to the Amsler-Krumeich classification, 16 eyes (64.0%) had grade 2, and 4 eyes (16.0%) had grade 3. The mean baseline steepest keratometric value (Kmax) and the thinnest central corneal thickness were 54.24 ± 4.67 D and 468.69 ± 42.86 μm , respectively, as determined by Scheimpflug imaging.

• **DEMARCATIION LINE DEPTH MEASUREMENTS:** The Table summarizes the depth measurements by the human observers and the software at 3 months postoperatively. The software measured the demarcation line at 321.54 ± 47.71 μm , as compared to 322.86 ± 45.77 μm for Operator #1 and 309.21 ± 40.98 μm and for Operator #2. Post hoc analysis with Bonferroni correction showed no significant difference between Operator 1 and 2 ($P = .902$; mean difference = -13.66), between Operator #1 and software ($P = 1.000$; mean difference = -12.33), and between Operator #2 and software ($P = 1.000$; mean difference = 1.33). The average time spent by the operator per OCT

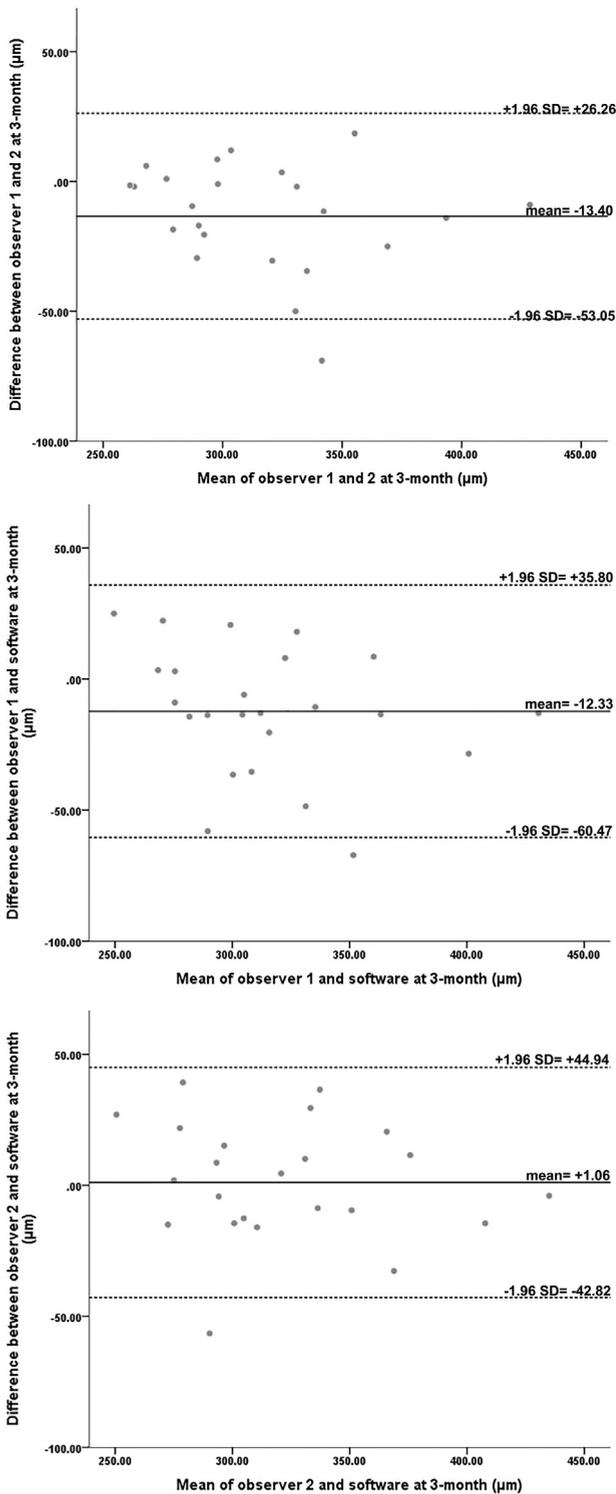


FIGURE 2. Bland-Altman plots show the agreement between Observer #1 and Observer #2 (Top plot), Observer #1 and the software (Middle plot), and Observer #2 and the software (Bottom plot). Also showing the mean bias between observers for each and the 95% confidence intervals (limits of agreement) for the differences (± 1.96 SD).

examination was 31 seconds, as compared to 1 second by the software. The average time reported is the time spent in browsing 1 video scan and identifying the demarcation line and subsequently assessing its depth in the best representative section.

- **REPRODUCIBILITY AND REPEATABILITY OF DEMARCATION LINE MEASUREMENTS:** The ICCs between different operators (software or human), representing reproducibility, were relatively high at 3 months. ICC was calculated at 0.884 ($P < .001$) for Operator #1 and 0.847 ($P < .001$) for Operator #2, compared to the software, and 0.890 ($P < .001$) between the 2 independent human operators. The calculated ICC values for the 2 measurements of the same operator, representing repeatability, were also high at 0.922 ($P < .001$) for Operator #1 and 0.925 ($P < .001$) for Operator #2.

- **BLAND-ALTMAN DEMARCATION LINE RESULTS:** Bland-Altman plots of measurement differences between the software and each of the operators, and between the operators, showed that the measurement differences were independent of the depth of the measurements (Figure 2). There was a good agreement between Observer #1 and Observer #2, between Observer #1 and the software, and between Observer #2 and the software, with 95% limits of agreement (-53.05 to 26.26 μm , -60.47 to 35.80 μm , and -42.82 to 44.94 μm , respectively).

DISCUSSION

CROSS-LINKING HAS BEEN SHOWN TO BE A SUCCESSFUL procedure to halt disease progression in keratoconus. However, primary treatment failure has been reported at a rate of around 0 to 7.6% and long-term progression of the disease can still occur, potentially necessitating another cross-linking procedure.¹⁷⁻²⁰ The lack of solid in vivo biomechanical evidence of corneal strengthening has steered clinicians toward using the demarcation line presence and depth as a tool to gauge the depth of the treatment. Shallow treatments were associated with less stabilizing and flattening effects after cross-linking.^{7,8,21} The demarcation line depth, however, does not necessarily correlate with treatment success, but rather correlates with treatment depth. Additionally, the demarcation line depth might be a parameter to consider when planning a surface ablation procedure to regularize corneal topography or treat mild refractive error post corneal cross-linking. Moreover, a wide array of new cross-linking methods that have been developed over the past few years, such as ones using varying acceleration via increased mean radiant energy, transepithelial techniques,

and iontophoresis, have shown variable and sometimes conflicting data about the demarcation line presence and depth.^{7,8} The ability to objectively and reproducibly measure the demarcation line is a key component in the development, refinement, and further adoption of a new cross-linking technique.

Evaluating the demarcation line presence and depth has no gold standard. Initially described at the slit lamp,¹⁰ evaluation using Scheimpflug devices,²² OCT imaging,^{23,24} and in vivo confocal microscopy has been described.^{9,25,26} Of these methods, corneal OCT and confocal microscopy, using intensity increase threshold, were shown to correlate well, while demarcation line measurements derived from Scheimpflug imaging were deemed inaccurate.^{9,27} Thorsrud and associates have shown that the reproducibility of confocal microscopy was slightly better than OCT (both of which are human observer dependent) in determining the demarcation line depth.⁹ The ICC was 0.83 for OCT, compared to 0.93 for confocal microscopy (CM) relying on intensity increase and 0.92 for CM relying on keratocyte disappearance. In addition, there was a statistical difference between the mean demarcation depths measured on OCT images by the 2 observers, while no statistical difference was detected between the confocal microscopy readings. However, time-domain OCT was used to perform the measurement. Our study relied on spectral-domain OCT, which provides a higher resolution and accuracy and has been shown to provide better interobserver reliability when measuring laser in situ keratomileusis flap depth.²⁸ The problem with confocal microscopy is that it involves touching the patient's eye, requiring significant patient cooperation and examination time. Additionally, image analysis entails an experienced operator and is more difficult to automate. Finally, confocal microscopy is not commonly found in eye clinics, in contradistinction to OCT machines, which are much more ubiquitous, are more patient-friendly, and require basic operator and observer skills.

In an attempt to improve the repeatability and reproducibility of OCT measurements of the demarcation line post

corneal cross-linking, we have devised a software to automatically detect the demarcation line. The software would provide a standardized method to analyze OCT images by theoretically bypassing the human bias, in addition to performing a significantly faster evaluation, hence allowing for large data analysis, a key factor in reviewing the success of emerging techniques of cross-linking, with possible refinement and further development. Our data shows excellent correlation and reproducibility for OCT images as read by 2 independent observers. Interestingly, the software-analyzed demarcation line correlated very well with the human observers at 3 months. Moreover, the mean demarcation line depth measured by the software was very similar to that measured by the 2 observers, and was in between the 2 values; 309.21 ± 40.98 (Operator #2), 321.54 ± 47.71 (software), 322.86 ± 45.77 (Operator #1) ($P = .515$).

The demarcation depth values read by both software and human observers were less than the ones of Thorsrud and associates, as the latter group have instilled riboflavin dextran for 20 minutes only, which might have affected the total depth of penetration of the molecule and hence might have resulted in a shallower demarcation line.⁹ However, the measured demarcation line depth was comparable to other studies using a more faithful version of the Dresden protocol: Doors and associates, 313.00 ± 61.00 μm²³ and Brittingham and associates, 323.14 ± 76.04 μm.¹⁶

In conclusion, with the flourishing and varying landscape of corneal cross-linking techniques, establishing an objective, standardized, and reproducible measure of cross-linking depth is key. As OCT technology is becoming mainstream and essential to every clinic, eliminating subjective readings and relying more on fast, automated image analysis that can constantly improve using machine learning is the most natural first step. The latter seems to correlate overall with the human observers without the inter- and intraobserver discrepancies, hence standardizing success measures, an essential premise for both clinical decision making and research.

FUNDING/SUPPORT: THIS WORK IS SPONSORED BY THE NATIONAL COUNCIL FOR SCIENTIFIC RESEARCH (CNRS), LEBANON, grant no. CNRS-GRP-L 103495-103487. Financial Disclosures: The following authors have no financial disclosures: Shady T. Awwad, Maamoun Abdul Fattah, Manal Shokr, and Ahmad R. Dhaini. All authors attest that they meet the current ICMJE criteria for authorship.

REFERENCES

1. Kim BZ, Jordan CA, McGhee CN, Patel DV. Natural history of corneal haze after corneal collagen crosslinking in keratoconus using Scheimpflug analysis. *J Cataract Refract Surg* 2016;42(7):1053–1059.
2. Kolli S, Aslanides IM. Safety and efficacy of collagen cross-linking for the treatment of keratoconus. *Expert Opin Drug Saf* 2010;9(6):949–957.
3. Meiri Z, Keren S, Rosenblatt A, Sarig T, Shenhav L, Varssano D. Efficacy of corneal collagen cross-linking for the treatment of keratoconus: a systematic review and meta-analysis. *Cornea* 2016;35(3):417–428.
4. Esquenazi S, He J, Li N, Bazan HE. Immunofluorescence of rabbit corneas after collagen cross-linking treatment with riboflavin and ultraviolet A. *Cornea* 2010;29(4):412–417.
5. Wollensak G, Iomdina E, Dittert DD, Herbst H. Wound healing in the rabbit cornea after corneal collagen

- cross-linking with riboflavin and UVA. *Cornea* 2007;26(5):600–605.
6. Wollensak G, Spoerl E, Reber F, Seiler T. Keratocyte cytotoxicity of riboflavin/UVA-treatment in vitro. *Eye (Lond)* 2004;18(7):718–722.
 7. Kaya V, Utine CA, Yilmaz OF. Efficacy of corneal collagen cross-linking using a custom epithelial debridement technique in thin corneas: a confocal microscopy study. *J Refract Surg* 2011;27(6):444–450.
 8. Caporossi A, Mazzotta C, Paradiso AL, Baiocchi S, Marigliani D, Caporossi T. Transepithelial corneal collagen crosslinking for progressive keratoconus: 24-month clinical results. *J Cataract Refract Surg* 2013;39(8):1157–1163.
 9. Thorsrud A, Sandvik GF, Hagem AM, Drolsum L. Measuring the depth of crosslinking demarcation line in vivo: comparison of methods and devices. *J Cataract Refract Surg* 2017;43(2):255–262.
 10. Seiler T, Hafezi F. Corneal cross-linking-induced stromal demarcation line. *Cornea* 2006;25(9):1057–1059.
 11. Rodrigues EB, Johanson M, Penha FM. Anterior segment tomography with the cirrus optical coherence tomography. *J Ophthalmol* 2012;2012:806989.
 12. Dhaini AR, El-Oud S, Awwad S, Abdu Fattah M, Chokr M. System and method for automated detection and measurement of corneal haze and demarcation line in optical coherence tomography images. US 20180365833 A1; July 2017.
 13. Dhaini AR, Abdul Fattah M, El-Oud SM, Awwad ST. Automated detection and classification of corneal haze using optical coherence tomography in patients with keratoconus after cross-linking. *Cornea* 2018;37(7):863–869.
 14. Dhaini AR, Chokr M, El-Oud S, Abdul Fattah M, Awwad S. Automated detection and measurement of corneal haze and demarcation line in spectral-domain optical coherence tomography images. *IEEE Access* 2018;6:3977–3991.
 15. Bland JM, Altman DG. Measuring agreement in method comparison studies. *Stat Methods Med Res* 1999;8(2):135–160.
 16. Brittingham S, Tappeiner C, Frueh BE. Corneal cross-linking in keratoconus using the standard and rapid treatment protocol: differences in demarcation line and 12-month outcomes. *Invest Ophthalmol Vis Sci* 2014;55(12):8371–8376.
 17. Koller T, Mrochen M, Seiler T. Complication and failure rates after corneal crosslinking. *J Cataract Refract Surg* 2009;35(8):1358–1362.
 18. Raiskup-Wolf F, Hoyer A, Spoerl E, Pillunat LE. Collagen crosslinking with riboflavin and ultraviolet-A light in keratoconus: long-term results. *J Cataract Refract Surg* 2008;34(5):796–801.
 19. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-a-induced collagen crosslinking for the treatment of keratoconus. *Am J Ophthalmol* 2003;135(5):620–627.
 20. Caporossi A, Baiocchi S, Mazzotta C, Traversi C, Caporossi T. Parasurgical therapy for keratoconus by riboflavin-ultraviolet type A rays induced cross-linking of corneal collagen: preliminary refractive results in an Italian study. *J Cataract Refract Surg* 2006;32(5):837–845.
 21. Sinha RA, Dupps WJ Jr. Patient-specific computational modeling of keratoconus progression and differential responses to collagen cross-linking. *Invest Ophthalmol Vis Sci* 2011;52(12):9174–9187.
 22. Beckman Rehnman J, Janbaz CC, Behndig A, Lindén C. Spatial distribution of corneal light scattering after corneal collagen crosslinking. *J Cataract Refract Surg* 2011;37(11):1939–1944.
 23. Doors M, Tahzib NG, Eggink FA, Berendschot TT, Webers CA, Nuijts RM. Use of anterior segment optical coherence tomography to study corneal changes after collagen cross-linking. *Am J Ophthalmol* 2009;148(6):844–851.e842.
 24. Caporossi A, Mazzotta C, Baiocchi S, Caporossi T. Long-term results of riboflavin ultraviolet a corneal collagen cross-linking for keratoconus in Italy: the Siena eye cross study. *Am J Ophthalmol* 2010;149(4):585–593.
 25. Mazzotta C, Balestrazzi A, Traversi C, et al. Treatment of progressive keratoconus by riboflavin-UVA-induced cross-linking of corneal collagen: ultrastructural analysis by Heidelberg Retinal Tomograph II in vivo confocal microscopy in humans. *Cornea* 2007;26(4):390–397.
 26. Mazzotta C, Traversi C, Baiocchi S, et al. Corneal healing after riboflavin ultraviolet-A collagen cross-linking determined by confocal laser scanning microscopy in vivo: early and late modifications. *Am J Ophthalmol* 2008;146(4):527–533.
 27. Huebscher H, Fink W, Steinbrück D, Seiler T. Scheimpflug records without distortion—a mythos? *Ophthalmic Res* 1999;31(2):134–139.
 28. Hall RC, Mohamed FK, Htoon HM, Tan DT, Mehta JS. Laser in situ keratomileusis flap measurements: comparison between observers and between spectral-domain and time-domain anterior segment optical coherence tomography. *J Cataract Refract Surg* 2011;37(3):544–551.