

1 Characterisation of Cone Size and Centre in Keratoconic Corneas

2 Ashkan Eliasy¹, MEng; Ahmed Abass^{1*}, PhD; Bernardo T Lopes¹⁻³, MD, PhD; Riccardo Vinciguerra⁴,
3 MD; Haixia Zhang⁵, PhD; Paolo Vinciguerra⁶⁻⁷, MD; Renato Ambrósio Jr^{3,8}, MD, PhD; Cynthia J.
4 Roberts⁹, PhD; Ahmed Elsheikh^{1,10-11}, PhD

5
6 ¹ School of Engineering, University of Liverpool, Liverpool, UK

7 ² Rio de Janeiro Corneal Tomography and Biomechanics Study Group, Rio de Janeiro, Brazil

8 ³ Department of Ophthalmology, Federal University of Sao Paulo (UNIFESP), Sao Paulo, Brazil

9 ⁴ Department of Ophthalmology, Humanitas San Pio X Hospital, Milan, Italy.

10 ⁵ School of Biomedical Engineering, Capital Medical University, Beijing, China.

11 ⁶ Department of Biomedical Science, Humanitas University, Via Manzoni 56, Rozzano (MI), Italy.

12 ⁷ Eye Center, Humanitas Clinical and Research Center, Via Manzoni 56, Rozzano (MI), Italy.

13 ⁸ Department of Ophthalmology, Federal University of the State of Rio de Janeiro (UNIRIO), Rio de
14 Janeiro, Brazil.

15 ⁹ Department of Ophthalmology & Visual Science and Biomedical Engineering, The Ohio State
16 University, Columbus, Ohio, USA.

17 ¹⁰ Beijing Advanced Innovation Center for Biomedical Engineering, Beihang University, Beijing,
18 China.

19 ¹¹ NIHR Biomedical Research Centre for Ophthalmology, Moorfields Eye Hospital NHS Foundation
20 Trust and UCL Institute of Ophthalmology, UK.

21
22 ***Corresponding author:** Dr Ahmed Abass, School of Engineering, University of Liverpool, Liverpool
23 L69 3GH, UK, a.abass@liverpool.ac.uk

24
25 **Keywords:** Keratoconus; Cornea; Topography; Cone; Shape

26

27

28 **Abstract**

29 **Purpose:** To present a novel method to locate the centre of keratoconus and the transition zone
30 between pathological area and the rest of corneal tissue.

31 **Methods:** A spherical coordinate system was used to generate a spherical height map measured
32 relative to the centre of the optimal sphere fit, and normal to the surface. The cone centre was defined
33 as the point with the maximum height. Second derivatives of spherical height were then used to
34 estimate the area of pathology in an iterative process.

35 **Results:** There was mirror symmetry between cone centre locations in both eyes. The mean distance
36 between cone centre and corneal apex was 1.45 ± 0.25 mm (0.07-2.00), the mean cone height normal
37 to the surface was 37 ± 23 μ m (2-129) and 75 ± 45 μ m (5-243) in the anterior and posterior surfaces,
38 respectively. There was a significant negative correlation between the cone height and the radius of
39 the sphere of optimal fit ($p < 0.05$ for both anterior and posterior surfaces). On average, posterior cone
40 height was larger than the corresponding anterior cone height by 37 ± 24 μ m (0-158).

41 **Conclusions:** A novel method is proposed to estimate the cone centre and area, and explore the
42 changes in anterior and posterior corneal surfaces that take place with keratoconus progression. It
43 can help improve understanding of keratoconic corneal morphology and assist in developing
44 customised treatments.

45

46

47

48

49

50

51

52 **1. Introduction**

53 Keratoconus (KC) is a disease that causes alteration in the curvature of the cornea and localised
54 thinning (1-3). It commonly begins in early adolescence, progresses over the next two decades (4)
55 and can significantly reduce visual acuity and vision-related quality of life (5, 6). While the
56 characteristic topographic patterns of keratoconus can be identified on corneal topographic and
57 tomographic maps, it is still difficult to precisely locate the centre of the cone and the transition zone
58 between the pathology area and the rest of the corneal tissue (7-11). As classifying and managing
59 keratoconus can be more efficient when the affected corneal region is located, especially in the case
60 of customized corneal crosslinking (12-15), techniques were developed to address this challenge (16-
61 18). However, some of the available techniques to detect the keratoconus cone are based on methods
62 that analyse corneal tangential or axial curvature maps, which provide different values of maximum
63 curvature based on their specific algorithms (16-18).

64 Tangential curvature maps typically have high noise-to-signal ratios and are based on the second
65 derivative nature of the curvature calculation. This creates the need in elevation-based systems, such
66 as Scheimpflug tomographers, for smoothing or low-pass filtering to derive tangential curvature from
67 height data (19, 20). Conversely, axial maps assume centre points of surface curvature to be always
68 located on the central reference axis and this assumption reduces the sensitivity of the curvature
69 maps in identifying surface changes due to cone development (21). Mahmoud et al. (16) initially
70 proposed a method using axial and tangential maps to locate the cone position and to quantify its
71 magnitude. Later, axial and tangential curvature, and the relative elevation of both the anterior and
72 the posterior surfaces, as well as the pachymetric maps were included in the method which exhibited
73 improved accuracy in detecting the presence of keratoconus (22). Another method used Brillouin
74 spectroscopy which utilizes the scattering of light for the determination of localised materials elasticity
75 (23). The Brillouin frequency shift at the point of maximum posterior elevation in relation to the best-
76 fit sphere was also related to several curvature indices (24). Its magnitude showed a high correlation
77 with corneal stiffness reduction assessed by means of the Brillouin frequency shift (24). Schwiegerling
78 took Zernike polynomial corneal fitted surface away from the raw-height data to expose the cone

79 characteristics (25), however, this method was based on the idealistic assumption that only non-
80 keratoconic features of the cornea would be significantly removed when removing the 6th order
81 Zernike polynomial fitted surface from the raw-height data. A Zernike polynomial of such a radial order
82 is well classified as a high-order aberration fit that could filter many of the keratoconic features of the
83 eye when being removed, leaving serious doubt about analysing the residual elevation for obtaining
84 the keratoconus cone characteristics. Even though these methods have been demonstrated to be
85 good in detecting the presence of keratoconus and quantifying the stiffness associated with the local
86 pathology, they do not evaluate the size of the pathologic area. Furthermore, as the cone centre is
87 different in curvature, elevation, and pachymetry maps, there is a need for a method for detecting the
88 location of the cone axis normal to the surface, in its natural three-dimensional position.

89 While estimating the area of pathology from the elevation data offers a direct method, a particular
90 challenge is caused by the smooth transition between the natural curved shape of corneal surface
91 and the steeper curvature within the cone. Further, as the cone may be only a few microns above the
92 curved shape of the cornea, it may be difficult to detect given the nature of elevation data, which may
93 cause unacceptably high noise-to-signal ratios. The current study attempts to overcome this difficulty
94 by expressing corneal surface data normal to the surface and relative to the centre of the sphere to
95 generate a 'spherical height map'. This map eliminates the effect of corneal surface curvature and
96 hence increases the precision in locating cone centre and estimating the size of the affected area of
97 the cornea.

98

99 **2. Methods**

100 **2.1. Clinical Data**

101 In this retrospective study, we reviewed the tomography maps of right and left eyes of 309 clinically-
102 diagnosed keratoconus patients enrolled in the Vincieye Clinic and Humanitas Clinical and Research
103 Hospital (Milan, Italy). The institutional review board ruled that approval was not obligatory for this
104 record review study. However, the ethical standards set out in the 1964 Declaration of Helsinki and

105 their revision in 2013 were observed and all patients provided informed written consent before using
106 their de-identified data in the study (26, 27).

107 The inclusion criteria were the diagnosis of bilateral keratoconus made by an experienced corneal
108 specialist (PV) based on typical topographic patterns (e.g., inferior steepening, asymmetric bowtie,
109 skewed axis) and/or characteristic slit-lamp findings (e.g., Vogt's striae, Fleischer's ring, apical
110 thinning, or Rizutti's sign). Exclusion criteria included eye diseases other than keratoconus, extensive
111 corneal scarring, former ocular procedures such as collagen cross-linking or implantation of
112 intracorneal rings, connective tissue disease, as well as pregnancy or early puberty. All participants
113 underwent a complete ophthalmic examination, including a Pentacam HR (Oculus Optikgeräte
114 GmbH; Wetzlar, Germany) exam. Raw elevation data with a reference plane set at the corneal apex
115 (from U12 file) were extracted using customised Pentacam software (version 1.21r41) and stored in
116 comma-separated values (CSV) format (28). The data covered a square grid that was 14 mm wide
117 and had a regular spacing of 0.01 mm.

118 Patients were divided according to disease severity into three groups; mild, moderate and advanced,
119 based on the Topographic Keratoconus Classification (TKC) provided by the Pentacam topographer
120 (29). Mild keratoconus was defined with TKC classification of "Abnormal", "Possible", "- " and "1",
121 moderate keratoconus included TKC grades "1-2", "2" and "2-3", and advanced keratoconus included
122 TKC grades "3", "3-4" and "4".

123

124 **2.2. Cone location analysis**

125 The data were processed using custom-built MATLAB (2018b, The MathWorks, Inc., Natick,
126 Massachusetts, United States) codes created by the Biomechanical Engineering Group (BioEG) at
127 the University of Liverpool. Initially, the raw elevation data for anterior and posterior maps (relative to
128 a vertical plane positioned at surface apex) were imported for all patients. Only records that had a
129 quality score "OK" were processed. A sphere was then fitted – using the least squares method – to
130 the central area with 8 mm diameter of each corneal surface, and the coordinates of the centre point

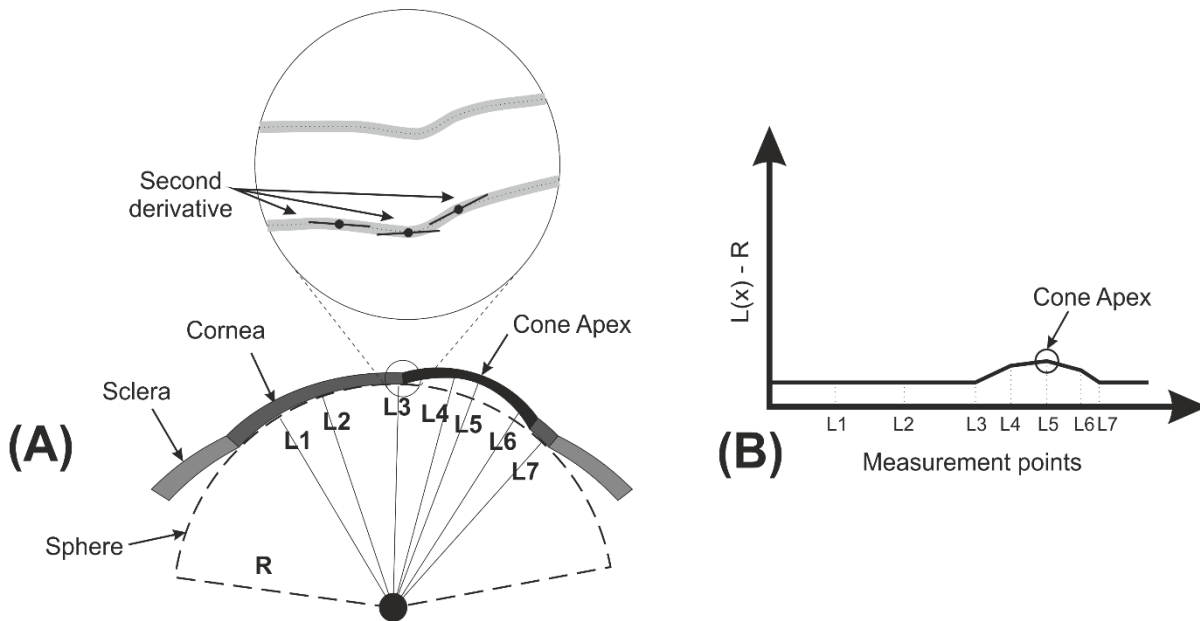
131 and the radius of the optimal fit sphere were determined. The radial distance from each data point on
132 a corneal surface to the centre of the sphere was then calculated. This was followed by subtracting
133 the radius of the sphere from these radial distances and the position and magnitude of the largest
134 positive difference were assumed to point at the location and height of the cone centre, respectively.

135 To estimate the area of pathology, height data relative to the optimal sphere were determined along
136 360 equally-spaced lines meeting at the cone centre and extending outwards using triangle-based
137 cubic interpolation (30). A first derivative of the height data was calculated to determine the tangent
138 to the surface along these lines. The second derivative was then calculated to represent the rate of
139 change of this gradient. Since the rate of gradient change experiences a change in direction when
140 the point of interest moves from the cone area to the surrounding healthy area, a sudden change in
141 the sign of the rate of change in tangent gradient is indicative of an intersection with the transition
142 zone between the pathologic area and the remaining corneal tissue, Figure 1. Locating the transition
143 zone between the area of pathology and the remaining corneal tissue using this method then allowed
144 calculating the cone area.

145 An iterative process was then initiated in which the cone area was removed from the topography data
146 before re-identifying the optimal sphere and repeating the subsequent steps. This process was
147 repeated until the difference between the results (cone height and centre location) of two subsequent
148 analyses became smaller than 1.0 μm . The process was applied separately for anterior and posterior
149 surfaces and no comparisons between the results were carried out before the analysis was
150 concluded.

151 The correlation of cone parameters (location and height of cone centre and cone area) with disease
152 severity was explored using the correlation coefficient 'R' and the corresponding significance value p
153 using bespoke MATLAB code.

154



155

156 Figure 1 (A) Optimal sphere of corneal posterior surface and distances from sphere centre to multiple
 157 points on the posterior surface. Variations in radial coordinates above the optimal sphere are used to
 158 locate the cone centre and estimate its height, while the second derivatives of elevation are used to
 159 estimate the transition zone between the cone and the rest of corneal tissue. (B) Distances between
 160 corneal surface points and optimal sphere are plotted and the largest value indicates cone height and
 161 centre location.

162

163 **2.3. Statistical analysis**

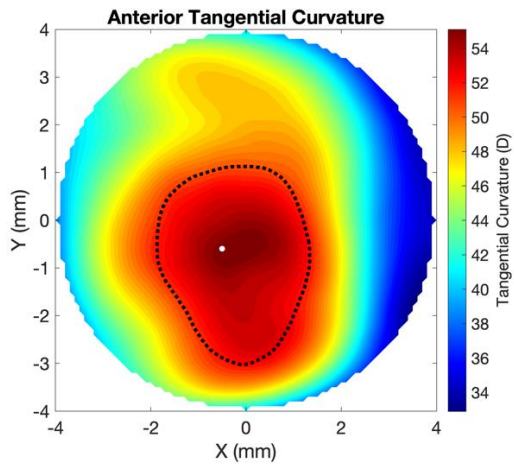
164 Data are expressed as mean, standard deviation and range. Matlab Statistics and Machine Learning
 165 Toolbox, 2019a (MathWorks, Natick, USA) were used to carry out the statistical analyses in this study.
 166 Spearman Correlation analysis was used to evaluate the relationships between parameters and
 167 Quade's rank analysis of covariance was used to evaluate the effect of co-variants. Nonparametric
 168 paired test of Wilcoxon signed rank was performed to compare left and right eyes where there was
 169 no normal distribution. The probability p , which is an element of the period $[0,1]$, was determined
 170 where values of $p > 0.05$ indicate the validity of the null hypothesis, otherwise, it indicates the
 171 significance of the phenomenon (31).

172

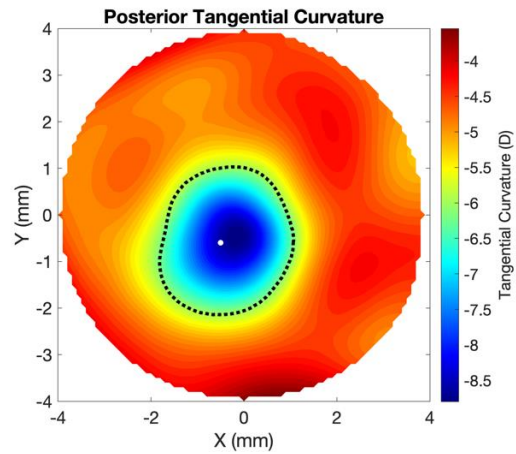
173 **3. Results**

174 For the 309 keratoconic patients included in the study, the mean, standard deviation and range of age
175 were 33 ± 11 years (9 – 72). Gender and ethnicity of patients were not recorded and therefore not
176 included in this analysis. Among the right eyes, those with mild, moderate and severe KC were 102,
177 130 and 77 respectively, while the corresponding numbers for left eyes were 90, 148 and 71. For
178 each eye, the location and normal height of the cone centre and the transition zone between the cone-
179 shape area and the remaining corneal tissue were estimated using the proposed method. Figure 2
180 presents a typical example where the cone centre and transition zone (presented by a black dot and
181 a dashed line, respectively) are plotted on corneal tangential curvature maps and standard elevation
182 maps for both the anterior and posterior surfaces.

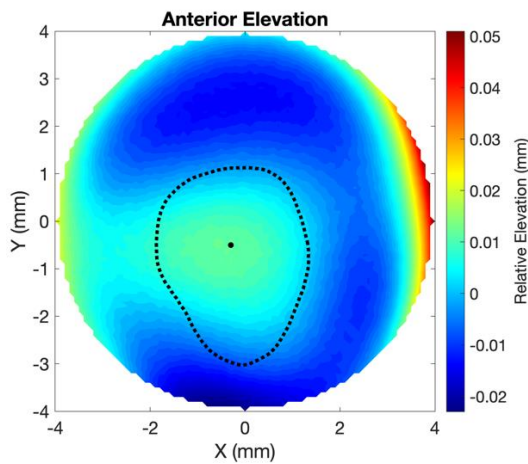
A



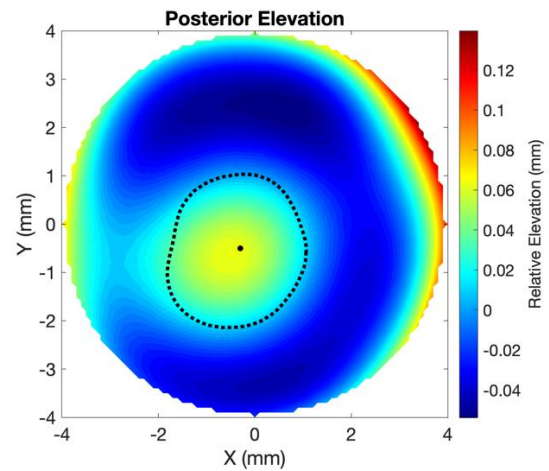
B



C



D



183 Figure 2 Location of cone centre and transition zone estimated using the proposed method for the
184 right eye of a 42 year-old patient with moderate keratoconus. The results are plotted on tangential
185 curvature maps (A, B) and maps of elevation relative to the optimal sphere (C, D).

186

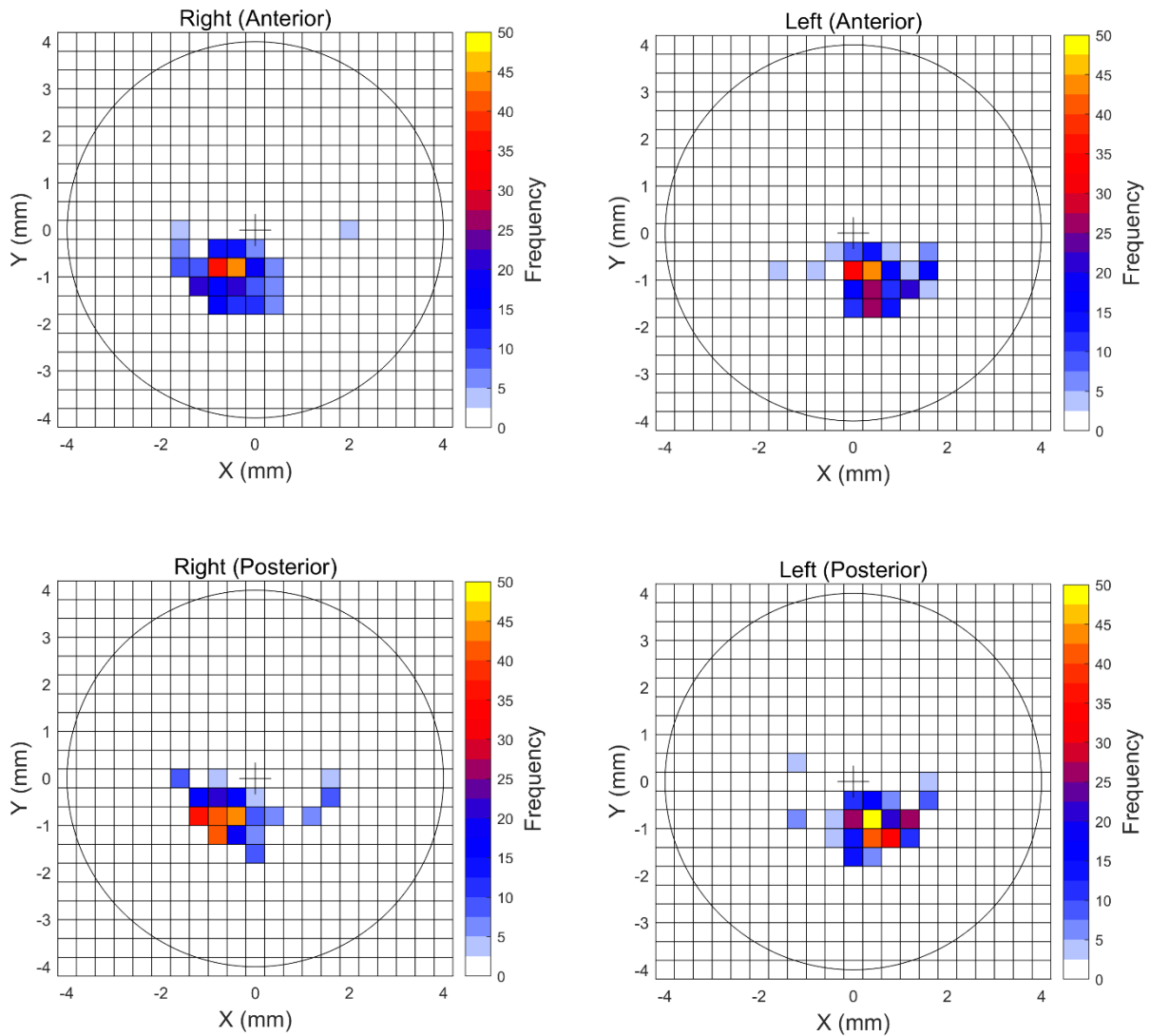
187 **3.1. Cone characteristics**

188 The results showed mirror symmetry between right and left eye groups. Whereas in right eyes, 76%
189 and 82% of anterior and posterior cone centres were located in the temporal-inferior quadrant,
190 respectively, the corresponding figures in left eyes were 82% and 84%. The posterior cone centre
191 was superiorly located relative to the anterior cone centre by 0.119 ± 0.216 mm in right eyes and
192 0.096 ± 0.227 mm in left eyes ($p= 0.070$). The anterior areas of the cone in right and left eyes were
193 also similar; with values of $7.36\pm 2.27\text{mm}^2$ (0.01 – 12.54) and 7.21 ± 2.22 mm^2 (1.13 – 12.54),
194 respectively ($p= 0.051$). The cone centre heights were also similar in right and left eyes at 36 ± 22 μm
195 (2 – 107) and 37 ± 23 μm (3 – 129), $p= 0.559$, in anterior surfaces and 74 ± 44 μm (8 – 244) and 75 ± 45
196 μm (5 – 243), $p= 0.619$, in posterior surfaces. The results further demonstrate consistently that
197 posterior cone height was larger than anterior cone height in 90% of cases and by 37 ± 24 μm (0 –
198 158) on average. On the other hand, the cone area presented was larger in the anterior surface
199 (7.77 ± 3.07 mm^2) than in the posterior surface (7.26 ± 3.92 mm^2 , $p< 0.001$)

200

201 **3.2. Cone centre location**

202 Considering only the majority of the cones, which are located in the temporal-inferior quadrant, the
203 anterior cone centre was located at 1.019 ± 0.403 mm (0.1 – 1.8) on the inferior side and 0.663 ± 0.434
204 (0.1 - 1.8) mm on the temporal side of left eyes and located at 0.939 ± 0.388 (0.1 – 1.7) mm on the
205 inferior side and 0.683 ± 0.424 (0.1 – 1.8) mm on the temporal side of right eyes. In posterior surfaces,
206 the cone centre was located at 0.938 ± 0.344 (0.2 – 1.6) mm towards the inferior side and 0.610 ± 0.359
207 (0.1 – 1.4) mm towards the temporal side in left eyes and at 0.813 ± 0.345 (0.2 – 1.5) mm towards the
208 inferior side and 0.734 ± 0.371 (0.1 – 1.5) mm towards the temporal side in right eyes, Figure 3.



210

211 Figure 3 Frequency of cone centre location in (A) anterior surfaces of right eyes, (B) anterior surfaces
 212 of left eyes, (C) posterior surfaces of right eyes, and (D) posterior surfaces of left eyes

213

214 The results further show a strong correlation between the locations of cone centres on the anterior
 215 and posterior surfaces ($p < 0.001$). This correlation could be used to estimate the shifts between the
 216 two cone centres using the relationships:

217

$$X(\text{Anterior}) = 0.591 \times X(\text{Posterior}) - 0.296$$

Equation 1

218

$$Y(\textit{Anterior}) = 0.715 \times Y(\textit{Posterior}) - 0.164$$

Equation 2

219

Where X(Anterior) and Y(Anterior) are the coordinates in mm of the anterior cone centres and

220

X(Posterior) and Y(Posterior) are the corresponding coordinates of the posterior cone centres.

221

222 **3.3. Correlation between cone characteristics and disease severity**

223

The results showed evidence that with increased disease severity, the distance from corneal apex to

224

cone centre reduced ($p < 0.001$, $R = -0.312$), while cone height increased ($p < 0.001$, $R = 0.716$). On the

225

other hand, the cone area did not show statistically significant differences among the disease stages

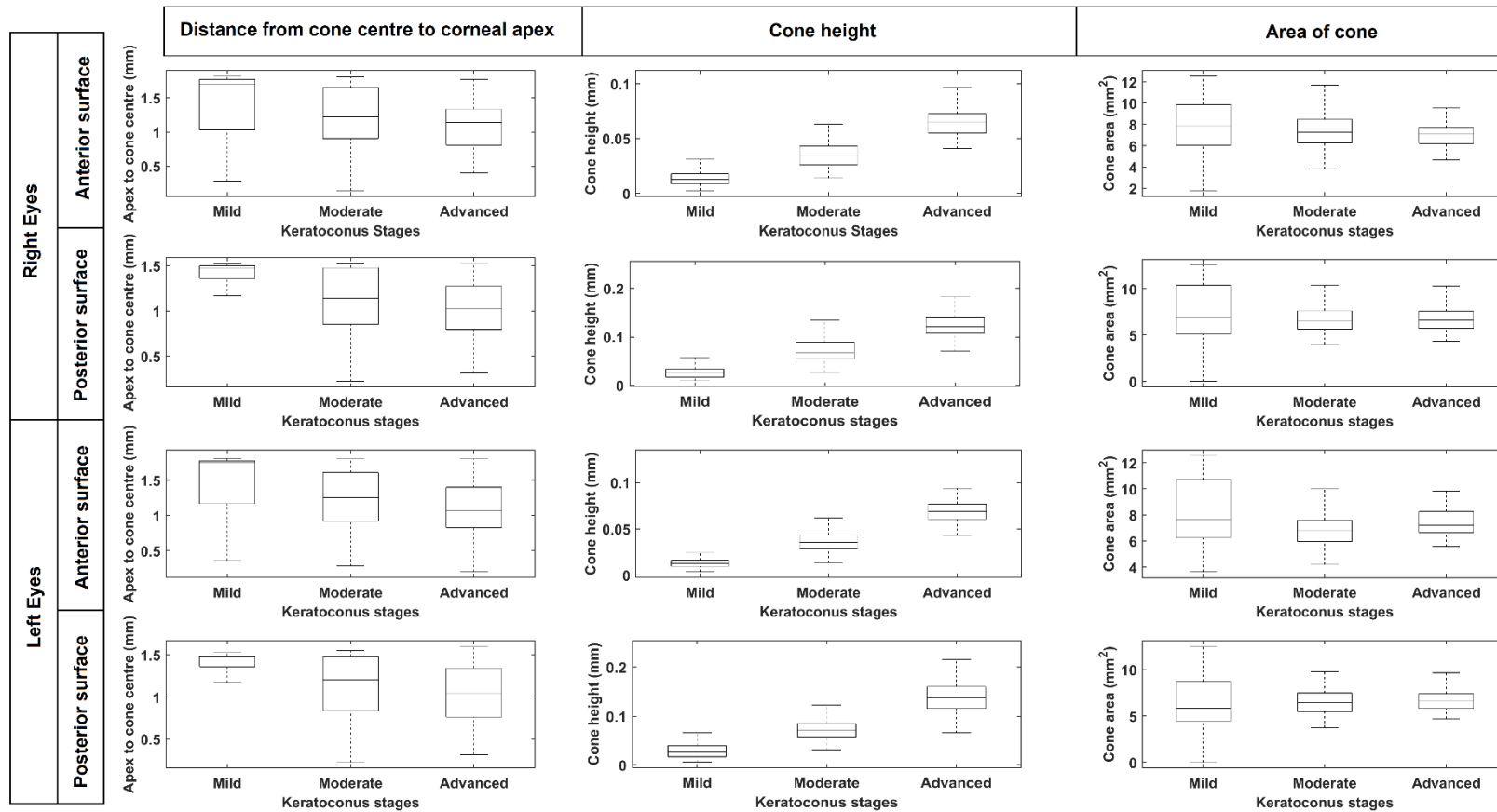
226

($p = 0.002$, $R = -0.092$), Figure 4. Further, no significant correlation was found between cone area and

227

height in left ($R = -0.087$, $p = 0.148$) and right ($R = 0.018$, $p = 0.769$) eyes.

228



229

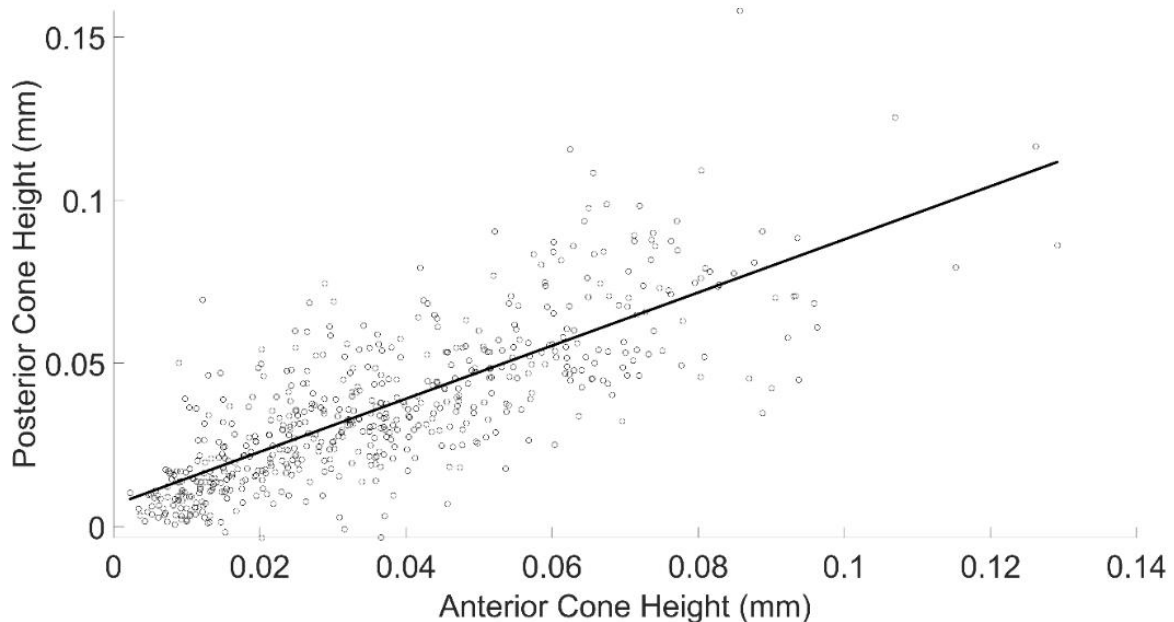
230 Figure 4 Mean, standard deviation, minimum and maximum values of distance from cone centre to corneal apex (left column), cone height (middle
 231 column) and area of cone (right column) for eyes with mild KC (left = 90, right = 102), moderate KC (left = 148, right = 130) and advanced KC
 232 (left = 71, right = 77). Results are presented for anterior and posterior surfaces of right and left eyes

233 **3.4. Posterior cone height in relation to anterior cone**

234 The results also show strong correlation between anterior cone height and posterior cone height ($p <$
235 0.001 , $R = 0.784$ for right eyes and $p < 0.001$, $R = 0.774$ for left eyes). This strong correlation was
236 evident when combining all the data or considering separately data for eyes with different KC severity
237 extents, Figure 5. The relationship between the two cone heights follows the relationship:

238
$$PCH = 0.8138 \times ACH + 0.007 , \quad (\text{Equation 3})$$

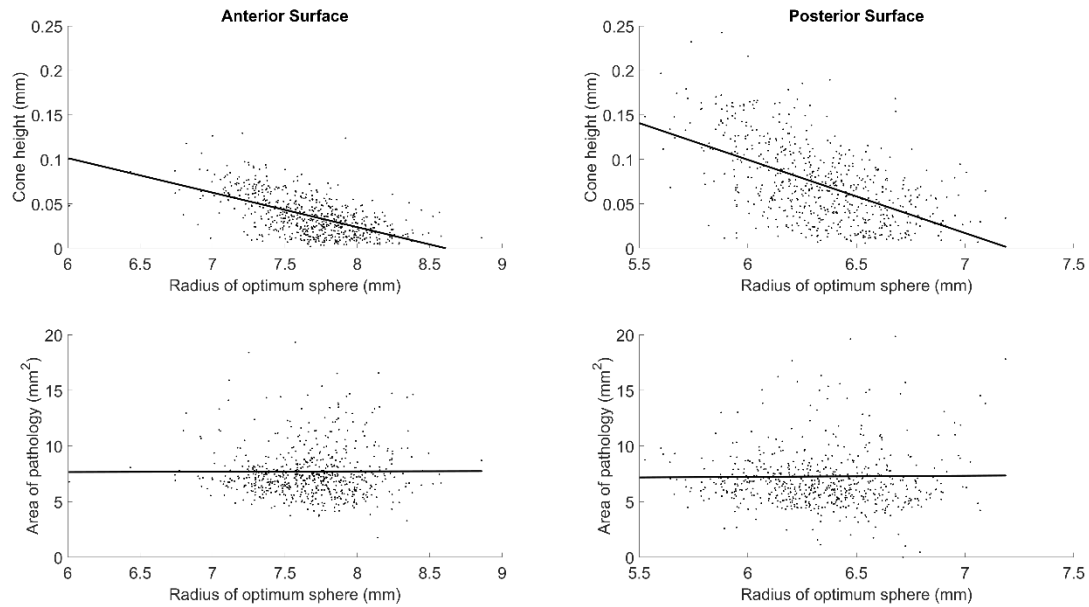
239 where PCH is the posterior cone height in mm and ACH is the anterior cone height.



240
241 Figure 5 Correlation between anterior cone height and posterior cone height when considering all
242 data

243 **3.5. Correlation of cone height and pathology area with radius of optimum sphere**

244 The results show significant correlation between the cone height and radius of the optimum sphere
245 for anterior surfaces ($R = -0.584$, $p < 0.001$) and posterior surfaces ($R = -0.568$, $p < 0.001$) in all eyes.
246 Meanwhile, there was no significant correlation between the area of pathology and the radius of the
247 optimum sphere for both anterior surfaces ($R = 0.012$, $p = 0.769$) and posterior surfaces ($R = 0.003$, $p =$
248 0.945), Figure 6.



249

250 Figure 6 Correlation of cone height and pathology area with the radius of the sphere of optimal fit for
 251 both anterior and posterior surfaces

252 **4. Discussion**

253 A novel method to detect the cone centre and height normal to the surface, as well as the transition
 254 zone between the area of pathology and the surrounding healthy corneal tissue in keratoconic
 255 patients, is proposed in this study. The method relies on spherical coordinates relative to the centre
 256 of the cornea's optimal sphere fit and measured normal to the surface, in order to reduce the effect
 257 of the cornea's natural curvature in determining the cone's geometric features. When applying the
 258 method to 618 eyes of 309 KC patients, more than 80% of cases had infra-temporal cones, which is
 259 intermediate between the 95% figure reported by Auffarth, Wang (32) and 65% reported by Demirbas
 260 and Pflugfelder (33), but different from findings by Wilson, Lin (34) where the majority of 48 eyes
 261 under study had the cone centre located in the inferior-nasal quadrant. The reason for this mismatch
 262 could be that Wilson, Lin (34) used a relatively small sample that may have particular characteristics
 263 that cannot be generalised. Our results also showed significant mirror-image symmetry
 264 (enantiomorphism) between right and left eye groups in cone location, similar to what was reported
 265 by Rabinowitz and McDonnell (7) and Holland, Maeda (35). As no direct comparison was made

266 between the fellow eyes of individual subjects in this study, the disease could be more advanced in
267 one eye than the other.

268 The results further showed a trend of increased cone height ($R= 0.716$, $p< 0.001$) and reduced
269 distance from corneal apex to cone centre ($R= -0.312$, $p< 0.001$) with disease severity – this trend
270 was significant in both anterior and posterior surfaces of right and left eyes. Cone height was also
271 negatively correlated with the radius of the optimum fit sphere in both the anterior surfaces ($R= -0.584$,
272 $p< 0.001$) and posterior surfaces ($R =-0.568$, $p< 0.001$).

273 In contrast, while having the radius of the optimal sphere as a co-variate, the cone area was not
274 correlated with the disease stages in the anterior surface ($R= 0.002$, $p=0.753$) and was weakly
275 correlated in the posterior surface ($R= 0.093$, $p= 0.003$). This lack of difference may be due to the
276 simultaneous inclusion of different cone morphologies. Perry et al., (12) described two types of cone
277 morphologies in advanced cases; the centrally restricted cone with nipple-shaped pattern and the
278 peripheral with more spread oval cones. As nipple cones typically have smaller areas and locate
279 closer to corneal apex compared with oval cones in severe keratoconus, the use of both cone height
280 and distance of cone centre to apex as biomarkers for keratoconus severity may be less effective,
281 leaving only cone height as a robust biomarker (3, 36-40).

282 There is also strong evidence that the posterior cone increased in height faster in 90% of cases than
283 the anterior cone which was likely affected by epithelial remodelling. This finding supports the notion
284 that the evaluation of both surfaces would be important for a reliable diagnosis (41). The study also
285 revealed strong correlation between the shift of the posterior cone (relative to the anterior cone) and
286 the height of the anterior cone. This is an important finding which can be used to provide a realistic
287 representation of cone geometry in numerical simulations of the biomechanics of keratoconic eyes. It
288 could also help the design and optimisation of corneal implants used to correct refractive errors in KC
289 patients.

290 Another important earlier study by Mahmoud et al. identified the 2mm-diameter circular zone of the
291 cornea with the steepest curvature and used it to locate the cone centre (36). The method was initially

292 developed for anterior surface axial and tangential curvature maps but later expanded to consider the
293 posterior surface, surface elevation and corneal thickness maps. While this method was sensitive in
294 separating keratoconic and normal corneas, and in locating and quantifying the alterations that occur
295 in the central area of the disease, it was not designed to evaluate the cone shape or locate its
296 transition zone.

297 The proposed method in this research is also different from the Belin/Ambrósio enhanced best-fit
298 sphere method (42, 43). In the Belin/Ambrosio method, the height of the cone is obtained by the
299 difference in Z coordinate between the cornea and the BFS obtained after excluding a fixed area
300 around the thinnest point. In the method presented in this study, the height is obtained by the radial
301 differences between the cornea and the optimal sphere, calculated normal to the surface, obtained in
302 an iterative process to exclude the pathologic area specific for each case. Another characteristic of
303 the proposed method is that by using radial distances, the method is expected to be less affected by
304 the natural curved shape of the eye.

305 With numerical simulations being extensively used in ophthalmology, the findings of this study could
306 be valuable for future research. Numerical models require geometric information to be able to perform
307 simulations and provide reliable results. To model eyes with keratoconus, availability of the
308 information provided in this paper would enable modelling of corneal geometry, including the
309 representation of the pathologic area which could then be simulated as softer than the surrounding
310 area. The proposed method can also be used on data provided by different corneal topographers to
311 identify the cone location, height and transition zone. This should enable researchers to develop
312 computer programs based on this logic and analyse mass information in a customised manner using
313 only the elevation data of the anterior and posterior cornea. In addition, in the era of artificial
314 intelligence, access to large datasets is crucial for machine learning purposes. One problem with data
315 collection is that information provided by different devices often cannot be used due to variations in
316 data format (39, 44). This method bridges this gap and enables consistent use of raw elevation data
317 allowing multi-device data collection that can be fed into Artificial Intelligence (AI) algorithms. This
318 would help in the process of clinical decision making. With this advancement, AI algorithms would be

319 able to help on the diagnose of keratoconus and on the treatment planning by, for example, increasing
320 the accuracy of contact lens fitting of patients with abnormal corneas and helping in the ring segment
321 surgery by improving ring size selection and defining its placement position.

322 One limitation of the study was the reliance on only keratoconic topography data in the analysis and
323 hence the lack of comparison to normal, healthy eyes. This was done as the method was intended
324 not for disease detection, but to support the management of keratoconus.

325 In conclusion, this study proposed a new method to explore the changes in anterior and posterior
326 corneal surfaces in patients with keratoconus and to define the cone-shaped area. The method is
327 intended to help improve understanding of corneal shape as keratoconus progresses and customise
328 treatment regimens such as collagen cross-linking and intracorneal ring implantation.

329

330 **Author Contributions**

331 A Eliasy: Writing original draft, Editing, Conceptualization, Formal analysis, Methodology, Software,
332 Validation & Visualization

333 A Abass: Writing original draft, Review, Conceptualization, Formal analysis, Methodology, Software,
334 Validation, Visualization & Supervision

335 B T Lopes: Writing original draft, Conceptualization, Software, Validation & Visualization

336 R Vinciguerra: Review, Editing & Data curation

337 H Zhang: Review, Formal analysis, Validation & Visualization

338 P Vinciguerra: Review, Editing & Data curation

339 R Ambrósio Jr: Review & Editing

340 C J Roberts: Review, Editing, Conceptualization, Investigation & Methodology

341 A Elsheikh: Writing original draft, Review, Funding acquisition, Investigation, Methodology, Project
342 administration, Resources & Supervision

343

344 **Acknowledgement**

345 This study has received funding from the European Union's Horizon 2020 research and innovation
346 programme Horizon 2020 IMCUSTOMEYE project under grant agreement ID 779960.

347

348 **Financial Disclosure(s):**

349 Renato Ambrósio, Paolo Vinciguerra, Riccardo Vinciguerra, Cynthia J. Roberts and Ahmed Elsheikh
350 are consultants for OCULUS Optikgeräte GmbH. Ahmed Elsheikh and Bernardo Lopes have received
351 research funding from OCULUS Optikgeräte GmbH. None of the remaining authors has financial
352 disclosures.

353

354 **References**

- 355 1. Appelbaum A. Keratoconus. Archives of Ophthalmology. 1936;15:900-21.
- 356 2. Bron AJ. Keratoconus. Cornea. 1988;7(3):163-9.
- 357 3. Krachmer JH, Feder RS, Belin MW. Keratoconus and related noninflammatory corneal thinning
358 disorders. Survey of ophthalmology. 1984;28(4):293-322.
- 359 4. Rabinowitz YS. Keratoconus. Survey of Ophthalmology. 1998;42(4):297-319.
- 360 5. Efron N, Hollingsworth JG. New perspectives on keratoconus as revealed by corneal confocal
361 microscopy. Clin Exp Optom. 2008;91(1):34-55.
- 362 6. Nejabat M, Khalili MR, Dehghani C. Cone location and correction of keratoconus with rigid gas-
363 permeable contact lenses. Contact Lens and Anterior Eye. 2012;35(1):17-21.
- 364 7. Rabinowitz YS, McDonnell PJ. Computer-assisted corneal topography in keratoconus. Journal of
365 Refractive Surgery. 1989;5(6):400-8.
- 366 8. Klyce SD. Information fidelity in corneal topography. Br J Ophthalmol. 1995;79(9):791-2.
- 367 9. Lebow KA, Grohe RM. Differentiating contact lens induced warpage from true keratoconus using
368 corneal topography. The CLAO journal : official publication of the Contact Lens Association of
369 Ophthalmologists, Inc. 1999;25(2):114-22.
- 370 10. Maguire LJ, Bourne WM. Corneal topography of early keratoconus. Am J Ophthalmol.
371 1989;108(2):107-12.
- 372 11. Maeda N, Klyce SD, Smolek MK. Neural network classification of corneal topography. Preliminary
373 demonstration. Investigative ophthalmology & visual science. 1995;36(7):1327-35.
- 374 12. Perry HD, Buxton JN, Fine BS. Round and oval cones in keratoconus. Ophthalmology. 1980;87:905-9.

- 375 13. Seiler TG, Fischinger I, Koller T, Zapp D, Frueh BE, Seiler T. Customized Corneal Cross-linking: One-
376 Year Results. *Am J Ophthalmol*. 2016;166:14-21.
- 377 14. Scarcelli G, Besner S, Pineda R, Yun SH. Biomechanical characterization of keratoconus corneas ex
378 vivo with Brillouin microscopy. *Investigative ophthalmology & visual science*. 2014;55(7):4490-5.
- 379 15. Dauwe C, Touboul D, Roberts CJ, Mahmoud AM, Kerautret J, Fournier P, et al. Biomechanical and
380 morphological corneal response to placement of intrastromal corneal ring segments for keratoconus. *Journal*
381 *of cataract and refractive surgery*. 2009;35(10):1761-7.
- 382 16. Mahmoud AM, Roberts CJ, Lembach RG, Twa MD, Herderick EE, McMahon TT, et al. CLMI: the cone
383 location and magnitude index. *Cornea*. 2008;27(4):480-7.
- 384 17. Vega-Estrada A, Alio JL. The use of intracorneal ring segments in keratoconus. *Eye Vis (Lond)*.
385 2016;3:8.
- 386 18. Shetty R, Matalia H, Srivatsa P, Ghosh A, Dupps Jr WJ, Sinha Roy A. A Novel Zernike Application to
387 Differentiate Between Three-dimensional Corneal Thickness of Normal Corneas and Corneas With
388 Keratoconus. *American Journal of Ophthalmology*. 2015;160(3):453-62.e2.
- 389 19. Abass A, Clamp J, Bao F, Ambrosio R, Jr., Elsheikh A. Non-Orthogonal Corneal Astigmatism among
390 Normal and Keratoconic Brazilian and Chinese populations. *Curr Eye Res*. 2018:1-8.
- 391 20. Khurana AK. *Theory And Practice Of Optics And Refraction*. 3 ed. India: Elsevier India Pvt. Limited;
392 2008.
- 393 21. Lopes BT, Ramos IC, Dawson DG, Belin MW, Ambrosio R, Jr. Detection of ectatic corneal diseases
394 based on pentacam. *Z Med Phys*. 2016;26(2):136-42.
- 395 22. Mahmoud AM, Nunez MX, Blanco C, Koch DD, Wang L, Weikert MP, et al. Expanding the cone
396 location and magnitude index to include corneal thickness and posterior surface information for the
397 detection of keratoconus. *Am J Ophthalmol*. 2013;156(6):1102-11.
- 398 23. Polian A. Brillouin spectroscopy uses the scattering of light for the determination of materials
399 elasticity. *Journal of Raman Spectroscopy*. 2003;34(7-8):633-7.
- 400 24. Seiler TG, Shao P, Eltony A, Seiler T, Yun SH. Brillouin Spectroscopy of Normal and Keratoconus
401 Corneas. *Am J Ophthalmol*. 2019;202:118-25.
- 402 25. Schwiegerling J. Cone dimensions in keratoconus using Zernike polynomials. *Optom Vis Sci*.
403 1997;74(11):963-9.
- 404 26. Vinciguerra R, Ambrosio R, Jr., Elsheikh A, Roberts CJ, Lopes B, Morenghi E, et al. Detection of
405 Keratoconus With a New Biomechanical Index. *J Refract Surg*. 2016;32(12):803-10.
- 406 27. Ambrosio R, Jr., Lopes BT, Faria-Correia F, Salomao MQ, Bühren J, Roberts CJ, et al. Integration of
407 Scheimpflug-Based Corneal Tomography and Biomechanical Assessments for Enhancing Ectasia Detection. *J*
408 *Refract Surg*. 2017;33(7):434-43.
- 409 28. Belin MW, Khachikian SS. An introduction to understanding elevation-based topography: how
410 elevation data are displayed - a review. *Clin Experiment Ophthalmol*. 2009;37(1):14-29.
- 411 29. Goebels S, Eppig T, Wagenpfeil S, Cayless A, Seitz B, Langenbacher A. Staging of keratoconus indices
412 regarding tomography, topography, and biomechanical measurements. *Am J Ophthalmol*. 2015;159(4):733-
413 8.
- 414 30. Renka RJ, Renka RL, Cline AK. A TRIANGLE-BASED C^1 INTERPOLATION METHOD. *The Rocky Mountain*
415 *Journal of Mathematics*. 1984;14(1):223-37.
- 416 31. Everitt BS, Skrondal A. *The Cambridge Dictionary of Statistics*. 4 ed. Cambridge, UK: Cambridge
417 University Press; 2010.
- 418 32. Auffarth GU, Wang L, Volcker HE. Keratoconus evaluation using the Orbscan Topography System.
419 *Journal of Cataract and Refractive Surgery*. 2000;26(2):222-8.
- 420 33. Demirbas NH, Pflugfelder SC. Topographic pattern and apex location of keratoconus on elevation
421 topography maps. *Cornea*. 1998;17(5):476-84.
- 422 34. Wilson SE, Lin DT, Klyce SD. Corneal topography of keratoconus. *Cornea*. 1991;10(1):2-8.
- 423 35. Holland DR, Maeda N, Hannush SB, Riveroll LH, Green MT, Klyce SD, et al. Unilateral keratoconus:
424 incidence and quantitative topographic analysis. *Ophthalmology*. 1997;104(9):1409-13.

- 425 36. Mahmoud AM, Roberts CJ, Lembach RG, Twa MD, Herderick EE, McMahon TT, et al. CLMI the cone
426 location and magnitude index. *Cornea*. 2008;27(4):480.
- 427 37. Twa MD, Nichols JJ, Joslin CE, Kollbaum PS, Edrington TB, Bullimore MA, et al. Characteristics of
428 corneal ectasia after LASIK for myopia. *Cornea*. 2004;23(5):447-57.
- 429 38. Maguire LJ, Bourne WM. Corneal topography of early keratoconus. *American journal of*
430 *ophthalmology*. 1989;108(2):107-12.
- 431 39. Maeda N, Klyce SD, Smolek MK. Neural network classification of corneal topography. Preliminary
432 demonstration. *Investigative ophthalmology & visual science*. 1995;36(7):1327-35.
- 433 40. Wilson SE, Klyce SD. Screening for corneal topographic abnormalities before refractive surgery.
434 *Ophthalmology*. 1994;101(1):147-52.
- 435 41. Gomes JA, Tan D, Rapuano CJ, Belin MW, Ambrósio Jr R, Guell JL, et al. Global consensus on
436 keratoconus and ectatic diseases. *Cornea*. 2015;34(4):359-69.
- 437 42. Belin MW, Khachikian SS. Keratoconus/ectasia detection with the oculus pentacam: Belin/Ambrósio
438 enhanced ectasia display. *Highlights Ophthalmol*. 2007;35(6):5-12.
- 439 43. Luz A, Lopes B, Hallahan KM, Valbon B, Ramos I, Faria-Correia F, et al. Enhanced combined
440 tomography and biomechanics data for distinguishing forme fruste keratoconus. *Journal of Refractive*
441 *Surgery*. 2016;32(7):479-94.
- 442 44. Smolek MK, Klyce SD. Screening of prior refractive surgery by a wavelet-based neural network.
443 *Journal of Cataract & Refractive Surgery*. 2001;27(12):1926-31.

444