Author’s response to reviews

Title: The ChromaTest, a Digital Color Contrast Sensitivity Analyzer, for Diabetic Maculopathy

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Version: 2 Date: 7 January 2008

Author’s response to reviews: see over
Reviewer's report
Title: The ChromaTest, a Digital Color Contrast Sensitivity Analyzer, for Diabetic Maculopathy
Version: 1 Date: 28 September 2007
Reviewer: Tony Casswell
Reviewer's report:
This is an interesting paper indicating that testing tritan in diabetics could be a useful screening tool.

- Major Compulsory Revisions
(1) pg3: Methods: No mention of how control data was obtained. Pg 4 line 20 Control data was obtained from unpublished data collected by G.B. Arden from diabetic patients without any diabetic retinopathy prior to this study. (Figure 1)
(2) pg5, par 2: Selection of eyes for analyses. Please clarify how this was done e.g. was the authors using one eye per subject or both eyes for the analyses? The final 115 eyes with NPDR and 35 with CSME comprised of how many subjects? If the dataset consist of patients who contributed both eyes and patients who contributed only one eye, then it might affect the statistically analysis. I feel that only one eye from each patient should be used in analysis unless the authors can demonstrate that the TCCT and PCCT of Right Eye and Left Eye of each patient are independent of each other, ie there is no correlation between them. Pg 5 line 14 150 eyes of 150 patients were included in this study. Of the 150 eyes, 115 eyes had untreated NPDR (Figure 2) and 35 eyes had untreated CSMO (Figure 3).
(3) Pg 5, par 3: Any statistical significant difference between the diabetic groups (NPDR & CSME) and age-matched controls? Pg 5 line 20 When compared to controls (Figure 3), PCCT for NPDR had no statistical significance (p=0.15) whereas PCCT for CSMO was significant (p=0.002).
(4) Pg5, par 3: Suggest a bar/column chart showing the TCCT, PCCT of NPDR, CSME as well as respective age-matched controls groups. See Figure 1-3
(5) Studies have demonstrated that diabetes duration correlates strongly with increases in lens optical density, even among patients with relatively short diabetes duration. Consequently, any tritan deficit seen in diabetics may be wholly or partly due to the pre-retinal absorption of short-wavelength light resulting from lens yellowing. Did the authors take into consideration lens-yellowing effect suffered by diabetics in the analyses? Pg 7 line 19 Cataract and pseudophakia were not excluded as both are more common in diabetics and exclusion would have limited the usefulness of the Chromatetest in screening. It is understood that lens-yellowing effects due to cataract may cause pre-retinal absorption of short-wavelength light resulting in tritan deficits. This may have influenced the overall sensitivity and specificity of the study, but it was a representation of the realistic setting clinicians experience in their practice.

(6) Pg 6, par 1,2: What is the 95% confidence interval for the sensitivity and specificity stated? Is the 72% sensitivity and 74% specificity stated statistically significant? Pg 6 line 6 71% (95% confidence interval: 53-85%) and 70% (95% confidence interval: 60-78%)
(7) Pg 7 par 2 & par 3: TCCT above/below normal levels: Are these age-matched normal levels? Are these differences statistically significant? Table 1: $\chi^2$ test: $p<0.0001$ What does “above normal levels” implies? It is not immediately apparent whether it implies the TCCT is worse or better than the normal level. A small sentence should be added for those individuals who never had any experience of TCCT measurement to make it easier to understand such as: The higher the TCCT score the more abnormal the result. Pg 8 line 3 In colour contrast testing, the higher the TCCT or PCCT score, the more abnormal the result compared to age-matched normal levels.

(8) The authors aim to assess the ability of the Chromatest as a screening tool for CSME. In practice, it would actually be better if the authors assess the ability of the Chromatest to screen for sight-threatening diabetic retinopathy (PDR and CSME) rather than just CSME. Unfortunately, there were not enough patients with untreated PDR to study and we felt PDR was easier to diagnose on digital fundus photography

(9) it is not clear why “those patients with CSME classified due to exudate and retinal thickening within 1 disc diameter of the fovea are excluded” to improve sensitivity. Do the authors mean exudates with no central macular thickening? Yes. Pg 6 line 10 When patients with CSMO with central macular thickening only are analysed, sensitivity to detect CSMO improves to 83.3% (CI: 58-96%) $p<0.0001$.

(10) Further comment on conditioning and speed of the test would be helpful. If conditioning is a a problem corrected by a longer test time, can the test be regarded as a quick 5 minute process? Pg 9 line 5 Conditioning following testing with the right eye may also allow patients to perform better on their left eye. From anecdotal evidence, time for testing of the second eye was observed by the investigators to be shorter than the first eye. Repeated testing which was not done in our study may alleviate this problem.

- Minor Essential Revisions
The author can be trusted to make these. For example, missing labels on figures, the wrong use of a term, spelling mistakes.
- Discretionary Revisions
These are recommendations for improvement which the author can choose to ignore. For example clarifications, data that would be useful but not essential. Please note that both the comments entered here and answers to the questions below constitute the report, bearing your name, that will be forwarded to the authors and published on the site if the article is accepted.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable
Reviewer's report
Title: The ChromaTest, a Digital Color Contrast Sensitivity Analyzer, for Diabetic Maculopathy
Version: 1 Date: 19 November 2007
Reviewer: Keith A Goatman
Reviewer's report:
General
An interesting study let down by a vague methodology section and weak statistical analysis.
This is very much a pilot study, including only low numbers of patients with CSME, and reusing the same data for training and testing purposes.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. Abstract mentions 22 eyes with CSME, but the results seem to show 35 eyes with CSME. Pg 2 line 11 150 eyes in 150 patients were recruited into this study. 35 eyes with no previous laser photocoagulation were shown to have clinically significant macular oedema (CSMO) and 115 eyes with untreated non-proliferative diabetic retinopathy (NPDR) on fundus biomicroscopy.

2. Method
The methodology section is too vague regarding the method used to determine specificity and sensitivity ("pass/fail criterion"). I couldn't replicate the sensitivity and specificity quoted (for instance, a threshold of 18% on the TCCT gave a sensitivity of 74% (26/35) and specificity 54% (62/115)). I think it's more usual to quote sensitivity then specificity. It's also usual to include confidence intervals on sensitivities and specificities, especially where numbers are small as here.

"In each BCVA group" is confusing, as I think the authors mean in all eyes rather than in each group separately. Pg 6 line 3 Each age group (eg. 30-49 years old, 50-69, 70-89) separated by 2 decades was assigned pass-fail criterion for TCCT as previous data suggests age related change in threshold for tritan colour. Sensitivity and specificity for screening of CSMO using pass-fail criterion for age matched TCCT results achieved 71% (95% confidence interval: 53-85%) and 70% (95% confidence interval: 60-78%), respectively (Table 1).

It should be made clear in the methodology that the test and training sets are the same (not just mentioned in the discussion).

Pg 4 line 22 Test and training sets are both from the group studied in this report.

I also have concerns about the statistical analysis:
(a) Ranges and SDs are quoted for parameters which are clearly not normally distributed (e.g. VA). Pg 5 line 15 Median age was 60 years. Median duration of diabetes was 16.0 years. Median LogMar BCVA for NPDR patients was 0.2 and for CSMO patients was 0.20. Median PCCT for NPDR was 3.9% and for CSMO patients was 5.6%.

(b) What is the "non-parametric t test" used here? As I understand it, the t test is a parametric test, so a non-parametric t test isn't a t test, it's some alternative (such as Wilcoxon Rank Sum test). As the data is not normally distributed a t-test is, rightly, out of the question. Using a Wilcoxon Rank Sum test on this data I got quite different p-values than the authors, with both PCCT and TCCT appearing significantly different (p < 0.01) between CSME/non-CSME groups. Some more details of the test used (including software used) and justification for the test used is important. Pg 5 line 19 Wilcoxon Rank Sum Test analysis revealed no statistical significant difference between CSMO and NPDR eyes for PCCT (p=0.17). When compared to
controls (Figure 3), PCCT for NPDR had no statistical significance (p=0.15) whereas PCCT for CSMO was significant (p=0.002).

Discussion
Several times "normal levels" are mentioned. What are these normal levels? Were they determined by this study or somewhere else?
Pg 4 line 20 Control data was obtained from unpublished data collected by G.B. Arden from diabetic patients without any diabetic retinopathy prior to this study. (Figure 1)

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Discretionary Revisions (which the author can choose to ignore)
What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions
Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests:
I declare that I have no competing interests

Reviewer's report
Title: The ChromaTest, a Digital Color Contrast Sensitivity Analyzer, for Diabetic Maculopathy
Version: 1 Date: 16 November 2007
Reviewer: Deborah Broadbent
Reviewer's report:
General
This is an interesting paper presenting the use of a relatively well established technology in a new field. The authors have demonstrated that in a limited group of patients the test is effective at detecting diabetic maculopathy, but have not
really indicated how they think that the test can be used to improve the detection of maculopathy and possibly referrable retinopathy in view of the fact that there exists a national screening programme based on a more effective method. It may well be that the ChromaTest could be used as an adjunct to improve detection of clinically significant macular oedema once surrogate markers have been identified by digital photography, but this is not discussed. This is alluded to in the abstract but not explored in the discussion.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

It is not acceptable to refer to people with diabetes as “diabetics”. Please change this throughout the document. The correct notation is people / patients with Type 1 or Type 2 diabetes. This has been changed.

Abstract Results

The first sentence is not clear. Please indicate that after exclusion only 115 eyes in 150 patients were recruited into the study and that of these 22 eyes had clinically significant macular oedema on slit lamp biomicroscopy.

Para 1, Line 2. The authors state that various studies have looked at cost-effectiveness but only quote one relatively old paper. Suggest add more references. This has been added.

Para 1, Line 3. 7 field 30 degree stereo colour photographs is the gold standard for detection of diabetic retinopathy. Neither stereomacular colour photographs nor fluorescein angiography are the standard for screening for DR. In the UK the National Screening Programme for Diabetic Retinopathy utilises non-stereo digital photography as this meets the Diabetes UK standards for sensitivity and specificity. Pg 3 line 3 Although 7 field 30 degree stereo colour fundus photographs are the gold standard for diabetic screening, both remain relatively expensive and difficult to obtain4, 5.

Para 1, Line 7. In the discussion protan colour vision is also cited as being affected in diabetic maculopathy. The development of a blue-yellow defect has previously been described in diabetic retinopathy. The authors do not refer to this. A blue-yellow defect can also occur in glaucoma. How do the authors think the ChromaTest distinguish between diabetic retinopathy and glaucoma since patients with glaucoma and other eye conditions have been excluded from this study? Pg 6 line 20 Abnormal protan and especially tritan colour vision is associated with diabetic retinopathy13. Blue-yellow defect has also been described in both diabetic retinopathy and glaucoma14. In contrast to the optotype used for testing macular function, the Chromatest has a separate glaucoma module for which it is designed to measure peripheral colour sensitivity changes in an arcuate manner using a central fixation point. This study did not cross examine patients with glaucoma and diabetic retinopathy using both glaucoma and macular modules, but it is feasible that further testing may reveal an overlap in colour defect for these patients.
Methods
Para 3. The authors need to give the normal responses for the ChromaTest. Without them it is difficult to interpret the results. Pg 4 line 20 Control data was obtained from unpublished data collected by G.B. Arden from diabetic patients without any diabetic retinopathy prior to this study. (Figure 1)

Results
Although standard deviations are given confidence limits should be quoted as the numbers in the study are small. Pg 6 line 6 71% (95% confidence interval: 53-85%) and 70% (95% confidence interval: 60-78%)

Para 4. This paragraph is confusing. Do the authors mean in the first sentence that overall, whatever the BCVA, the sensitivity and specificity for detection of CSMO are as given? . Pg 6 line 3 Each age group (eg. 30-49 years old, 50-69, 70-89) separated by 2 decades was assigned pass-fail criterion for TCCT as previous data suggests age related change in threshold for tritan colour.
Does the second sentence refer to all patients with a logMAR of 0.1 or better?
Were there any patients with CSMO and logMAR 0.1 or better? Yes In which case is the ChromaTest better at detecting CSMO in patients with good vision than those with poor vision? Yes. This was quoted by Ong et al in subanalysis and therefore a similar subanalysis was performed in this manuscript.
Para 5. What does this sentence signify? Are the authors referring to sensitivity for detection of NPDR alone? When patients with NPDR and CSMO who had logMar BCVA of 0.1 or better are analysed, sensitivity to detect CSMO improves to 75% (CI: 47-91%) and specificity to 85% (CI: 67-89%) p=0.0002.

Conclusion
This is actually discussion! This has been changed
Para 2. Last sentence. Why might the use of smaller letters give better results for CSMO? What is the evidence to back up this statement? Pg 7 line 12 The use of smaller letters (1.5 degree; Chromatest module for age related macular degeneration) might give better results for CSMO as it may test macular function better than the larger 6.5 degree optotype.

Para 3. Line 2. Is likely to be identical to what? Pg 7 line 17 Although the mechanism of diabetic retinopathy is likely to be identical in both type 1 and type 2 diabetes, previous studies such as the Early Treatment Diabetic Retinopathy Study and Diabetic Retinopathy Study have investigated each type of diabetes separately.

Para 4. Why was congenital colour blindness not confirmed by other means?
Pg 8 line 8 This was not confirmed with any other mode of investigation as the study was aimed at mimicking realistic clinical setting where high volume testing can be conducted without further time consuming tests.

Para 4. How do the authors account for the poor results in 4 eyes without severe NPDR? What concurrent but undiagnosed disease do the authors think they might have had? Would fundus fluorescein angiography have helped?
We postulate that these 7 eyes may have had concurrent disease indistinguishable by indirect biomicroscopy such as more advanced ischaemia. Ultimately, fluorescein angiography may have further elucidated the true pathology.

Para 5. Please give the correct definition for CSMO for the 7 eyes quoted. The definition of CSMO should also be quoted earlier in the paper. Pg 8 line 15. 8 eyes had CSMO qualified as 1 disc diameter of retinal thickening within 1 disc diameter of the fovea. 2 eyes had exudates with associated retinal thickening within 500 microns of the fovea.

Para 5. What evidence do the authors have for their speculation that patients had learned responses? Pg 9 line 5 Conditioning following testing with the right eye may also allow patients to perform better on their left eye. From anecdotal evidence, time for testing of the second eye was observed by the investigators to be shorter than the first eye. Repeated testing which was not done in our study may alleviate this problem.

Para 9. I am very unclear as to where the authors see the role of the ChromaTest. They discuss the fact that physicians are less good than ophthalmologists at detecting retinopathy. However they have completely ignored the fact that all patients with diabetes in the UK are regularly screened for diabetic retinopathy using digital photography.

The authors need to consider how the use of the ChromaTest will augment this methodology since it clearly does not have the sensitivity or specificity to replace it. Pg 10 line 12. Perhaps with further investigation, TCCT testing may become a supplement for detecting and monitoring sight threatening pathology without much equipment or trained technicians. However, with current data, all forms of TCCT testing including the Chromatetest do not qualify for use in screening for CSMO.

The discussion could also usefully consider the use of optical coherence tomography in this regard. Pg 10 line 10 Furthermore, optical coherence tomography has become a powerful tool in screening and monitoring CSMO with sensitivity and specificity rates of near 80% and 90%, respectively.

References
These are incorrectly cited in the paper and there are typos. This has been corrected
There is also a better reference for the “Exeter Standards” for sensitivity and specificity in Diabetes Medicine. The British Diabetes Association is now known as Diabetes UK. This has been added.
although CSME is correct as the ETDRS studies were conducted in the US, convention in the UK refers to CSMO. This has been changed

Methods
Para 1. What is the relevance of collection of risk factor data to this paper?
Para 3. It might be useful to describe in non-technical terms how the ChromaTest assesses and reports proton and tritan colour defects.

Results
Para 1. It would be useful to indicate from “Fifty eyes..” onward that these patients were exclusions. Why were the patients with proliferative retinopathy excluded?
Para 4. Conventionally sensitivity is quoted before specificity. Pg 6 line 3 Each age group (eg. 30-49 years old, 50-69, 70-89) separated by 2 decades was assigned pass-fail criterion for TCCT as previous data suggests age related change in threshold for tritan colour. Sensitivity and specificity for screening of CSMO using pass-fail criterion for age matched TCCT results achieved 71% (95% confidence interval: 53-85%) and 70% (95% confidence interval: 60-78%), respectively (Table 1).

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions
Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Needs some language corrections before being published
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I declare that I have no competing interests