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### RESEARCH ARTICLE

# **Corneal laser procedure for vision improvement in patients**

# with late stage dry age-related macular degeneration - a

# retrospective observational cohort study [version 1; peer

# review: 2 approved with reservations]

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#### Abstract

<u>Purpose</u>: To determine the safety and efficacy of corneal photovitrification (CPV), a new corneal laser procedure, for vision improvement in patients with late stage dry age-related macular degeneration (AMD).

<u>Design</u>: Retrospective observational cohort study <u>Participants</u>: 32 eyes of 17 patients with late stage dry AMD; each eye received a single CPV corneal laser procedure and had 12 months (12m) post-treatment (Tx) follow-up.

<u>Methods</u>: Pre- and post-Tx examinations included slit-lamp biomicroscopy, subjective manifest refraction, best corrected distance and near visual acuity (BCDVA and BCNVA), and potential visual acuity (PVA). Additional examinations including contrast sensitivity (CS), corneal topography (CT), ray tracing aberrometry (RTA) and microperimetry (MP) were obtained for a subgroup (n=12) of eyes. <u>Main Outcome Measures</u>: BCDVA, BCNVA, PVA, CS, CT, RTA and MP measurements

<u>Results</u>: <u>Safety</u> – There were no complications or adverse events. <u>Efficacy</u> – Mean ( $\pm$  SD) BCDVA improved significantly (p < 0.004) from 20/238 (1.08 logMAR) at baseline to 20/144 (0.86 logMAR) at 12m post-Tx corresponding to 11.0 ( $\pm$  13.1) letters gained. Mean contrast sensitivity improved significantly (p < 0.05) by a factor of 1.86 from baseline at 12m post-Tx.

<u>Conclusions</u>: Subject to the limitation of a small sample size, this pilot study indicates that the CPV corneal laser procedure is safe and efficacious for vision improvement in patients with late stage dry

### Open Peer Review

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AMD. The CPV Tx mechanism of action involves retinal irradiance distribution modifications that may stimulate patient use of functional, rather than atrophied, retinal regions.

#### **Keywords**

cornea, laser, retina, vision improvement, age-related macular degeneration



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gateway.

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#### Introduction

Age-related macular degeneration (AMD) is a leading cause of vision impairment globally1. Several FDA-approved pharmacologic treatments are available for the neovascular form of AMD (also termed "wet" AMD); in particular, anti-vascular endothelial growth factor (anti-VEGF) injections are broadly used to manage the disease by reducing its progression and, in many cases, by providing some vision improvement<sup>2</sup>. However, management of dry AMD and especially geographic atrophy (GA), late stage AMD, has proven to be more challenging. There are no FDA-approved pharmacologic treatments<sup>3</sup> and only limited success in providing vision improvement has been obtained by use of intraocular implants<sup>4</sup>, of which only the implantable miniature telescope (IMT)<sup>5</sup> is FDA-approved. Dry AMD procedures such as subthreshold laser therapy<sup>6</sup> and photobiomodulation<sup>7</sup> are directed primarily toward improving retinal function for early to intermediate stage AMD patients. Low vision aids such as prism spectacles<sup>8</sup> and electronic glasses<sup>9</sup> are also available but have not been broadly used by late stage dry AMD patients. The purpose of the present study is to describe a new corneal laser procedure that offers significant vision improvement in patients with late stage dry AMD.

#### Methods

This retrospective observational cohort study (registered with ClinicalTrials.gov NCT04349254 on 16 April 2020) was completed in conformance with ethical principles of the World Medical Association Declaration of Helsinki. The study protocol (Pro00044329) was approved on 4 August 2020 by an institutional review board (Advarra, Aurora, Ontario, Canada). Written Informed consent, with a provision for release of medical records, was obtained from each patient prior to treatment. Patients were primarily referred by optometrists and treated in the clinic during the period February through November 2018. Clinic records of 32 eyes of 17 patients [8F, 9M; mean (± SD) age: 81.7 (± 8.8) y; range: 58-96 y; all of Caucasian ancestry] with late stage dry age-related macular degeneration who had received one treatment in each eve using the same device and protocol and with 12-month (12m) follow-up examinations were identified and patient records were examined during the period August through October 2020. Eyes were either pseudophakic or phakic with no visually significant cataract. All patient eyes had vision impairment, with mean  $\pm$  SD best spectacle-corrected distance and near visual acuities (BCDVA and BCNVA) of 20/238 (1.08 ± 0.37 logMAR; 31 letters) and 20/199 (1.00 ± 0.29 logMAR; 35 letters), respectively. The study size was limited by the availability of records but the size was confirmed to provide statistical significance of outcome measures.

Inclusion criteria included age of  $\geq 55$  y and, in the eye to be treated, diagnosed late stage dry AMD, moderate to profound BCDVA impairment (in the range of 20/44 to 20/1000), normal corneal topography (*i.e.*, without distorted or unclear mires) and examinations extending to at least 12 months post-Tx. Exclusion criteria included previous corneal surgery and visually significant ocular disease other than AMD.

Examinations included slit-lamp biomicroscopy; optical coherence tomography; subjective manifest refraction (SMR); BCDVA and BCNVA; potential visual acuity (PVA)<sup>10</sup> using Gonzalez-Markowitz charts (Precision Vision, Woodstock, IL) at 50 cm examination distance. For a subset of eyes (n=12), additional examinations included: 1) contrast sensitivity (CS) using Pelli-Robson charts (Precision Vision, Woodstock, IL), 2) corneal topography (CT) and ray tracing aberrometry (RTA) using an iTrace analyzer (Tracey Technologies, Houston, TX) and 3) retinal sensitivity, fixation stability and preferred retinal locus using a Macular Integrity Assessment (MAIA) microperimeter (MP; Centervue, Fremont, CA). SMR, BCDVA and BCNVA examinations were completed pre-Tx for 32 eyes and at 1 month (1m), 3m, 6m, and 12m post-Tx for 29, 28, 28 and 32 eyes, respectively; SMR measurements were recorded for all eyes pre-Tx but only for 12 eyes post-Tx. PVA examinations were completed pre-Tx for 20 eyes. Other examinations (CS, CT, RTA and MP) were completed pre-Tx and at post-Tx times extending to 12m post-Tx for 12 eyes (CS, CT and RTA) and 8 eyes (MP).

Treatments were completed using a Clear-K<sup>®</sup> Low Vision Aid System (Optimal Acuity Corporation, Austin, TX) to deliver pulsed laser energy simultaneously to the cornea in 4 spots of 0.5 mm diameter arranged symmetrically 90° apart and located on a 6.0 mm diameter ring centered on the pupillary centroid as shown in Figure 1. Laser parameters included 2  $\mu$ m wavelength, 150 ms pulse duration and 48 to 50 mJ energy per spot. Laser light was transmitted from the console through an optical fiber array terminated by a handpiece that docks onto a sapphire applanation window/suction ring (SAWSR)



**Figure 1.** Clear-K® treatment pattern of 4 spots of 0.5 mm diameter spaced 90° apart (in this case, located on 30°, 120°, 210° and 300° semimeridians) on the 6.0 mm optical zone centered on the pupillary centroid. Actual Tx spots are barely visible under room lighting conditions.

assembly mounted on the eye. Laser energy was delivered through the SAWSR onto the eye in order to provide a fixed location of treatment spots with epithelial protection (by the sapphire window acting as a heat sink) from thermal damage. Treatments produced small corneal changes in shape that acted to redirect light onto functional regions of the retina. Patients were reclined to a supine position, given a drop of topical anaesthetic in the eye to be treated, and then treated.

Statistical significances of paired outcomes were assessed by Wilcoxon signed rank tests. Intereye correlations in bilateral treatments and correlations between potential visual acuity test measurements and visual acuity changes were assessed by Pearson correlation coefficients; statistical significances of the correlations were evaluated by bootstrap resampling. OD and OS logMAR values for correlated bilateral treatments were averaged for each outcome (BCDVA and BCNVA at baseline and at each follow-up time) in order to calculate statistical significances of post- *vs.* pre-Tx differences<sup>11</sup>. Many outcomes are reported as mean ( $\pm$  standard deviation) values. Microsoft Excel software (2010) functions were used for statistical analysis.

#### Results

Safety

No complications or significant adverse events occurred.

#### Efficacy

The mean BCDVA and BCNVA of the treated eyes increased from baseline at each follow-up (f/u) time, as shown in Figure 2<sup>12</sup> in terms of mean letters of vision gained on standard eye charts and in Figure 312 in terms of a histogram of percentages of changes in lines of vision at 12m post-Tx. Table 1<sup>12</sup> summarizes descriptive statistics of outcomes for bilateral treatments [calculated with intereye correlation, since Pearson correlation coefficients are positive and large (mean: 0.6) for all outcomes], for unilateral treatments, and for all (unilateral plus uncorrelated bilateral) treatments. For all treatments (and for bilateral Txs only), all outcomes are statistically significant at the p<0.05 level. The largest mean (± SD) gain of 14.6 (± 11.1) letters in BCDVA was achieved at 1m post-Tx; the mean BCDVA gain was stable at ca. 11 to 12 letters from 3m to 12m post-Tx. 58.6% (17 of 29) of treated eyes gained 15 or more letters (3 or more lines) of BCDVA at 1m post-Tx compared to baseline; this success percentage decreased to 43.8% (14 of 32 eyes) at 12m post-Tx, possibly due to regression of treatment effect and/or progressive dry AMD vision loss. Figure 212 also shows the expected mean BCDVA loss for untreated late stage AMD eyes for a similar cohort from another study<sup>13</sup>, amounting to 4.1 letters lost at 12m. So, the 11.9 letter mean gain in BCDVA at 12m post-Tx for CPV treated eyes is actually 15 letters mean better vision than expected for untreated eyes.



Figure 2. Top timelines - Mean letters gained for Clear-K® corneal laser (CL) best corrected distance visual acuity (BCDVA) and best corrected near visual acuity (BCNVA) outcomes. Bottom timeline – Mean BCDVA letters lost for a similar cohort of untreated eyes (from Ref. 13).



VA Changes at 12m Post-Tx

Figure 3. Visual acuity (VA) changes from baseline for treated eyes at 12m post-Tx. The histogram shows the percentage of eyes that lost 1, 2 or 3 or more lines of vision, were unchanged, or gained 1, 2, or 3 or more lines of best corrected distance visual acuity (BCDVA) and best corrected near visual acuity (BCNVA).

Table 1. Letters gained: Best corrected distance visual acuity (BCDVA)outcomes (top table) and best corrected near visual acuity (BCNVA)outcomes (bottom table) statistics for treated eyes at 1m through12m post-Tx times. Entries contain the mean and standard deviation ofletters gained, sample size (n) and p-value (where appropriate).

BCDVA Outcomes	1m	3m	6m	12m
Bilateral Txs with intereye correlation	14.6 ± 11.1 n=14 p=0.003	11.2 ± 10.8 n=13 p=0.005	12.0 ± 10.0 n=13 p=0.004	11.9 ± 13.0 n=15 p=0.004
Unilateral Txs	15 n=1	7.5 ± 10.6 n=2	2.5 ± 3.5 n=2	-2.5 ± 3.5 n=2
All Txs	14.6 ± 10.9 n=29	10.9 ± 10.6 n=28	11.3 ± 10.0 n=28	11.0 ± 13.1 n=32
BCNVA Outcomes	1m	3m	6m	12m
<b>BCNVA Outcomes</b> Bilateral Txs with intereye correlation	<b>1m</b> 15.3 ± 11.4 n=12 p=0.004	<b>3m</b> 14.4 ± 12.1 n=13 p=0.004	<b>6m</b> 13.4 ± 10.5 n=12 p=0.002	<b>12m</b> 14.5 ± 12.0 n=13 p=0.002
BCNVA Outcomes Bilateral Txs with intereye correlation Unilateral Txs	<b>1m</b> 15.3 ± 11.4 n=12 p=0.004 n/a	<b>3m</b> 14.4 ± 12.1 n=13 p=0.004 5 n=1	<b>6m</b> 13.4 ± 10.5 n=12 p=0.002 10 n=1	<b>12m</b> 14.5 ± 12.0 n=13 p=0.002 2.5 ± 3.5 n=2

Pre-Tx potential visual acuity (PVA) measurements<sup>10</sup> demonstrated variable improvements compared to pre-Tx BCDVA measurements: 6 eyes had less than 10 letters (2 lines) improvement, 6 eyes had between 10 to 14 letters (2 to 2.8 lines) improvement and 8 eyes had 15 or more letters (3 or more lines) improvement. 1m post-Tx mean BCDVA improvements correlated moderately well (Pearson correlation coefficient = 0.44; p < 0.03) with pre-Tx mean PVA improvements. The Pearson correlation coefficient = 0.32 (p < 0.12) for 3m post-Tx mean BCDVA improvements with pre-Tx mean PVA improvements was also moderately good. Pearson correlation coefficients for 6m and 12m post-Tx mean BCDVAs compared to pre-Tx mean PVAs were near-zero and were not statistically significant. The decrease in correlation may be caused by partial loss of treatment effect and, in part, by the progressive loss of BCDVA in dry AMD eyes. In the "best" mean PVA improvement group (with 15 or more letters improvement relative to baseline BCDVA), the mean (± SD) post-Tx BCDVA improvements were 21.0 ( $\pm$  12.1) and 15.2 ( $\pm$  13.6) letters at 1m and 3m, respectively, compared to lesser BCDVA improvements of 8.8 (± 12.0) and 5.4 (± 8.7) letters at 1m and 3m, respectively, for the PVA improvement group of 14 or less letters improvement relative to baseline BCDVA.

The mean binocular BCDVA and BCNVA values also increased significantly compared to baseline values. No symptoms of aniseikonia, polyplopia or dysphotopsia were found in all or most patients although one patient had aniseikonia that was probably due to a large difference between spectacle lenses. Amsler grid tests typically demonstrated line straightening and reduction and/or relocation of dark and missing areas.

Slit-lamp biomicroscope examination of treated corneas showed that treated spots were indented and lightly opacified; corneal epithelia were intact. Goldmann applanation tonometry measurements showed that mean intraocular pressures were unchanged at each post-Tx time.

Mean monocular contrast sensitivity (CS; at *ca.* 1 cycle/degree) of the treated eyes, as measured under photopic conditions without glare, increased as a function of follow-up time [significantly (p < 0.05) at all f/u times] – *e.g.*, from log CS (mean  $\pm$  SD) = 0.73  $\pm$  0.40 pre-Tx to 1.00  $\pm$  0.33 at 12m post-Tx, representing a mean CS increase by a factor of 1.86 from baseline. Mean binocular CS also increased as a function of f/u time by amounts similar to monocular increases.

Pre-Tx, the mean subjective manifest refraction (SMR) of the subset (n=8) of treated eyes with both SMR and aberrometry measurements was -0.41 D sphere - 0.81 D cylinder X 113°, 2.50 D add; -0.81 ( $\pm$  0.46) D spherical equivalent (SE). At 1m post-Tx, the mean SMR was -0.31 D sphere - 0.53 D cylinder X 90°, 2.50 D add; -0.58 ( $\pm$  0.43) D SE corresponding to a mean ( $\pm$  SD) hyperopic SE shift of +0.23 ( $\pm$  0.33) D from baseline. The changes in SMR values from pre-Tx to 1m post-Tx were small, as were SMR changes from baseline to 3m and longer post-Tx. At 12m post-Tx, the mean ( $\pm$  SD) SMR SE change from baseline was -0.98 ( $\pm$  0.76) D. None of the SE changes were statistically significant.

Ray tracing aberrometry (RTA) measurements provided information on retinal irradiance distribution modifications (IDMs) and objective refraction (OR) changes. Pre-Tx, rays of light incident on the cornea produced a "tight" pattern of retinal irradiation. Post-Tx, rays of light incident on the 3 mm optical zone (OZ) of the cornea were redistributed outward from the pre-Tx pattern center on the retina by a maximum mean ( $\pm$  SD) IDM value of 37  $\pm$  20 µm. Pre-Tx, the mean OR of the treated eyes with aberrometry measurements was 0.16 D sphere - 1.65 D cylinder X 85°; -0.67 (±0.93) D SE. At 1m post-Tx, the mean OR was -0.22 D sphere - 1.92 D cylinder X 101°; -1.18 (± 0.77) D SE corresponding to a mean (± SD) myopic SE shift of -0.51 ( $\pm$  0.52) D from baseline by aberrometry (in contrast to the SMR mean hyperopic SE shift of 0.23 D). At 12m post-Tx, the mean (± SD) aberrometry myopic SE shift from baseline was -0.12 (± 0.86) D, a smaller shift than the SMR myopic SE shift. Mean (± SD) total aberrations increased from 0.42 ( $\pm$  0.21) µm at baseline to 0.53 ( $\pm$ 0.33) µm and 0.44 (± 0.27) µm at 1m and 12m post-Tx, respectively. Most of the aberrometric changes were due to increased lower order (defocus and astigmatism) changes; both defocus and astigmatism increased. None of the total aberration changes were statistically significant.

Corneal topography (CT) measurements provided information on corneal refractive changes, averaged within the 3 mm optical zone to calculate an Effective Refractive Power (Eff RP) and Astigmatism (Astig). Pre-Tx, mean ( $\pm$  SD) Eff RP and Astig values were 44.22 ( $\pm$  1.09) D and 1.51 ( $\pm$  1.21) D, respectively. At 1m and 12m post-Tx, mean ( $\pm$  SD) Eff RP changes were 0.39 ( $\pm$  0.32) D and 0.22 ( $\pm$  0.45) D, respectively, while mean ( $\pm$  SD) Astig changes were 0.04 ( $\pm$  0.67) D and 0.06 ( $\pm$  0.45) D. None of the Eff RP or Astig changes are statistically significant.

Detailed (non-averaged) CT changes were obtained from CT difference maps. Figure 412 shows sample CT difference (1d post-Tx minus pre-Tx) maps in terms of Z Elevation and Refraction changes. In the left panel of Figure 4<sup>12</sup>, depressions are evident in the Z Elevation map with maximum depressions centered on treatment spots that are located on the 6 mm optical zone (OZ). Maximum depressions vary from spot to spot in the range of -10 to -22  $\mu$ m, with a mean (± SD) of -15.5 ( $\pm$  5.2) µm. In the right panel of Figure 4<sup>12</sup>, refractive increases are evident in the Refractive map with maximum increases on ca. the 4 mm OZ. Maximum refraction increases vary from spot to spot in the range of 1.0 to 2.1 D, with a mean (± SD) of 1.44 (± 0.51) D. At 1m post-Tx, Z Elevation and maximum Refraction changes decreased to mean (± SD) values of -10.6 (± 3.7)  $\mu m$  and 0.90 (± 0.38) D, respectively. At 12m post-Tx, the Z Elevation and maximum Refraction changes decreased further to mean (± SD) values of -7.4 (± 4.1)  $\mu$ m and 0.71 (± 0.46) D, respectively. For all eyes with CT measurements, the mean Z Elevation changes from baseline were approximately -18 µm at 1d post-Tx, decreasing to -12 µm and -8 µm at 1m and 12m post-Tx, respectively. The corresponding mean Refraction changes from baseline were approximately 2.1D, 1.1 D and 0.7 D at 1d, 1m and 12m post-Tx, respectively.



**Figure 4.** Corneal topography difference (1d post-Tx minus pre-Tx) maps of Z Elevation change (left; µm units) and Refractive change (right; diopter units) for one treated patient eye. Grids display 1 mm increments. Left map: Tx spots are located at 6.0 mm optical zone (OZ). Right map: maximum refractive changes are located at *ca*. 4 mm OZ. Tx spots were located as shown in Figure 1.

Microperimetry exams showed that fixation stability (FS) improved post-Tx, as determined by 95% bivariate contour ellipse area (BCEA) measurements; the 95% BCEA is the area containing 95% of the fixation points during a microperimeter scan of ca. 6 minutes duration. The mean (± SD) 95% BCEA decreased from  $68.6^{\circ 2}$  (± 57.9°<sup>2</sup>) pre-Tx to  $42.7^{\circ 2}$  (±  $30.3^{\circ 2}$ ) at 1m post-Tx and  $31.5^{\circ 2}$  (± 25.1°<sup>2</sup>) at 4m post-Tx, with near statistical significance (p = 0.09 and 0.05 at 1m and 4m, respectively). The Pearson correlation coefficient between 95% BCEA and BCDVA (in logMAR units) was large (0.63) for all 30 FS data points. Four of the eight eyes with MP exams had large shifts  $(5.3^{\circ} \pm 1.9^{\circ})$  in preferred retinal loci (PRLs) that typically reduced the overlap of fixation points with atrophied regions of the retina. (Two of the eyes did not have usable 1m exams but did have usable 3m exams that showed large PRL shifts.) Figure 512 shows an example of the PRL change in one eye due to CPV Tx. Two of the eight eyes had almost no post-Tx shifts in PRLs but these were eyes with good pre-Tx FS and almost no post-Tx FS change.

#### Discussion

Laser irradiation of the cornea by CPV Tx is a new corneal laser procedure that differs from invasive corneal procedures such as conductive keratoplasty (CK)<sup>14</sup>, laser-assisted *in situ* keratomileusis (LASIK)<sup>15</sup>, laser thermal keratoplasty (LTK)<sup>16</sup> and small incision lenticule extraction (SMILE)<sup>17</sup> in many ways including that, for CPV Tx, no corneal tissue is punctured, cut or removed and the epithelium is protected from thermal damage. The laser is "eye safe" meaning that the laser light is completely absorbed in the cornea; none of the laser light propagates through the corneal refraction change shown in Figure 4 act as aspheric multifocal lenses to redistribute light

entering the cornea in order to produce a retinal irradiance distribution modification (IDM) for vision improvement. Laser Raman spectromicroscopy measurements<sup>18</sup> indicated that tissue in CPV treated spots has reduced water content, probably leading to tissue compaction. Atomic force microscopy measurements18 indicated that tissue in CPV treated spots has increased modulus, leading to a change of treated anterior corneal stroma from a gel-like state with viscoelastic character to a more glass-like state with elastic character. Tx spots are lightly opacified and are confined to the anterior stroma upon slit-lamp biomicroscopy examination; Tx spots are not cosmetically significant under normal room lighting. Since Z Elevation and Refraction changes persist, although decreasing as a function of follow-up time, it is likely that CPV effects of reduction of water content and increase of modulus also persist. None of the eyes in this pilot study have received more than one CPV Tx so the possible benefit of multiple CPV Txs on eyes (treated simultaneously and/or sequentially) to maintain or even increase vision improvement remains to be investigated.

The corneal shape and refraction changes described above produce prompt redistribution of visible light similar to "prismatic effects" produced by prism spectacles<sup>8</sup>. Unlike prism spectacles, however, the four treatment spots create a quatrefoil pattern of corneal shape and refractive change (Figure 4) for 360 degrees that resembles four lenses, which each redistributes light rays. Pre-treatment, a location in visual space that maps onto an area of dysfunctional retina in an AMD patient is perceived as part of a blind spot. However, after CPV treatment, light rays from this location are mapped onto four different regions of the retina. If any of these regions are functional, then visual information about that location is transmitted



**Figure 5. Microperimeter images pre-Tx (left) and 3m post-Tx (right) for one eye.** <u>Pre-Tx</u>: the distribution of fixation points (blue dots) was centered at bottom left with most of the points within the atrophic retina (in white). <u>3m Post-Tx</u>: the distribution of fixation points was centered superiorly with respect to the atrophic retina. Retinal sensitivity measurements (shown in color coding at 37 stimulus points over 10° diameter) – the black (zero sensitivity) stimulus points overlap the atrophic retina. The distribution of fixation points moved from overlap with the atrophic area (pre-Tx) superiorly onto a more functional retina (3m post-Tx). The distribution of fixation points also decreased from a 95% Bivariate Contour Ellipse Area (BCEA containing 95% of the fixation points) of 171.6°<sup>2</sup> pre-Tx to 46.2°<sup>2</sup> at 3m post-Tx.

to the central brain. The success of a "one size fits all" procedure for a patient population with different geometries of dysfunctional regions on their retinas results from the relatively high probability that at least one of the four lenses will enable the retina to transmit information about any location in visual space with compromised vision.

Ray tracing measurements indicate that the displacement of images is ca. 40 µm. This is not a large enough shift to move images from the fovea all the way to functional areas of the retina in most of our patients. However, this shift can allow images near the boundary of dysfunctional areas to move onto functional areas, and thereby restore some visual function. In addition, CPV treatment produces refractive changes over a large portion of the central cornea (*cf.* Figure 4). These large refractive changes distribute blurry versions of images in blind spots over a larger region of the retina. In addition, ray tracing measurements were made for on-axis light beams; off-axis light beams are likely to experience a larger shift in their location on the retina.

It is notable that the eye movement strategy of patients changed. Six of the eight patients with microperimeter (MP) exams experienced large shifts in their preferred retinal locus (PRL) of fixations. Typically, the new PRL was displaced away from atrophied areas of the retina, and thus allowed the patient to gain more central visual information with each saccade. (An example of this pattern is shown for one eye in Figure 5). It is unclear how the changes in retinal irradiance distribution produced by CPV Tx helped eyes to find a better PRL. One possibility is that before treatment, the motor learning system of patients was in a "false optimum", in which small deviations from the fixation location resulted in decreased visual function. Then, following treatment, visual information was spread over a larger region of the retina, helping the motor learning system to find a "true optimum". Further study is needed to determine patterns (and causes) of PRL changes following CPV treatment.

Another significant change in eye movements following treatment was an improvement in fixation stability, which may make it easier for the brain to perform spatial integration of visual information. These changes may also be related to a shift in the PRL, as patients making saccades into a damaged area of the retina may partially compensate by making larger fixational eye movements to attempt to scan images over functional regions of the retina. Therefore, the change in eye movements can be thought of as helping to restore more normal visual function. [It should be noted that the fixation stability observed in patient eyes with AMD in this study is much worse than in normal eyes (mean 95% BCEA = ca.  $3^{\circ 2}$  for patients in their  $80s^{19}$ ), so the treated eyes are still in need of further functional improvement.] Further study is needed to determine if and how CPV treatment improves fixation stability.

A potential concern is that the quatrefoil pattern of refractive changes produced by CPV Tx could result in multiple or fragmented visual perception. However, patients experienced unified vision. The visual information transmitted *via* multiple lenses combines, as each lens transmits the same information about a single location in visual space onto multiple regions of the retina. Functional combination of this information is akin to spatial integration, which the brain routinely carries out and which can result in acuity far greater than the spacing between cone photoreceptors<sup>20,21</sup>. This combination can also be thought of as a form of vision multiplexing<sup>22</sup>, which is an example of the wider phenomenon of sensory cue combination remains an area of active research, the phenomenon is well-established.

Since potential visual acuity (PVA) measurements<sup>10</sup> correlate well with near-term (1m post-Tx) BCDVA improvements, PVA screening may be very useful as predicted previously<sup>26</sup>. Patient expectations may also be guided by PVA measurements.

There were no safety problems associated with the minimalist corneal laser procedure used in this study. CPV Tx produces minimal corneal changes without risks of intraocular surgery.

The only FDA-approved device for vision improvement in dry AMD patients is the implantable miniature telescope (IMT)<sup>5</sup>. At 12m post-implantation, IMT patients achieved mean improvements of 3.47 and 3.18 ETDRS lines for BCDVA and BCNVA, respectively, from baseline<sup>5</sup>, mostly because of telescopic magnification inherent in the procedure. Since all the IMT patients had cataracts, the IMT study authors attributed ca. 1 line of BCDVA improvement to cataract removal<sup>27</sup>, so the net BCDVA vision improvement in IMT patients was ca. 2.5 lines at 12m post-implantation. Patients with CPV Txs achieved mean improvements of 2.2 and 2.7 lines of BCDVA and BCNVA, respectively, at 12m post-Tx without the risks and safety problems associated with the very invasive IMT surgery and without added magnification. It should also be noted that the IMT produces "tunnel vision" in the implanted eye, while CPV treatment does not.

For CPV Tx, the "best" mean PVA improvement group (with 15 or more letters PVA improvement relative to baseline BCDVA) achieved a mean post-Tx BCDVA improvement of 21.0 letters at 1m post-Tx. The large standard deviations associated with each group and follow-up time (cf. Table 1) may be due, at least in part, to the range of accuracy with which light rays are redirected onto functional retinal areas. In this pilot study, each eye received the same CPV Tx. The possible benefit of custom CPV Txs (for example, by changing the pattern and energy density of Tx spots) that increase the accuracy of light ray redistribution onto the most functional retinal areas in each eye remains to be investigated.

CPV treated patients typically experienced rapid and comfortable Txs with no post-Tx requirements for new medications or visual rehabilitation training (as is the case, for example, for IMT patients<sup>5</sup>). The present CPV study involved both unilateral and bilateral Txs, depending on whether one or both eyes needed vision improvement. A CPV bilateral Tx regimen contrasts with the IMT unilateral Tx regimen that is required because the IMT device produces "tunnel vision" and patients need an untreated fellow eye for peripheral vision and ambulation<sup>5</sup>.

Another CPV study<sup>28</sup> demonstrated that bilateral Txs of both wet and dry AMD eyes produced similar vision improvements as in the present study. There is considerable merit to using combination therapy for wet AMD eyes in which anti-VEGF injections reduce the progression of the disease and CPV Tx provides significant vision and vision-related quality of life improvements.

Limitations of the present pilot study are:

- 1 small sample size,
- 2 retrospective analysis of outcomes and
- 3 follow-up of only 12 months post-Tx.

A prospective clinical study on a larger patient cohort with inclusion of additional measurements over a period extending to 24 months post-Tx is planned.

The CPV procedure for vision improvement is a new modality that may be broadly useful to benefit patients affected by late stage AMD.

#### Data availability

#### Underlying data

Vision improvement outcomes plus additional measurements

DRYAD: Data from: Corneal laser procedure for vision improvement in patients with late stage dry age-related macular degeneration. https://doi.org/10.5061/dryad.sn02v6x2x<sup>12</sup>

This project contains the following underlying data:

 F1000Research\_Dataset\_1\_-\_Corneal\_laser\_procedure\_with\_age\_ranges.xls (Vision improvement outcomes (BCDVA, BCNVA, PVA and CS) and additional measurements (SMR, CT, RTA and MP))

Data are available under the terms of the Creative Commons Zero "No rights reserved" data waiver (CC0 1.0 Public domain dedication).

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#### References

- Wong WL, Su X, Li X, et al.: Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. Lancet Glob Health. 2014; 2(2): e106–16. PubMed Abstract | Publisher Full Text
- Holekamp NM: Review of neovascular age-related macular degeneration treatment options. Am J Manag Care. 2019; 25(10 Suppl): S172–S181. PubMed Abstract
- Bandello F, Sacconi R, Querques L, et al.: Recent advances in the management of dry age-related macular degeneration: A review [version 1; peer review: 2 approved]. F1000Res. 2017; 6: 245. PubMed Abstract | Publisher Full Text | Free Full Text
- Dunbar HMP, Dhawahir-Scala FE: A discussion of commercially available intra-ocular telescopic implants for patients with age-related macular degeneration. Ophthalmol Ther. 2018; 7(1): 33–48.
  PubMed Abstract | Publisher Full Text | Free Full Text
- Hudson HL, Lane SS, Heier JS, et al.: Implantable miniature telescope for the treatment of visual acuity loss resulting from end-stage age-related macular degeneration: 1-year results. Ophthalmology. 2006; 113(11): 1987– 2001.

#### PubMed Abstract | Publisher Full Text

 Eng VA, Wood EH, Boddu S, et al.: Preventing progression in nonexudative age-related macular degeneration with subthreshold laser therapy: a systematic review. Ophthalmic Surg Lasers Imaging Retina. 2019; 50(3): e61-e70.

#### PubMed Abstract | Publisher Full Text

- Markowitz SN, Devenyi RG, Munk MR, et al.: A double-masked, randomized, sham-controlled single center study with photobiomodulation for the treatment of dry age-related macular degeneration. Retina. 2020; 40(8): 1471–1482.
  PubMed Abstract | Publisher Full Text | Free Full Text
- Markowitz SN, Reyes SV, Sheng L: The use of prisms for vision rehabilitation after macular function loss: an evidence-based review. Acta Ophthalmol. 2013; 91(3): 207–11.
  - PubMed Abstract | Publisher Full Text
- Wittich W, Lorenzini MC, Markowitz SN, et al.: The effect of a head-mounted low vision device on visual function. Optom Vis Sci. 2018; 95(9): 774–784.
  PubMed Abstract | Publisher Full Text | Free Full Text
- Gonzalez EG, Tarita-Nistor L, Markowitz SN, et al.: Computer-based test to measure optimal visual acuity in age-related macular degeneration. Invest Ophthalmol Vis Sci. 2007; 48(10): 4838–45.
  PubMed Abstract | Publisher Full Text
- Murdoch IE, Morris SS, Cousens SN: People and eyes: statistical approaches in ophthalmology. Br J Ophthalmol. 1998; 82(8): 971–3.
  PubMed Abstract | Publisher Full Text | Free Full Text
- Berry M: Data from: Corneal laser procedure for vision improvement in patients with late stage dry age-related macular degeneration, Dryad, Dataset. 2020.

http://www.doi.org/10.5061/dryad.sn02v6x2x

 Wong WT, Kam W, Cunningham D, et al.: Treatment of geographic atrophy by the topical administration of OT-551: results of a phase II clinical trial. Invest Ophthalmol Vis Sci. 2010; 51(12): 6131–9.
PubMed Abstract | Publisher Full Text | Free Full Text

- McDonald MB: Conductive keratoplasty: a radiofrequency-based technique for the correction of hyperopia. Trans Am Ophthalmol Soc. 2005; 103: 512–36. PubMed Abstract | Free Full Text
- Azar DT, Koch DD: LASIK: fundamentals, surgical techniques and complications. Marcel Dekker, Inc., New York. 2003. Reference Source
- Koch DD, Kohnen T, McDonnell PJ, et al.: Hyperopia correction by noncontact holmium:YAG laser thermal keratoplasty: U.S. phase IIa clinical study with 2-year follow-up. Ophthalmology. 1997; 104(11): 1938–47. PubMed Abstract | Publisher Full Text
- Sekundo W: Small incision lenticule extraction (SMILE): principles, techniques, complication management and future concepts. Springer Verlag, New York. 2015.
  Publisher Full Text
- Serdarevic O, Heller D, Berry M: Corneal photovitrification-basic science experiments. Lasers Surg Med. 2017; 49: 466–467.
- Morales MU, Saker S, Wilde C, et al.: Reference clinical database for fixation stability metrics in normal subjects measured with the MAIA microperimeter. Transl Vis Sci Technol. 2016; 5(6): 6.
  PubMed Abstract | Publisher Full Text | Free Full Text
- 20. Westheimer G, Hauske G: Temporal and spatial interference with vernier acuity. Vision Res. 1975; 15: 1137-41. PubMed Abstract | Publisher Full Text
- Lee BB, Wehrhahn D, Westheimer, et al.: The spatial precision of macaque ganglion cell responses in relation to vernier acuity of human observers. Vision Res. 1995; 35(19): 2743–58.
  PubMed Abstract | Publisher Full Text
- 22. Peli E: Vision multiplexing: an engineering approach to vision rehabilitation device development. Optom Vis Sci. 2001; 78(5): 304–15. PubMed Abstract | Publisher Full Text
- Hillis JM, Ernst MO, Banks MS, et al.: Combining sensory information: mandatory fusion within, but not between, senses. Science. 2002; 298(5598): 1627-30.
  PubMed Abstract | Publisher Full Text
- Kording KP, Wolpert DM: Bayesian integration in sensorimotor learning. Nature. 2004; 427(6971): 244–7.
  PubMed Abstract | Publisher Full Text
- Doya K, Ishii S, Pouget A, et al.: Bayesian Brain: Probabilistic Approaches to Neural Coding. Cambridge, MA: MIT Press. 2007. Reference Source
- Harris MJ, Robbins D, Dieter JM, et al.: Eccentric visual acuity in patients with macular disease. Ophthalmology. 1985; 92(11): 1550–3.
  PubMed Abstract | Publisher Full Text
- Hudson HL, Stulting RD, Heier JS, et al.: Implantable telescope for end-stage age-related macular degeneration: long-term visual acuity and safety outcomes. Am J Ophthalmol. 2008; 146(5): 664–673.
  PubMed Abstract | Publisher Full Text
- Serdarevic O, Tasindi E, Dekaris I, et al.: Vision improvement in dry and wet age-related macular degeneration (AMD) patients after treatment with a new corneal CPV procedure for light redirections onto the retina. Acta Ophthalmol. 2017; 95(S259).
  Publisher Full Text

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### Mukharram M Bikbov

Ufa Eye Research Institute of Academy Of Sciences of Republic of Bashkortostan, Ufa, Bashkortostan, Russian Federation

The idea of laser remodeling of the cornea to create a new focus on the retina is very interesting, but what exactly this laser affects the cornea is not entirely clear.

If such studies had been conducted before, it would be interesting to make a link to them. It also remains unclear how the laser has a universal effect on corneas with different topography with different indicators of spherical and cylindrical components in all patients.

The technique is theoretically more similar to thermokeratoplasty and should have an effect similar to treating presbyopia, with an increase in the central refractive power of the cornea and an increase in near visual acuity, providing a kind of telescopic effect similar to intraocular lens implantation in AMD. It would be interesting to compare the effectiveness of treatment in one eye with the second eye of an intact patient.

It is also necessary to clarify the selection criterion for patients with macular lesion volume in dry AMD.

Is the work clearly and accurately presented and does it cite the current literature?  $\ensuremath{\mathsf{Yes}}$ 

## Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?  $\ensuremath{\mathbb{No}}$ 

### If applicable, is the statistical analysis and its interpretation appropriate?

I cannot comment. A qualified statistician is required.

# Are all the source data underlying the results available to ensure full reproducibility? Partly

Are the conclusions drawn adequately supported by the results?  $\ensuremath{\mathbb{No}}$ 

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: ophthalmology, corneal surgery

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 01 July 2021

### https://doi.org/10.5256/f1000research.30832.r87602

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### ? Uwe Oberheide 匝

Technische Hochschule Köln, Cologne, Germany

### Omid Kermani 问

Eye Clinic at Neumarkt, Cologne, Germany

To start with the positive: The idea, to multiply and redirect the incoming light by corneal laser treatment is very appealing. Unfortunately, no evidence has been produced here. Comments to be made: The term "vitrification" as used here is not known as a distinct result from any known laser-tissue-interaction. The given wavelength, pulse duration and energy suggest that there is a thermal effect, maybe subthreshold? Since there is no histological proof of how the corneal tissue has interacted with the treatment it remains speculative. Maybe the authors have performed a pre-clinical in-vitro investigation? If so, it would be very helpful to fully understand the character of laser-tissue interaction. If not, it should be mentioned and it should be explained in which way the laser-tissue interaction is different from laser thermokeratoplasty, a very well known treatment that was used for hyperopic and presbyopic treatments. The principle of operation is not comprehensible for the reader. The localization of the laser spots do not explain or justify postulated multiplaction and redirection of light. With symmetrical application, one would not expect an upward deflection (as shown with the fixation spots), but a symmetrical redistribution/distortion. However, the wavefront measurements made pre/post that could show this are not presented. Were the points applied as a function of the steep/flat axis positions? Always at the points given as examples? Then one would also have to compare the effect in relation to the previous refractive forces. The discussion with generation of four lenses, which overlap individually, is theory only. No proof has been made. The light still passes the central corneal area, while the treatment is placed peripherally at four points (4-6mm zone) probably

leading to a refractive power increase. This increase of central corneal refractive power could as well and primarily have contributed to the higher near visual acuity in the eyes. The number of cases is in deed very small, each eye accounts for 3 percent. In addition, the results are mixed with different subgroups and the statistics are not very meaningful - standard deviations are sometimes larger than the actual measured value. Here, it would be better to indicate the range. The comparison of 15 gained lines in comparison to untreated eyes is meaningless here - 11 gained (standard deviation is 13!!). The other eyes would have lost 4 lines, because the disease pattern certainly does not allow statistics here and one would have to take the second eye (with bilateral disease) as reference.

Is the work clearly and accurately presented and does it cite the current literature?  $\ensuremath{\mathsf{Yes}}$ 

Is the study design appropriate and is the work technically sound?

No

Are sufficient details of methods and analysis provided to allow replication by others?  $\ensuremath{\mathbb{No}}$ 

If applicable, is the statistical analysis and its interpretation appropriate?  $\ensuremath{\mathbb{No}}$ 

Are all the source data underlying the results available to ensure full reproducibility?  $\ensuremath{\mathbb{No}}$ 

Are the conclusions drawn adequately supported by the results?  $\ensuremath{\mathbb{No}}$ 

*Competing Interests:* No competing interests were disclosed.

Reviewer Expertise: laser surgery of the eye

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

Author Response 29 Jul 2021

Michael Berry, Optimal Acuity Corporation, Austin, USA

We thank the reviewers for taking the time to read and comment on our manuscript. However, we take issue with many of their comments and are concerned that some comments do not conform to widely accepted standards for clinical trials in the ophthalmology community. Detailed responses follow:

"To start with the positive: The idea, to multiply and redirect the incoming light by corneal laser treatment is very appealing. Unfortunately, no evidence has been produced here." This comment is puzzling. Our paper provides extensive evidence in the form of corneal topography demonstrating depressions in the surface of the eye and refractive changes following laser treatment (Fig. 4) and microperimetry exams that clearly show a shift to a new preferred retinal locus (PRL) along with increased fixation stability (Fig. 5). Thus, our laser treatment produced demonstrable changes in the optics of the eye, along with demonstrable changes in patient eye movements. Most importantly, our core result is that visual acuity improved at 12 months post-treatment (p < 0.002 for BCNVA and p < 0.004 for BCDVA) as did contrast sensitivity (p < 0.05). This is the bottom line for patients.

"The comparison of 15 gained lines [*sic*, we think the reviewers meant "letters"] in comparison to untreated eyes is meaningless here - 11 gained (standard deviation is 13!!)."

This comment does not appear to conform to accepted standards for clinical trials in ophthalmology:

1. It is common to use statistics to evaluate whether an effect present in data with scatter is significant or not. We found a very high level of significance for all conditions tested (p < 0.01). This analysis refutes the claim that the "comparison ... is meaningless..."

2. Many FDA-approved treatments that are part of the ophthalmology community's standard-of-care are based on studies where the standard deviation exceeds the mean effect. For example, the effectiveness of aflibercept (Eylea) was reported to be a gain of 5.9  $\pm$  13.8 (mean  $\pm$  SD) letters of visual acuity at 12 months post-treatment (Eleftheriadou *et al., Ophthalmol. Ther.* 2018;7:361-368). Similar results are seen for 0.5 mg ranibizumab (Lucentis), which reported a gain of 7.2 letters with a standard error of ~1 letter for 240 patients (Rosenfeld *et al., N. Engl. J. Med.* 2006;355:1419-1431). The corresponding standard deviation is SD = 1 \* sqrt(240) = 15.5 letters.

Thus, according the reviewer's standards, anti-VEGF treatments for wet AMD would be dismissed as "meaningless", and papers describing the clinical results would not be publishable.

3. Another example is the Implantable Miniature Telescope (IMT), the FDA-approved device for treatment of dry AMD. In the initial IMT study (Lane SS, *et al. Am J Ophthalmol* 2004;137:993-1001), the mean ( $\pm$  SD) values of BCNVA letters gained were 11.5 ( $\pm$  15.8) at 3m, 7.1 ( $\pm$  17.4) at 6m and 8.5 ( $\pm$  9.8) at 12m post-implantation. The BCDVA letters gained were 11.1 ( $\pm$  11.5) at 3m, 12.1 ( $\pm$  9.4) at 6m and 12.0  $\pm$  (8.1) at 12m post-implantation. These standard deviations are very large and the ratios of standard deviations/means are larger for most (4 of 6) of the IMT outcomes compared to the outcomes we cite in this paper.

"In addition, the results are mixed with different subgroups and the statistics are not very meaningful - standard deviations are sometimes larger than the actual measured value. Here, it would be better to indicate the range."

We direct the reader to Figure 3, which shows the full distribution and range of treatment

efficacies, for the change in visual acuity 12 months post-treatment.

"The other eyes would have lost 4 lines [*sic*, we think the reviewers meant "letters"], because the disease pattern certainly does not allow statistics here and one would have to take the second eye (with bilateral disease) as reference."

The disease does not progress at the same rate in both eyes, so it is not clear how this control would be an improvement over citing results from the literature with many more subjects.

"The number of cases is indeed very small, each eye accounts for 3 percent."

The paper clearly states, in Discussion, that one of the limitations of the study is a small sample size. That said, the improvement in visual acuity is large enough that the data provide high statistical certainty (p < 0.002 for BCNVA improvement at 12 months post-treatment), even for our "small" sample size.

"The principle of operation is not comprehensible for the reader."

Laser irradiation caused a reduction in water content and an increase in modulus of the cornea (reference 18). In addition, we used corneal topography to directly observe a depression on the surface of the eye in the laser-treated regions (Fig. 4a). These depressions then changed the refractive power of the optics of the eye (Fig. 4b). By changing the eye's refraction, light rays were deflected onto different locations on the retina. These are all experimentally-determined facts.

Ultimately, we agree that there are aspects of how our treatment restores vision that are not completely understood and require further study. But many elements of the "principle of operation" underlying this treatment have been determined by data presented or cited in this paper.

"The discussion with generation of four lenses, which overlap individually, is theory only. No proof has been made."

We presented measurements using corneal topography that showed that our laser treatment produced four regions of depression of the surface of the eye (Fig. 4). This is experimental data, not a theory. As far as the impact that these depressions will have on the refraction of light, the paper claims in Discussion that this effect "resembles four lenses". This qualified statement, made in Discussion, is entirely appropriate. We stated in the previous manuscript that the full effects of this perturbation are not fully understood and will require further investigation. What is certain, however, is that these depressions will refract light differently than in the untreated eye. This statement is not "theory only"; it relies on Snell's law, which has been known since at least the early 1600s.

"The localization of the laser spots do not explain or justify postulated multiplication and redirection of light."

We have noted in the paper that "Further study is needed to determine patterns (and causes) of PRL changes following CPV treatment". It is often the case that a discovery of a new effect precedes an understanding of the mechanism of action. To cite one example, the clinical efficacy of penicillin was well-established in the early 1940s but a complete understanding of its mechanism of action was not determined until the 1960s.

Competing Interests: No competing interests were disclosed.

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