Screening for Keratoconus and Related Ectatic Corneal Disorders

J. Bradley Randleman, MD[1,2], **William J. Dupps Jr., MD, PhD**[3,4,5,6], **Marcony R. Santhiago, MD, PhD**[7,8], **Yaron S. Rabinowitz, MD**[9,10,11,12], **Doug D. Koch, MD**[12], **R. Doyle Stulting, MD PhD**[13], and **Stephen D. Klyce, PhD**[14]

[1.]Department of Ophthalmology, Emory University, Atlanta, GA, USA

[2.]Emory Vision, Emory Eye Center, Atlanta, GA

[3.]Cleveland Clinic Cole Eye Institute, Cleveland, OH, USA.

[4.]Department of Biomedical Engineering, Lerner Research Institute, Cleveland Clinic, OH, USA.

[5.]Transplant Center, Surgery Institute, Cleveland Clinic, OH, USA.

[6.]Department of Biomedical Engineering, Case Western Reserve University, OH, USA

[7.]Department of Ophthalmology at University of Sao Paulo, Sao Paulo, Brazil

[8.]Department of Ophthalmology at Federal University of Rio de Janeiro, Sao Paulo, Brazil

[9.]Cornea Genetic Eye Institute, Beverly Hills, California;

[10.]Institute for Translational Genomics and Population Sciences, Los Angeles BioMedical Research Institute at Harbor-UCLA Medical Center, Torrance, California;

[11.]The Jules Stein Eye Institute, University of California-Los Angeles, Los Angeles, California

[12.]Cullen Eye Institute, Baylor College of Medicine, Houston, Texas.

[13.]Stulting Research Center at Woolfson Eye Institute, Atlanta, GA

[14.]Department of Ophthalmology, Mount Sinai School of Medicine, New York, NY, USA.

We read with great interest, but ultimately great concern, the recent article ambitiously titled "Global Consensus on Keratoconus and Ectatic Corneal Diseases."[1] Undoubtedly this process was a significant undertaking, and we commend the leadership of the representative Cornea Societies for their efforts.

We, however, have serious concerns about the "take-home" messages from the Definition/ Diagnosis Section, and believe these represent opinions that are unsupported by scientific data, potentially misleading, and not representative of the current standard of care with respect to keratoconus detection and refractive surgery screening.

Address for Corresponding Author: J Bradley Randleman, MD, Emory University Department of Ophthalmology, Emory Vision, 5671 Peachtree Dunwoody Rd NE, Suite 400, Atlanta, GA 30342, 404-778-2264, jrandle@emory.edu.

How is keratoconus (and related ectatic corneal disorders) best identified at its earliest stage? What constitutes the most accurate screening protocol? Many solid screening protocols exist already using Placido-based corneal topography to evaluate anterior surface changes.[2–7] Beyond these, additional screening metrics are being investigated, including epithelial thickness mapping,[8, 9] and posterior corneal surface and relative corneal thickness metrics as highlighted by the authors. Unfortunately, the consensus statements do not reflect the ongoing controversies and scientific pursuits to answer these fundamental questions.

Specifically, we take issue with the following statements, which are abstracted, word for word, from the paper's Table 2:

1. The following are mandatory to diagnose keratoconus:

   a. Abnormal Posterior Elevation

   b. Abnormal Corneal Thickness Distribution

2. The best current and widely available diagnostic test to diagnose early keratoconus is tomography (Scheimpflug or optical coherence tomography)

3. Posterior corneal elevation abnormalities must be present to diagnose early or subclinical keratoconus

These are bold statements that have both scientific and medico-legal consequences. The extensions of these concepts would clearly mean that Placido-based corneal topography, utilized by most practitioners today, is neither necessary nor sufficient to screen patients for ectatic corneal disorders in clinical practice or in refractive surgery screening protocols. To make such bold statements, one would anticipate significant support from the peer-reviewed literature. Yet, no citations are put forth as evidence. In the introduction, the authors state "*The advent of corneal topography, and more recently corneal tomography, has increased the ability of ophthalmologists to identify corneal ectasia at a much earlier stage than was previously possible.*" Yet, to support this, they cite only an opinion/review article.[10]

In order to validate a device to screen for early/subclinical keratoconus, one needs to follow patients over time to confirm that those identified by the device actually do develop keratoconus. There are multiple reports in the literature supporting 'early' topographic changes that go onto develop keratoconus over time both in the fellow eye of unilateral patients and in family members of patients with keratoconus,[3] and this work been duplicated by several investigators. We are to date unaware of any literature reporting the development of keratoconus after isolated posterior elevation or thickness changes.

In the Discussion we find the following statement: *The emergence of corneal/anterior segment tomography and the realization of the importance of the posterior cornea as an early indicator of ectatic change are reflected in the expert panel's opinion that both changes on the posterior corneal surface and alteration in the corneal thickness progression are necessary to diagnose keratoconus.*

Again, this statement was not accompanied by any reference. We were disappointed to see the lack of citations for these statements but are not surprised. In fact, we are not aware of a single peer-reviewed publication containing primary patient data submitted to rigorous peer-

review (rather than review or opinion pieces), demonstrating that posterior corneal surface changes and/or thickness profile alterations must be present to diagnose keratoconus at any stage, let alone the earliest stages. We challenge the panel to cite peer-reviewed evidence that supports their assertions.

In fact, in reviewing the limited citations available in this paper, one of the coordinators' own studies appear to refute their statements. In evaluating pachymetric parameters generated by Scheimpflug imaging (Pentacam, Oculus, Inc.), the authors compared two predefined populations: 44 eyes diagnosed with keratoconus and 113 eyes from normal subjects.[11] In this comparison, no metric had 100% sensitivity and specificity, meaning that no metric was able to identify all patients as either normal of as having keratoconus, even though by definition the populations had already been identified and defined.

Using PubMed to search the key words "keratoconus, ectasia and ectatic corneal disease": (keratoconus AND (ectasia OR ectatic corneal disease), 456 articles are found, excluding the work in question. Collectively, we have published approximately 50 articles that come up using these criteria; yet, only one was cited. Setting aside our collective body of work on this topic, several recent peer-reviewed articles cast doubt on the panel's suppositions regarding keratoconus detection using tomographic imaging, specifically posterior corneal and thickness metrics, alone. Bae and colleagues[12] evaluated a group of patients with highly asymmetric keratoconus and found that no posterior corneal or thickness metric was able to differentiate the populations. In their analysis, only anterior curvature metrics were significantly different between these populations. Reddy and colleagues[13] comparatively evaluated dual Scheimpflug imaging in normal eyes and eyes with early or manifest keratoconus and found anterior curvature metrics, rather than posterior corneal or thickness metrics, were the best at distinguishing between normal and early keratoconus. Other recent papers have reported similar issues.[14–16]

Given the large body of peer reviewed work that supports the importance of Placido-based topographic imaging for keratoconus detection and refractive surgical screening, the paucity of data that demonstrates the superiority of tomography in these same populations, and the remaining controversy surrounding the relative role of anterior corneal (topographic) and posterior corneal or thickness (tomography) metrics, we are at a loss to understand how the panel could have reached the conclusions they did.

The Panel Process

While none of us can speak to the specific process of this panel, we anticipate that the method in which experts were selected, the questions that were asked, and the manner in which the questions were presented played a pivotal role in the conclusions reached. The paper describes the methods of literature review and indicates that the coordinators were responsible for literature review and identification of appropriate journal articles to send to the panelists, design of methodology, development of questionnaires, decision-making process after each round. We are unable to ascertain what papers the coordinators deemed relevant for the panel to review, as none are explicitly cited.

We anticipate that, if a different set of questions and articles were presented to the panel initially and in subsequent rounds, markedly different results would have been obtained. Otherwise, we cannot explain how a group of corneal specialists from any location could completely ignore the importance and significance of Placido-based corneal topography in the identification of all ectatic corneal disorders, including keratoconus.

The Peer Review Process

This paper was received for publication January 8, 2015, a revision received January 25, 2015, and it was accepted for publication on January 26, 2015. As past and present Journal Editors, we know that full, rigorous peer review takes some time, and find it difficult to envision an entire review and revision process occurring in less than 18 days.

While every journal strives to shorten the time between article submission and publication, these data suggest an unusual situation in the normal peer-review process, with special handling of this paper. We therefore conclude it does not qualify as original research, and should be treated--as evident from the text--as an opinion article.

Financial Bias and the Spirit of Full Disclosure

The paper's author statement says that no authors had any financial relationships to disclose. While this might be true in the narrowest interpretation of this report, within the context of full disclosure that all journals strive for today we find it difficult to rectify that statement with the known, ongoing financial relationships some of the section coordinator authors have with tomographic screening technologies and indeed their leading role in developing these technologies. This has particular relevance since these coordinators were explicitly responsible for study development

Conclusions

The findings from this paper then, far short of a "global consensus," should be interpreted as opinions, nothing more. The literature does not support these opinions, taken to their logical conclusion, as fact.

To be clear, we are not arguing against the use of tomography for patient screening and evaluation of corneal ectatic disorders. We collectively agree that tomography provides unique information about 3-dimensional shape in the corneal evaluation process, and many of us utilize this technology regularly in our clinical practices and research endeavors.

We, however, wholeheartedly disagree with the opinion set forth in this paper that Placido-imaging and other non-tomography methods are insufficient for diagnosing keratoconus, or that tomography is clearly superior and absolutely necessary for this important task. There is simply no evidence to justify that statement, and much evidence to refute it, including a century and a half of keratoconus diagnoses that would be impossible if the conclusions of the Delphi panel were accepted as true. Ultimately, we believe the question of whether tomography is absolutely necessary for diagnosis of keratoconus is ill posed, of little practical value, and ultimately unanswerable because of the unattainable level of evidence

required. Tomography is extremely valuable for better understanding the disease we call keratoconus and for identifying features of the disease in screening subjects. But it is not mandatory for patient screening using any reasonable criteria for what constitutes mandatory, and it should not be promoted as such.

Therefore, we advocate for a tempered approach to these topics, based on rigorous scientific analysis, and we advocate for the continued use of topographic data in the patient evaluation process. Finally, we advocate for the continued pursuit of knowledge in this area through well-constructed scientific studies and analyses.

Acknowledgments

References

1. Gomes JA, Tan D, Rapuano CJ et al. Global consensus on keratoconus and ectatic diseases. Cornea 2015;34:359–69. [PubMed: 25738235]

2. Binder PS, Lindstrom RL, Stulting RD et al. Keratoconus and corneal ectasia after LASIK. J Refract Surg 2005;21:749–52. [PubMed: 16329368]

3. Li X, Rabinowitz YS, Rasheed K, Yang H. Longitudinal study of the normal eyes in unilateral keratoconus patients. Ophthalmology 2004;111:440–6. [PubMed: 15019316]

4. Li X, Yang H, Rabinowitz YS. Longitudinal study of keratoconus progression. Exp Eye Res 2007;85:502–7. [PubMed: 17681291]

5. Li X, Yang H, Rabinowitz YS. Keratoconus: classification scheme based on videokeratography and clinical signs. J Cataract Refract Surg 2009;35:1597–603. [PubMed: 19683159]

6. Rabinowitz YS, Rasheed K. KISA% index: a quantitative videokeratography algorithm embodying minimal topographic criteria for diagnosing keratoconus. J Cataract Refract Surg 1999;25:1327–35. [PubMed: 10511930]

7. Klyce SD, Karon MD, Smolek MK. Screening patients with the corneal navigator. J Refract Surg 2005;21:S617–22. [PubMed: 16212291]

8. Li Y, Tan O, Brass R, Weiss JL, Huang D. Corneal epithelial thickness mapping by Fourier-domain optical coherence tomography in normal and keratoconic eyes. Ophthalmology 2012;119:2425–33. [PubMed: 22917888]

9. Reinstein DZ, Archer TJ, Gobbe M. Corneal epithelial thickness profile in the diagnosis of keratoconus. J Refract Surg 2009;25:604–10. [PubMed: 19662917]

10. Belin MW, Villavicencio OF, Ambrosio RR, Jr. Tomographic parameters for the detection of keratoconus: suggestions for screening and treatment parameters. Eye Contact Lens 2014;40:326–30. [PubMed: 25320954]

11. Ambrosio R, Jr., Caiado AL, Guerra FP et al. Novel pachymetric parameters based on corneal tomography for diagnosing keratoconus. J Refract Surg 2011;27:753–8. [PubMed: 21800785]

12. Bae GH, Kim JR, Kim CH, Lim DH, Chung ES, Chung TY. Corneal topographic and tomographic analysis of fellow eyes in unilateral keratoconus patients using Pentacam. Am J Ophthalmol 2014;157:103–9 e1. [PubMed: 24452012]

13. Reddy JC, Rapuano CJ, Cater JR, Suri K, Nagra PK, Hammersmith KM. Comparative evaluation of dual Scheimpflug imaging parameters in keratoconus, early keratoconus, and normal eyes. J Cataract Refract Surg 2014;40:582–92. [PubMed: 24680519]

14. de Sanctis U, Loiacono C, Richiardi L, Turco D, Mutani B, Grignolo FM. Sensitivity and specificity of posterior corneal elevation measured by Pentacam in discriminating keratoconus/ subclinical keratoconus. Ophthalmology 2008;115:1534–9. [PubMed: 18405974]

15. Muftuoglu O, Ayar O, Ozulken K, Ozyol E, Akinci A. Posterior corneal elevation and back difference corneal elevation in diagnosing forme fruste keratoconus in the fellow eyes of unilateral keratoconus patients. J Cataract Refract Surg 2013;39:1348–57. [PubMed: 23820305]

16. Ruisenor Vazquez PR, Galletti JD, Minguez N et al. Pentacam Scheimpflug tomography findings in topographically normal patients and subclinical keratoconus cases. Am J Ophthalmol 2014;158:32–40 e2. [PubMed: 24709808]