1 **Detection of Keratoconus with the new Corvis ST Biomechanical Index.**

2 Riccardo Vinciguerra, MD[1]; Renato Ambrósio Jr, MD, PhD[2-3], Ahmed Elsheikh, PhD[4-5]; Cynthia J.

3 Roberts, PhD[6], Bernardo Lopes, MD[2-3], Emanuela Morenghi, PhD[7], Claudio Azzolini, MD[1], Paolo

4 Vinciguerra, MD[8-9].

5 **Affiliation:**

6 [1]Department of Surgical Sciences, Division of Ophthalmology, University of Insubria, Varese, Italy.

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

8 [3]Department of Ophthalmology, Federal University of São Paulo – São Paulo, Brazil

9 [4]School of Engineering, University of Liverpool – Liverpool, United Kingdom

10 [5]NIHR Biomedical Research Centre for Ophthalmology, Moorfields Eye Hospital NHS Foundation
11 Trust and UCL Institute of Ophthalmology, UK

12 [6]Department of Ophthalmology & Visual Science, Department of Biomedical Engineering, The

13 Ohio State University – Columbus, OH, USA

14 [7]Biostatistic Unit, Humanitas Research Hospital, Rozzano (Milano), Italy

15 [8]Eye Center, Humanitas Clinical and Research Center, Via Manzoni 56, Rozzano (MI) – Italy.

16 [9]Vincieye Clinic, Milan, Italy.

17 **Corresponding author:**

18 Dr Paolo Vinciguerra, Humanitas Clinical and Research Center, Via Manzoni 56, 20089 Rozzano

19 (Milan), Italy Email: paolo.vinciguerra@humanitas.it , phone +390255211388, fax +390257410355

1 **Running head**

2 Corvis Biomechanical Index for the diagnosis of keratoconus

3 **PRECIS**

4 A new multivariate biomechanical index for the diagnosis of keratoconus, based on thickness

5 profile and corneal deformation parameters, is introduced and validated on external database.

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

26

1 **ABSTRACT:**

2 **Purpose:** To evaluate ability of the new Biomechanical Index (BI), based on thickness profile and

3 corneal deformation parameters, to separate normal from keratoconus patients.

4 **Materials and Methods:** Six hundred and sixty-two patients were included in this multicenter

5 retrospective study. Patients were enrolled in two clinics located in different continents to test the

6 capability of the BI to separate healthy and keratoconic eyes in more than one ethnic group.

7 Database 1 comprised 255 healthy and 79 keratoconus whether database 2 included 227 healthy and

8 101 keratoconus. The biomechanical response data were analyzed and logistic regression was

9 employed to combine the best individual parameters in database 2. Optimal cutoff points of the BI

10 was obtained, subsequently, the formula was externally validated in Database 1.

11 **Results:**

12 The final formula included Deformation Amplitude ratio at 1 and 2 mm, Applanation 1 velocity,

13 Highest Concavity Radius and Arth (Horizontal thickness profie).

14 The ROC curve analysis of database 2 showed an Area Under the Curve (AUC) of 0.978 with a cut-

15 off value of 0.5. This cut off correctly classified 97.3% of the cases with 99.6% specificity and

16 92.1% sensitivity. In the validation dataset (database 1) the same cut-off point classified correctly

17 100% of the cases with 100% specificity and 100% sensitivity.

18 **Conclusion:**

19 In conclusion BI showed to be highly sensitive and specific alone to separate healthy from ectatic

20 eyes. The presence of an external validation dataset confirms this finding and suggest the possible

21 use of BI in everyday clinical practice to aid the diagnosis of ectasia.

22

23

24

25

26

INTRODUCTION

The early diagnosis of corneal ectasia is of foremost importance both in the screening for refractive surgery and for the early treatment of keratoconus.

If we consider the refractive point of view, the occurrence of ectasia after a refractive procedure is very rare and feared occurrence because of the problems related to a vision threat or reduction in a patient that previously had a very high quality corrected visual acuity. However, many cases of ectasia have been reported after LASIK despite patients' low risk scores on standard screening tests.[1,2] On the other hand, some patients with recognized ectatic risk factors remain stable many years after LASIK.

Conversely, considering the diagnosis of the ectatic disease in the general population, keratoconus is normally diagnosed in adolescence or childhood[3-5] and the time of diagnosis is a negative prognostic factor for increased risk of corneal transplant.[6] The early diagnosis and, as a consequence, its early treatment with corneal collagen cross-linking at the first sign of progression can halt keratoconus at a stage where visual acuity is still high.

Current clinical instruments, such as topography and tomography, can detect alteration in the shape of the cornea but cannot measure the mechanical stability which is thought to be the initiating event of the disease. For this reason, there has been increasing interest in developing instruments to measure the in-vivo biomechanical properties of the cornea. The first one to be developed was the Ocular Response Analyzer (ORA, Reichert Inc., Depew, NY)[7]. The ORA is a adapted non-contact tonometer (NCT) designed first to provide a more accurate measurement of intraocular pressure (IOP) through compensation for corneal biomechanics. It examines corneal behavior during a bi-directional applanation process induced by an air jet, and produces estimates of corneal hysteresis and corneal resistance factor, along with a set of 36 waveform-derived parameters.[8-10] The most recent version of the device enables the measurement of 2 new keratoconus-specific parameters: the keratoconus match index (KMI) and the keratoconus match probability (KMP). The capability of ORA to diagnose keratoconus was tested in several articles[10-12] but never reached the gold standard.

1   The Corvis ST (OCULUS Optikgeräte GmbH; Wetzlar, Germany) was later introduced as

2   an NCT, which monitors the response of the cornea to an air pressure pulse using an ultra-high

3   speed (UHS) Scheimpflug camera, and uses the captured image sequence to produce estimates of

4   IOP and deformation response parameters.[13] At the present time, Corvis do not provide an

5   automatic analysis of corneal biomechanics such as the KMI or the KMP.

6   The aim of this article is to develop a combined parameter (Biomechanical Index-BI) based

7   on different Corneal Deformation Parameters (CDP) provided by the Corvis ST to separate

8   keratoconus from normal subjects.

9

10 **MATERIALS AND METHODS**

11 Six hundred and sixty-two patients were included in this multicenter retrospective study. The

12 patients were enrolled in two clinics located in 2 different continents to include variability from

13 different continents and to test the capability of the Biomechanical Index (BI) to separate healthy

14 and keratoconic eyes in more than one ethnic group. A total of three hundred and thirty-four

15 patients (255 healthy and 79 keratoconus) were enrolled from Vincieye Clinic in Milan, Italy

16 (Database 1) and three hundred and twenty-eight patients (227 healthy and 101 keratoconus) from

17 the Rio de Janeiro Corneal Tomography and Biomechanics Study Group – Rio de Janeiro, Brazil

18 (Database 2). Institutional review board (IRB) ruled that approval was not required for this record

19 review study, and it was conducted according to the ethical standards set in the 1964 Declaration of

20 Helsinki, as revised in 2000. However, subjects provided informed consent before using their data

21 in the study.

22 All patients had a complete ophthalmic examination, including the Corvis ST and Pentacam

23 (OCULUS Optikgeräte GmbH; Wetzlar, Germany) exams.

24 The inclusion criteria of this study for the keratoconic population was the presence of a bilateral

25 clear keratoconus without any previous ocular surgeries, such as corneal collagen cross linking or

26 intracorneal rings implant. Conversely, the inclusion criteria the healthy subjects were the presence

1 in the database of a Corvis ST exam, a Belin Ambrosio Enhanced Ectasia Index total deviation

2 (BAD-D) from the Pentacam less than 1.6 standard deviations (SD) from normative values in both

3 eyes and a signed informed consent. Exclusion criteria were any previous ocular surgery or disease,

4 myopia over 10D and any concomitant or previous glaucoma or hypotonic therapies.   The BAD-D

5 cut off of 1.6 SD was used because it is described as the best performing screening parameter with

6 values of 1.65/1.88 associated, respectively, with a 95% and 97.5% confidence interval with an

7 acceptable false negative rate of less than 1%.[14] Only Corvis ST exams with quality score "OK"

8 were included in the analysis. Additionally, a second manual, frame-by-frame analysis of the exam,

9 made by an independent masked examiner, was performed to ensure quality of each acquisition.

10 The main criterion was good edge detection over the whole deformation response, with the

11 exclusion of alignment errors (x-direction). Similarly, blinking errors were omitted. Moreover, all

12 exams re-evaluated of Vincieye Clinic were blindly by an expert of Anterior Segment (Dr R.

13 Ambrosio) to confirm the diagnosis. Similarly, all the exams of Rio de Janeiro clinic were blindly

14 re-evaluated by Dr P. Vinciguerra. All measurements with the Corvis ST were taken by the same

15 experienced technicians. The Corvis ST uses an ultrahigh-speed Scheimpflug camera that captures

16 4330 images per second and covers 8.0 mm of the cornea in a single horizontal meridian. The

17 instrument's light source is an LED light of 455 nm wavelength. The air impulse produces a

18 maximum pressure of 25 kiloPascals. A quality score (QS) is available just after the measurement is

19 taken for assessing the reliability of the measurement. This is based on a series of parameters that

20 are obtained so that a QS is also available for the pachymetry and IOP data.[13]

21 Only one eye per patient was randomly included in the analysis to avoid the bias of the relationship

22 between bilateral eyes that could influence the analysis result.

23

24 The Corvis ST output parameters by the research software 1.2b1191 from each measurement were

25 exported to a spreadsheet and analyzed to

26

1   *Corneal deformation parameters (CDPs)*

2   CDPs provided by Corvis ST include: A1 Velocity (speed of corneal apex at first applanation), A2

3   Velocity (speed of corneal apex at second applanation), Peak Distance (distance between the two

4   bending peaks created in the cornea at the maximum concavity state), Highest concavity radius

5   (radius of the central cornea at the maximum concavity state, based on a parabolic fit) and

6   Deformation Amplitude (maximum depth of deformation at the highest concavity state).

7   The Deformation Amplitude (DA) refers to the largest displacement of corneal apex in the

8   anterior-posterior direction at the moment of highest concavity.[8, 13] During the measurement, the

9   Whole Eye globe Movement (WEM), another measured parameter, affects DA. As the cornea

10   deforms and approaches maximum displacement, the whole eye displays a slow linear motion in the

11   anterior-posterior direction. When the cornea reaches maximum displacement, the whole eye

12   motion becomes more pronounced and nonlinear in nature, as the air puff pressure continues to

13   increase to a consistent maximum value. The deflection amplitude (DefA) is displacement of the

14   corneal apex in reference to the overlayed cornea in initial state. Therefore, the deformation

15   amplitude is the sum of pure corneal deflection amplitude and whole eye movement. The Deflection

16   area describes the "displaced" area of the cornea in the analyzed horizontal sectional plane due to

17   the deformation of the cornea.

18   Other parameters can be extrapolated from the highest concavity (HC) moment: ad Inverse

19   Concave Radius and Peak Distance. The Inverse Concave Radius (1/R) is plotted over the time of

20   the air pulse and the integrated sum is calculated between the first and second applanation events.[8,

21   13] The Peak Distance describes the distance between the two highest points of the cornea's

22   temporal-nasal cross-section at the highest concavity moment, which is not the same as the

23   deflection length.[8]

24   Two new parameters called central-peripheral deformation amplitude ratio (DA Ratio) and

25   deflection amplitude ratio (DefA ratio), describe the ratio between the deformation/deflection

26   amplitude at the apex and the average deformation/deflection amplitude in a nasal and temporal

zone 1 or 2 mm (2 mm for DefA ratio) from the center. The greater the difference between the center and defined paracentral regions, the less resistant is the cornea to deformation. Therefore, one would expect higher values of DA Ratio and DefA Ratio to be associated with softer corneas. The Delta Arclength (HCdArclength), another new parameter, describes the change of the Arclength during the highest concavity moment from the initial state, in a defined 7mm zone. This parameter is calculated 3.5mm from the apex to both sides in the horizontal direction. The temporal changes in the delta arclength are also calculated for the exact same zone and a plot is generated. Corvis ST is able to generate, additionally to the simple central corneal thickness, a new index, called Arth, fully based on the thickness profile of the horizontal Scheimpflug camera as follow:

1. Corneal thickness is calculated from the thinnest point to the periphery in 0.2 mm steps and the percentage thickness increase (PTI) is calculated. At each position PTI values describe how many percent the cornea is thicker than at the thinnest point.

2. The ratio between the percentage values (PTIs) and the corresponding normative value for each position is calculated along the complete thickness profile.

3. The average ratio for all positions provides the Pachymetric Progression Index: A value higher than one indicates a faster thickness increase than usually, a lower value indicates a slower thickness increase towards the periphery than usually.

4. The ratio between corneal thickness at the thinnest point and the Progression index provides ARTh (ARTh = CT thinnest / Pachym etric Progression). A smaller value indicated a thinner cornea and / or a faster thickness increase towards the periphery.

STATISTICAL ANALYSIS:

Receiver operating characteristic (ROC) curves were applied to determine the overall predictive accuracy of corneal deformation parameters and the combination of them, as described by the area under the curve (AUC). These curves are obtained by plotting sensitivity versus 1-specificity, which is calculated for each value observed. An area of 100% implies that the test perfectly discriminates

1 between groups.

2 Logistic regression with forward stepwise inclusion was employed to combine the best individual

3 indices for the creation of the Corvis Biomechanical Index (BI) using database 2. The parameters

4 included in the analysis were IOP, Pachymetry (CCT), Deformation Amplitude, Applanation 1

5 Velocity, Peak Distance, HCdArclength, HC Deflection Area, DAratio 2mm, DAratio 1mm, DefA

6 ratio, Inverse Concave Radius, Radius HC and ARTh.

7

8 Only for the creation of the formula, outliers were excluded. Outliers were defined as > 3rd quartile

9 plus 1.5 IQD (interquartile distance: distance between 1. and 3rd quartile) or < 1st quartile minus

10 1.5 IQD. Outliers were removed for CCT, IOP, IOP_{FEM}, HC Def. Amp, DA ratio 2mm, DAratio

11 1mm, A1 velocity, ARTh, Radius HC, Integrated Inverse Radius and Mean Inverse Radius. These

12 parameters were chosen to exclude outliers because were known to have a good ROC curves. In the

13 case of A1 velocity it was included because known from previous studies, to be either correlated

14 with IOP[15] or known to be able to increase the sensitivity and specificity in multivariate analysis

15 (data from unpublished data from other datasets). After the creation of the formula, outliers were re-

16 included to test the capability of BI to separate normal from keratoconus in the complete dataset 2.

17 Optimal cutoff points of the BI was obtained from the ROC curves as those closest to the perfect

18 classification point. Subsequently, to exclude over fitting, the formula was externally validated in

19 Database 1.

20 The statistical analysis was performed with SPSS version 23 (IBM Corp. in Armonk, NY, USA).

21

22 **RESULTS:**

23 Two hundred and eighty-nine left eyes and three hundred and seventy-three right eyes were

24 included.

25 Database 1 comprised 136 left and 198 right eye whether database 2 included 153 left and 175 right

26 eyes. The mean age ± standard deviation of normal eyes was 43±17 years in database 1 and 37±17

1   years in database 2, conversely the mean age of keratoconic patients was 37±12 in database 1 and

2   32 ±12 in database 2.

3   Considering only the keratoconic population in database 1 the mean Kmax was 54.11±6.17 and

4   mean BAD-D value was 8.26±0.44, in database 2 mean Kmax was 55.53±9.24 and mean BAD-D

5   was 9.98±17.23, all these difference were not statistically significant (p>0.05).

6   In Table 1 and 2 are summarized the Topographic Keratoconus Classification (TKC) provided by

7   Pentacam for both database.

8

9   The stepwise logistic regression, based on database 2 produced the following formula:

10

11   **BI** = EXP (Beta) / (1+ EXP(Beta))

12   where

13   Beta = B1 * DAratio 1mm + B2 * DAratio2mm + B3 * ARTh + B4 * HC Radius + B5 * A1

14   Velocity + B6

15

16   With: B1= -36.17, B2 = 7.98; B3= -0.027, B4 = -1.41, B5 = -65,95, B6 = 50.04

17   Beta values of all parameters used in the equation were highly significant (p<0.01).

18

19   The ROC curve analysis of database 2 showed an Area Under the Curve (AUC) of 0.978 with a cut-

20   off value of 0.5 (Figure 1). This cut off correctly classified 97.3 % of the cases with 99.6 %

21   specificity and 92.1 % sensitivity.

22   In the validation dataset (database 1) the same cut-off point classified correctly 100% of the cases

23   with 100 % specificity and 100 % sensitivity (Figure 2).

24   The ROC curve analysis of the combined dataset showed an Area Under the Curve (AUC) of 0.986

25   and a very good predictive accuracy of BI (Figure 3).

26

1 Table 3 shows the gain in sensitivity and specificity with each step of the logistic regression,

2 whereas Figure 4 shows the increase of the AUC.

3

4 **DISCUSSION:**

5 It is well known that keratoconic corneas are significantly "weaker" or had lower elastic modulus

6 than normal corneas.[16, 17] These results were proven with stress-strain measurement using strip

7 extensiometry experiments. However, in the last years a new theory for biomechanical pathogenesis

8 of keratoconus was proposed basing on the existing biomechanical models and clinical topographic

9 and tomographic data.[18] This theory, later supported by the studies of Scarcelli et al[19], proposed that

10 the initiating event in keratoconus could be a focal reduction in biomechanical properties, resulting

11 in thinning as the weaker area strains more than the surrounding stronger areas. The cause may be

12 an underlying pathology, or perhaps a genetic predisposition with an external insult as a trigger,

13 such as eye rubbing in a focal region.

14 The consequence is that the focal reduction in elastic modulus generates greater deformation for the

15 same load. This is followed by bulging with increased curvature, which redistributes the stress and

16 the cycle continues. Thus, it is the disparity in corneal properties which drives the continued

17 progression.

18 A direct consequence of this theory is that it might be possible to diagnose an ectasia before this

19 biomechanical cycle of decompensation leads to increase of curvature and thickness reduction.

20 For this reason the in-vivo evaluation of corneal biomechanics for the diagnosis of keratoconus has

21 always been of foremost interest.

22

23 This multicenter study included more than 600 cases from two different continents. The exclusion

24 of one eye per patient eliminated the risk of a bias due to the relationship between bilateral eyes.

25 Considering the population of the two dataset, database 2, had a slightly higher amount of early

26 keratoconus cases, in particular 6 cases were classified as normal by the TKC but abnormal with the

1   BAD-D and the double experts revision (P.V. and R.A.). For this reason database 2 was used to

2   create the formula because thought to be more challenging.

3

4   The main result of our study is the diagnostic capability of BI alone to distinguish between normal

5   and keratoconus. Indeed, the multivariate diagnostic model created showed to be highly sensitive

6   and specific with an overall AUC of 0.986. In both database BI correctly classified more than 95%

7   of the cases. In the validation dataset 100% of the eyes were correctly classified.

8   It is the first time in literature, to our knowledge, that a combination of Corvis parameter is able to

9   provide these results. All the published studies, indeed, produced a AUC lower than 0.900[20-22], even

10   though some of these studied refer to subclinical cases.[23]

11   However, this dynamic Scheimpflug device is relatively new and many similar studies were

12   performed with the Ocular Response Analyzer. The majority of the manuscripts, however, even

13   those where the Waveform Derivatives are evaluated produced a lower AUC[11, 12, 24-26]. Hallahan et

14   al and Ventura et al showed comparable AUC, nevertheless those studies included a significant

15   lower number of cases and controls and did not have an external validation.[10, 27]

16   The presence of an external validation is of foremost importance when considering a multivariate

17   analysis, first of all to exclude over fitting, secondly because the cut-off value in one database may

18   not produce the same results in a second independent one.

19   The inclusion of this validation in our study, which produced even better results than in database 2,

20   confirms the diagnostic performance of BI. It is the first time in literature, to our knowledge, that a

21   high number validation dataset is used to confirm the diagnostic ability of an ectasia detection

22   formula.

23

24   A possible criticism of our study could be the decision to use Arth and A1 velocity, the first one

25   because it is a pure thickness profile, already with a very good AUC and the second one because its

26   AUC is not as good as the others parameters included. However, as showed in table 2, sensitivity

1 and specificity increased meaningfully with the addition of the other 4 CDPs, that confirms the

2 importance of the biomechanics in evaluating ectasia. Furthermore, Arth can be considered either a

3 thickness parameter inside the multivariate analysis to separate normal from keratoconus as well as

4 a correction parameter for the possible difference in thickness between the patients to correctly

5 evaluate biomechanics. As matter of fact it is known that many CDPs are correlated with

6 thickness.[28, 29] Regarding the inclusion of A1 velocity, even though its poor single capability of

7 separating healthy from keratoconus, its presence increased the sensitivity by 2 percentage point

8 (see table 1). We hypothesize that, given its correlation with IOP (known from previous

9 unpublished or under review studies) it compensates for the difference in the IOP in the single cases.

10 Instead of A1 velocity one could also use IOP but A1 velocity worked better in the combination.

11 Furthermore its beta value was highly significant.

12

13 A deliberate limitation of our study was the exclusion from the databases of form fruste keratoconus

14 (FFKC) and subclinical cases. Another study is in process, with very promising results, to test the

15 capability of BI alone and in combination with Pentacam indexes to separate healthy from FFKC.

16

17 In conclusion, our study introduces BI for keratoconus diagnosis that showed to be highly sensitive

18 and specific alone to separate healthy from ectatic eyes. The presence of an external validation

19 dataset from another continent confirms this finding and suggest the possible use of BI in everyday

20 clinical practice to aid the diagnosis of ectasia. More studies are in progress to show the capability

21 of BI alone and in combination with tomographic indexes to separate healthy from subclinical cases.

22

23

24

25

26

References

1.   Ambrosio R, Jr., Dawson DG, Salomao M, et al. Corneal ectasia after LASIK despite low

preoperative risk: tomographic and biomechanical findings in the unoperated, stable, fellow eye. J

Refract Surg 2010;26(11):906-11.

2.   Chan CC, Hodge C, Sutton G. External analysis of the Randleman Ectasia Risk Factor Score

System: a review of 36 cases of post LASIK ectasia. Clin Experiment Ophthalmol 2010;38(4):335-

40.

3.   Hall KG. A Comprehensive Study of Keratoconus. Br J Physiol Opt 1963;20:215-56.

4.   Rabinowitz YS, Rasheed K, Yang H, Elashoff J. Accuracy of ultrasonic pachymetry and

videokeratography in detecting keratoconus. J Cataract Refract Surg 1998;24(2):196-201.

5.   Rabinowitz YS. Keratoconus. Surv Ophthalmol 1998;42(4):297-319.

6.   Reeves SW, Stinnett S, Adelman RA, Afshari NA. Risk factors for progression to

penetrating keratoplasty in patients with keratoconus. Am J Ophthalmol 2005;140(4):607-11.

7.   Luce DA. Determining in vivo biomechanical properties of the cornea with an ocular

response analyzer. J Cataract Refract Surg 2005;31(1):156-62.

8.   Roberts CJ. Concepts and misconceptions in corneal biomechanics. J Cataract Refract Surg

2014;40(6):862-9.

9.   Mikielewicz M, Kotliar K, Barraquer RI, Michael R. Air-pulse corneal applanation signal

curve parameters for the characterisation of keratoconus. Br J Ophthalmol 2011;95(6):793-8.

10.   Hallahan KM, Sinha Roy A, Ambrosio R, Jr., et al. Discriminant value of custom ocular

response analyzer waveform derivatives in keratoconus. Ophthalmology 2014;121(2):459-68.

1   11.   Galletti JG, Pfortner T, Bonthoux FF. Improved keratoconus detection by ocular response

2   analyzer testing after consideration of corneal thickness as a confounding factor. J Refract Surg

3   2012;28(3):202-8.

4   12.   Touboul D, Benard A, Mahmoud AM, et al. Early biomechanical keratoconus pattern

5   measured with an ocular response analyzer: curve analysis. J Cataract Refract Surg

6   2011;37(12):2144-50.

7   13.   Ambrósio Jr R, Ramos I, Luz A, et al. Dynamic ultra high speed Scheimpflug imaging for

8   assessing corneal biomechanical properties. Revista Brasileira de Oftalmologia 2013;72:99-102.

9   14.   Villavicencio OF GF, Henriquez MA, Izquierdo L Jr, Ambrosio RR Jr, Belin MW.

10   Independent Population Validation of the Belin/Ambrosio Enhanced Ectasia Display: Implications

11   for Keratoconus Studies and Screening. Int J Kerat Ect Cor Dis 2014;3(1):1-8.

12   15.   Vinciguerra R, Elsheikh A, Roberts C, et al. Influence of Pachymetry and Intraocular

13   Pressure on Corneal Deformation Parameters Provided by Corvis ST: Normative Values and

14   Suspect Pathology. Submitted to JRS 2016.

15   16.   Andreassen TT, Simonsen AH, Oxlund H. Biomechanical properties of keratoconus and

16   normal corneas. Exp Eye Res 1980;31(4):435-41.

17   17.   Anderson K, El-Sheikh A, Newson T. Application of structural analysis to the mechanical

18   behaviour of the cornea. J R Soc Interface 2004;1(1):3-15.

19   18.   Roberts CJ. Biomechanics in Keratoconus. Textbook of Keratoconus: New Insights, 1 ed.

20   New Delhi: Jaypee Brothers Medical Publishers, 2012.

21   19.   Scarcelli G, Besner S, Pineda R, Yun SH. Biomechanical characterization of keratoconus

22   corneas ex vivo with Brillouin microscopy. Invest Ophthalmol Vis Sci 2014;55(7):4490-5.

23   20.   Ali NQ, Patel DV, McGhee CN. Biomechanical responses of healthy and keratoconic

24   corneas measured using a noncontact scheimpflug-based tonometer. Invest Ophthalmol Vis Sci

25   2014;55(6):3651-9.

1   21.   Steinberg J, Katz T, Lucke K, et al. Screening for Keratoconus With New Dynamic

2   Biomechanical In Vivo Scheimpflug Analyses. Cornea 2015;34(11):1404-12.

3   22.   Tian L, Huang YF, Wang LQ, et al. Corneal biomechanical assessment using corneal

4   visualization scheimpflug technology in keratoconic and normal eyes. J Ophthalmol

5   2014;2014:147516.

6   23.   Pena-Garcia P, Peris-Martinez C, Abbouda A, Ruiz-Moreno JM. Detection of subclinical

7   keratoconus through non-contact tonometry and the use of discriminant biomechanical functions. J

8   Biomech 2015.

9   24.   Luz A, Lopes B, Hallahan KM, et al. Discriminant Value of Custom Ocular Response

10   Analyzer Waveform Derivatives in Forme Fruste Keratoconus: Custom Biomechanical Variables in

11   Forme Fruste Keratoconus. Am J Ophthalmol 2015.

12   25.   Ruisenor Vazquez PR, Delrivo M, Bonthoux FF, et al. Combining ocular response analyzer

13   metrics for corneal biomechanical diagnosis. J Refract Surg 2013;29(9):596-602.

14   26.   Galletti JD, Ruisenor Vazquez PR, Fuentes Bonthoux F, et al. Multivariate Analysis of the

15   Ocular Response Analyzer's Corneal Deformation Response Curve for Early Keratoconus

16   Detection. J Ophthalmol 2015;2015:496382.

17   27.   Ventura BV, Machado AP, Ambrosio R, Jr., et al. Analysis of waveform-derived ORA

18   parameters in early forms of keratoconus and normal corneas. J Refract Surg 2013;29(9):637-43.

19   28.   Huseynova T, Waring GOt, Roberts C, et al. Corneal biomechanics as a function of

20   intraocular pressure and pachymetry by dynamic infrared signal and Scheimpflug imaging analysis

21   in normal eyes. Am J Ophthalmol 2014;157(4):885-93.

22   29.   Liu J, Roberts CJ. Influence of corneal biomechanical properties on intraocular pressure

23   measurement: quantitative analysis. J Cataract Refract Surg 2005;31(1):146-55.

24

25