Author's response to reviews

Title: Automated analysis of digital fundus autofluorescence images of geographic atrophy in advanced age-related macular degeneration using confocal scanning laser ophthalmoscopy (cSLO)

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Author's response to reviews: see over
Dear editor,

we would like to submit our revised manuscript

*Automated analysis of digital fundus autofluorescence images of geographic atrophy in advanced age-related macular degeneration using confocal scanning laser ophthalmoscopy (cSLO)*

for publication in BMC ophthalmology.

The reviewer Fridbert Jonasson suggested to take the advice of an English-speaking professional. Therefore, with assistance of an English-speaking professional and depending on the review of Fridbert Jonasson we revised our article in the following points (sometimes we took the suggestions of the English-speaking professional instead of the reviewer’s suggestions):

- **Review:** I would suggest to change the title from: “Automated analysis of digital confocal scanning laser ophthalmoscopy fundus autofluorescence images of geographic atrophy in advanced age-related macular degeneration.” To:
  “Automated analysis of digital confocal scanning laser ophthalmoscopy fundus autofluorescence images of geographic atrophy in age-related macular degeneration.”
  Revised: “Automated analysis of digital fundus autofluorescence images of geographic atrophy in advanced age-related macular degeneration using confocal scanning laser ophthalmoscopy (cSLO)”

- **Review:** Abstract: Methods, Page 2, line 1: “…allows to process images with lower quality.” Allows images of lower quality to be processed? Please explain further.
  Revised: Abstract: Methods, Page 2, line 2, “…process low-quality images.”

- **Review:** Results, Page 2, line 1: “The new method (C) identifies vascular structures that interfere with GA.” Do these vascular structures not rather interfere with the delineation of GA?
  Revised: changed in “…with the delineation of GA”

- **Review:** Page 2, Results, line 1 & 2. “It is not inferior to formerly used procedures (A; B).” ? May be the authors are suggesting that the new method is comparable to the two previously used procedures (A; B).
  Revised: changed in “Results are comparable to those of two commonly used procedures …”

- **Review:** Conclusion, Page 2, line 1: “The novel procedure compares in objectivity and inter-reader agreement to established ways to quantify GA.” May be the authors are suggesting that: “The novel procedure compares favorably in objectivity and inter-reader agreement to established ways of quantifying GA.”?
  Revised: “…is comparable…”

- **Review:** Next sentence: “It has the potential of speeding up …etc” Has it the potential or does it speed up the process?
  Revised: “It considerably speeds up the lengthy measurement process in AF with will defined GA zones.”

- **Review:** Background, Page 3, line 1: “Age-related macular degeneration (AMD) has become the most common cause of legal blindness in industrialized nations beyond 50 years of age [1-4].” I would suggest: “Age-related macular
degeneration (AMD) is the most common cause of legal blindness among industrialized nations beyond age 50 years (1-4).”

• Review: Methods, Page 4, line 17: “and instead of this the contour is minimally smoothed and widened there.” I think the last word “there” is redundant and in the following line may be “thus” is more appropriate than “so”. Revised: “…and instead the contour is minimally smoothed and widened. As a result the process…”

• Review: Page 4, fifth line from bottom: “Images of bad quality often contain….”. I would suggest using “poor” rather than “bad” quality. Revised: “…poor quality...”

• Review: Page 4, fourth line from bottom: “….before achieving the true borders of the GA.” Do the authors mean: “…. before identifying the true borders?...”. Revised: “…before identifying the true borders of the GA.”

• Review: Validation, Page 5, line 2: “The data for both eyes exist [13] and are used for validating.” I would suggest for instance: “The data for both eyes is available and is used for validating in the present study.” Revised: changed in “Validation is based on the material collected in a previous study [13], with published data from the right eye only. Data for both eyes are available [13] and are used for validation.”

• Review: Page 5, line 2: “The same readers evaluated ....etc”. Were they masked to previous results with different methods? Revised: “The same readers evaluated the same material, but using the new method. The images were evaluated in random order and the readers had no access to the previous results based on methods A and B.”

• Review: Page 5, line 6: “…. ANOVA techniques...” I suggest deleting “techniques” and in parenthesis write out ANOVA. Revised: “…ANOVA (Analysis of Variance)....”

• Review: Results, Page 5, line 1: “Table 1 shows the complete data of the study.” I would instead suggest: “Table 1 shows the results for the 40 eyes included in the study.” Revised: changed in “Table 1 shows the results for the 40 eyes included in the study.”

• Review: Page 5, line 8: There is probably a typographical error “expect” written instead of “except”. Page 5, paragraph 1, line 8: “Methods B and C differ not significantly...”. I suggest: “Methods B and C do not differ significantly...”. Revised: “…except that methods B and C also do not differ significantly…”

• Review: Discussion, Page 6, paragraph 2, line 3: “...but not due to the used method.” The reviewer suggests: “… but not due to the method used.” Revised: “… but not due to the used method.”

• Review: Page 6, paragraph 3, second line: “Training the readers before ...etc”. This sentence is not comprehensible Revised: “Method B has only one degree of decision freedom and should theoretically be the most objective. But the bias in objectivity of method C is, first of all, a result of more than one degree of decision freedom (in comparison with method
B). Therefore, the readers were trained in using method C. This made the objectivity of method C not significantly inferior to method B. The remaining bias of method C is redeemed by fewer outliers and less dispersion. Even within method C, there was a clear difference in how the readers interpreted the same AF images (see figure 3).

- Review: Page 7, paragraph 2, line 8: The word “contemporary” is probably not a good choice – at the same time or “concurrent” might be better
Revised: “… at the same time…”

- Review: Page 7, paragraph 2, line 9: “Additionally improved effectiveness…etc”. Do the authors mean additionally improved effectiveness must be demonstrated using the new method if it is to replace previous methods? Few sentences on this page are incomprehensible.
Revised: “Additionally, improved effectiveness must be demonstrated…”

- Review: Page 8, paragraph 1, line 3: “With this, a large part of GAs ….etc”. After the word “this” the word approach is probably missing.
Revised: Hence, a large proportion of Gas can be measured in short time…”

- Review: Page 8, paragraph 2, line 1-4: Delete
Revised: done

- Review: Page 8, paragraph 2, line 8: The word “papilla” may be replaced by “optic disc”.
Revised: The sentences “For example, the time-consuming manual whitewashing of interfering vessels has proved to be the main disadvantage of method B. Since automatic vessel detection does not interfere with objectivity, it is also possible to combine the algorithm with method B. A presentation of the possibility of automatic segmentation in qualified images, as well as manual mouse-driven contours in images with continuous passages from GA to papilla within the same tool, will facilitate the covering of a wide range of image qualities.” were removed.

- Review: Page 8, paragraph 3, line 2-3: “Consequently, the falsification….etc”. The sentence is difficult to understand. The following lines also appear to include important information but the sentences are difficult to understand.
Revised: “Consequently, care should be taken that no clinical relevance is attached to artificial differences due solely to repeated use of a method or to different users. Furthermore, a method comparison using the Bland-Altman design will only be meaningful if there are well-defined limits of agreement and clinically relevant bounds [15]”

- Review: Page 8, paragraph 3, line 9: The word “imaginable” is probably translation of the German word denkbar – “possible” would be a better choice.
Revised: The sentences “If, for example, the dispersion of method B does not touch the region of clinical relevance, a combination of segmentation by a threshold value with the vessel detection instead of the more pretentious region-growing is imaginable. The Data of the FAM-study (article submitted) shows a mean increment of GA area of 1,8 mm² per patient and year with a variability of 0,87mm² so far. For example: a possible upper bound of 0,6 mm² could be derived for clinical relevance.” were removed.

- We followed the suggestion of the reviewer to shorten and rewrite the conclusion chapter. We shortened some paragraphs and exchanged some in their order.

The second review from Eberhard Zenner contains only three points of criticism:
Review: Abstract: The authors refer to two previously published methods. They should briefly describe/introduce these methods.
Revised: Background: "With method A, atrophic areas are outlined on the screen using the mouse-driven cursor of the HEE software program. The areas are then measured and the data exported manually to an Excel spreadsheet by cut and paste. This completely manual, mouse-driven method A is time-consuming and can exaggerate subjective impressions. Mistakes can occur as a result of the error-prone interface between the user’s hand and the computer mouse [13]. This implies that the accuracy of mouse-driven contour painting depends not only on subjective impressions, but also on the user’s dexterity.
With method B, the images are exported as bitmap files from the HEE program. interfering vascular structures, which appear as dark atrophic areas, are manually repainted white using the mouse-driven paintbrush of Microsoft Paint. The modified images are then transferred to Global Lab Image 2 and the remaining dark areas are measured using a threshold procedure tool. The resulting data are exported to Microsoft Excel manually by cut and paste [13]."

Review: Abstract, Results: The authors should give reasons why the method C is not inferior to two formerly used procedures. Actually, this statement should appear in the Conclusions, rather than in the Results section of the abstract.
Revised: Conclusions: “Comparability, repeatability, and objectivity are crucial factors to consider when developing a new method. ... We conclude that method C is not inferior to the two commonly methods used in measuring GA areas.”

Review: Discussion (page 7): The third paragraph “The study presented is a pilot study” should rather appear in the Introduction
Revised: Introduction, methods: “Agreement between observers and between three different methods was evaluated by two independent readers in a pilot study.”