Author's response to reviews

Title: Reproducibility of Corneal Graft Thickness measurements with COLGATE in patients who have undergone DSAEK (Descemet Stripping Automated Endothelial Keratoplasty)

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Editor-in-chief

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Dear Editor,

Revision of Manuscript 1919134325636301 - Reproducibility of Corneal Graft Thickness measurements with COLGATE in patients who have undergone DSAEK (Descemet Stripping Automated Endothelial Keratoplasty)

We would like to thank the reviewers’ kind comments. We have made the following changes as shown below. In response to the editorial team’s question about ethics approval, our study was approved by Singhealth Institutional Review Board.

We look forward to your response.

Yours sincerely,

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Reply to reviewer 1 comments:

1) Reference number 1 is not the original reference for DSAEK. The authors may choose to leave it as is, but they should also cite one of the more original articles.

Thank you for your comments. We have made the change. Please refer to the new reference Melles GR, Wijdh RH, Nieuwendaal CP. A technique to excise the descemet membrane from a recipient cornea (descemotorhesis). Cornea. 2004;23(3):286-8 on pg 18 reference no. 1.

2) Reference 2 is old from 1993 and reference 3 is not citable. There are many contemporary OCT references that can be used.


3) I'm unaware of any sales data for the current OCT machines, but the Optovue is commonly used in the United States. It is not clear if the authors are referring to Fourier domain OCT that uses a moving mirror or previous time domain systems.

Both systems have moving mirrors. To avoid confusion, we have changed the sentence to “the most commonly used systems today are ... and the slit lamp OCT (Heidelberg Engineering, Heidelberg, Germany) which are time domain OCTs. As a result of involuntary eye movements...” on pg 5 line 78 -79

4) Please cite a reference documenting slow image acquisition. The word “reduced” resolution is used but were not told what the comparison is. They might consider citing the resolution of the various OCT systems or better yet, use a table to compare them. Can they cite a reference showing that the higher resolution instruments do not allow the image acquisition across the entire anterior chamber?

We apologize for the confusion and have clarified this comment, we meant that the fourier technology allows more scans to be captured per unit time compared to the time domain technology. As such we have omitted the word “slow” and kept the sentence as “image acquisition is usually of reduced resolution compared to newer systems using fourier domain technology” Pg 5 Line 79-80.
We have referenced the sentence “higher resolution instruments do not allow the image acquisition across the entire anterior chamber” to “Wylegala E, Teper S, Dobrowolski D et al. Anterior segment imaging: Fourier-domain optical coherence tomography versus time-domain optical coherence tomography. J Cataract Refract Surg. 2009;35(8):1410-4.” Pg 1 Ref no:3 and comparison of the various OCT systems to reference “Leung CK, Weinreb RN. Anterior chamber angle imaging with optical coherence tomography. Eye 2011. 25:261-7” pg 5 and Reference 4

We have also created a table comparing the various OCT machines as suggested. Please refer to table 1.

5) Since reference 4 belongs to the company and is not citable, the authors can use a better citable reference or place the Visante manual citation as a footnote.

-Thank you. We have deleted the reference and changed it to a foot note. Pls see pg 13

6) The sentence that begins: “The interobserver and intraobserver results for the time domain machine were similar to that previously published; reference 5 is listed. What is the previous publication they referred to?

-We have referenced the sentence “The interobserver and intraobserver...to that previously published” to reference number 2 “Li Y, Netto MV, Shekhar R, Krueger RR, Huang D. A longitudinal study of LASIK flap and stromal thickness with high-speed optical coherence tomography. Ophthalmology 2007;114(6):1124-32. Epub 2007 Feb 23.” Pls see pg 18 reference no. 2

7) The following data on the LOA and correlation coefficients are compared to what study?

-Thank you. The following data on LOA and Correlation coefficients are reported in our own previous study by Hall et al. Laser in situ keratomileusis flap measurements: Comparison between observers and between spectral-domain and time-domain anterior segment optical coherence tomography. J Cataract and Refract Surg 2011;37(3):544-51” on pg 18 reference no. 6

-To make it clearer, we have changed the sentence to “Using the time domain machine, the interobserver correlation coefficients (r) were 0.73 (-1.5mm from centre), 0.62 (centre) and 0.78 (+1.5mm from the centre). For spectral domain...LoA was much closer for the two observers, and interobserver correlation coefficients were (much stronger: 0.82 (-1.5mm from the centre).....and 0.88 (+1.5mm from the centre)” Please refer to page 13 lines 254-58

8) The Colgate reference is not citable as is because it is a presentation. The authors may consider it as an unpublished observation or as a footnote.

Thank you. The colgate reference has recently been published and we have changed it in the reference page. “Lee BH, Mehta J, Wong TY et al. Corneal graft
9) At the end of the paragraph references 5 and 14 are listed, but 7 through 13 are not listed until they are cited further in the text.
-Thank you. We have rearranged the references.

10) The last paragraph the Background belongs in the Discussion.
-Thank you. We have shifted the last paragraph in the background to the discussion. Pls see pg 13 lines 247-62
11) The 1st section of the Methods might be better as Image Acquisition instead of Scanning.
-Thank you. We have made the change. Pls see pg 7 line 120

12)"Dark" conditions are mentioned but are not defined
-Thank you . We have elaborated on the sentence to “ The ASOCT images... were obtained using high resolution cornea images in a completely dark room with no windows and the only lighted areas were the fixation target this equates to 20lux illumination” Pls see pg 7 lines 124-5

13) The operator adjusted the system... I assume they mean the system software, but they could also mean the orientation of the hardware”
- Thank you. We have changed the sentence to “ The operator adjusted the software to position the ... to maximize the vertex reflection”. Pls see pg 7 line 131

14) They should state that all images were obtained by the same operator for all 50 eyes.
-Thank you. We have added the statement “ the images were obtained by the same operator for all 50 eyes.” Pls see page 8Line 133
15) Most of the image processing paragraph is either not referenced or not explained. It would probably be better to describe the Colgate program at this point. The reader does not know what the Canny Edge software is or does. We do not know how the authors determined the output to be sampled steps in 10 pixels. I assume this is from unpublished observations. Similar comments can be made about the subsequent paragraph descriptions of selecting the boundaries.
- Thank you. The Colgate program and the canny edge software has been described in detail in the paper by Lee BH, Mehta J, Wong TY et al. Corneal graft detection for Descemet’s stripping automated endothelial keratoplasty using optical coherence tomography. Conf Proc IEEE Eng Med Biol Soc. 2010;2010: 3037-40. We have referenced this paper for more detailed description about the output sampling.
16) Did the 2 individuals who acquired the scans have any previous experience with the Colgate system or was this the 1st time they ever used it? The answer will help the reader understand the simplicity of the system if they used it for the first time.

-The two individuals were taught how to use the software but it was the first time using the software on the 50 ASOCT images.— We have added this statement to pg 9 line 161

17) The 1st sentence of the Results appears to be a repeat of the 1st sentence of Intraobserver Repeatability

-Thank you. We have deleted the first sentence under intraobserver repeatability. Pls see pg 10 line 183-4

18) In the comparison between automated and semi-automated, 4 sets of readings were taken. Were these readings on all 50 eyes? All of the results can be easily displayed in a table or 2 tables to help decrease the length of the manuscript

-Thank you. We have placed the results in tables 2 to 4. All readings were on 50 eyes. Pls see attached tables.

19) The limitations of analysis that the semi--automated method measured 2 times that of the manual method is not placed in the Results section, and is placed in the discussion for the 1st time.

- The automated method did not measure twice that of the manual for most of the grafts but did give consistently larger values than the semi-automated. We have added the sentence under results “In both observers, the automated method gave consistently larger values than the semi automated method”. Pls see pg 12 line 241-242

- We have also corrected the wording under discussion to “in particular graft areas of less than 80,000 um2 measured by the automated method had more than double the ....by the semi automated method” pls see pg 14 line 270

20) The authors refer to the semi-automated program as being similar to the Heidelberg Retina Tomograph. It also appears to be very similar to the software used by the Artemis high-frequency ultrasound system.

-Thank you, We have added the artemis as another example. Pls see pg 19. We have referenced it to reference no. 9

21) The authors should also mention that the Optovue system also utilizes similar caliber software in a similar manner with similar potential errors of measurement
-Thank you. We have included the above information in. Pls see pg 15 line 303-304

22) It is not clear to this reviewer how knowledge of the postoperative graft would allow the surgeon to better visually rehabilitate a case. For example, if the measurement shows a graph thicker than X um, do they recommend graft exchange irrespective of the visual acuity at that point in time? And if a graft measures on the thin side, but the vision is poor what would they recommend? Since it is well known that graft thickness and cell density do not correlate, this generalization needs to be more clearly thought out.

-We agree that cell density does not correlate to graft thickness, however graft thickness can be an indication as to how well the graft is functioning i.e. graft failure. In addition, there is increasing interest in the graft thickness and graft refractive power. If we know the expected hyperopia from the calculated graft thickness, this can help the surgeon determine the refractive end point especially when performing a combined DSEK with phacoemulsification. We have added the latter part in the conclusion. Pls see page 17 line 353-355

23) Do the authors think the software can also be used to measure anterior lamellar grafts or Lasik flaps?

-Yes it can. We have included it in the discussion “there are other uses of this software. Its use can be extended to evaluating penetrating keratoplasty grafts..., anterior and deep anterior lamellar grafts as well as lasik flaps” Pls see pg 16 line 322-323
1. Throughout the manuscript, the measurements that are being evaluated are referred to as the "DSAEK graft area". I understand that the authors are referring to the "area under the curve" of the cross-section of the DSAEK button, however, this phrasing is a bit confusing. It may be helpful early on the paper to include a schematic to visually demonstrate what is being measured (or at least to clarify this in the text). The confusion arises in that often when we refer to the area of the graft we think of the circumferential area. Graft thickness is most often thought of as a linear measurement, not as an area, and so it would be helpful to the readers to clarify this further.

- Thank you. We have included a figure to explain the area measured as figure 1.

2a. The authors used 50 images from 23 patients. They state that multiple horizontal scans were performed but only the best quality used for measurements. How did they decide how many images to use from each patient? Were these arbitrary numbers of patients and scans?

- These were arbitrary numbers of scans taken from patients since the objective of this paper was to assess the reliability of the software. Each scan is taken as a single entity since we are not comparing between patients. Hence, whether more than one scan comes from the same patient at different time points is not relevant to the objectives of this study.

2b. Can they further explain the characteristics of the images that were considered to be of high enough quality for inclusion in the study?

- We have refined the statement in the methods section that “To obtain the best quality image, the examiner adjusted the saturation and noise and optimized the polarization for each scan during the examination so as to obtain good discernible images with high signal to noise ratio.” Page 7 line 126-128

3. It would also be interesting (although perhaps outside of the realm of this study) to demonstrate how image quality changes the inter-observer and intra-observer reproducibility of the measurements. This would be somewhat akin to studies that were done by the Cornea Donor Study Group for the Specular Microscopy Ancillary Study.(1) Lass JH, Gal RL, Ruedy KJ, et al. An evaluation of image quality and accuracy of eye bank measurement of endothelial cell density in the Specular Microscopy Ancillary Study. Ophthaimology. 2005;112:431-40.
Thank you. We agree with the reviewer but really is out of the realm of this paper but this is an interesting point and we have included it in our discussion.

4. Overall, the manuscript is well-organized, however, I think there is too much material in the background section. Some of this can be moved into the discussion section. For instance, in the third paragraph of the background section: "However, there is much subjective variation in caliper placement by users, and inter-observer variations of measurements have been shown to have a SD of ...." I would consider putting everything between "have been shown to have an SD of...." and ".../semi-automated system would be more efficient, faster, and reduce the inherent error rate" into the discussion section. Similarly, I would consider putting the information in the last paragraph of the background section into the discussion section with the exception of the last two sentences.

Thank you. We have made the suggested changes. Pls see pg 13 line 247-262

5. The second to last paragraph of the background section is awkwardly worded. Please revise

Thank you. We have reworded the last paragraph. Page 6 line 103-6

6. Define AS-OCT within the manuscript. It is used first in the methods section under "Scanning" but is not defined.

We have made the change. Pls see pg 7 line 122

7. Figure 1. Where is figure 1 actually referenced within the text? Would recommend dividing the figure into "1A" and "1B" so that it can better clarified in the Legend what is being demonstrated in the two images. Particularly in the semi-automated image, is it possible to illustrate what the user is actually able to manually adjust when refining the edges of the graft?

Thank you. We have changed it figure 2A and 2B on Pg 8 Line 148 and line 154. In the semi automated image, the user is able to manually adjust the edges of the curve given by the software.

8. When referencing "table 1" and "table 2" in the results section, please place these in parenthesis and not just at the end of the paragraph. Alternatively, consider incorporating into the body of the text (ie -- "Table 1 shows the....."

Thank you. We have made the change. Page 10 line 195 and pg 11 line 212.