

**SECOND
EDITION**

CORNEAL CROSS-LINKING

EDITORS | Farhad Hafezi | J. Bradley Randleman

ASSOCIATE EDITOR | Sumitra S. Khandelwal

SLACK Incorporated

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DEDICATION

This book is dedicated to my beloved wife, Nikki; Team Hafezi (Leilah Alina, Lilian Malaya, and Lola Alexandra); and my parents, Alina and Abolfazl. Your love and support mean everything to me.

Farhad Hafezi, MD, PhD

This second edition is dedicated to the same people who supported me through the first edition: my darling Claudia, who has blessed me with her love and support throughout the years; my wonderful children, Taylor, Casey, and Mia, who have grown into the beautiful young women they are today; and my mother, Patricia, who left in body before the first edition, but remains with me in spirit always.

J. Bradley Randleman, MD

ABOUT THE EDITORS

Farhad Hafezi, MD, PhD, was born in 1967 and grew up in Fribourg, Switzerland. He studied medicine in Fribourg and Berne. Farhad Hafezi fluently speaks German (mother tongue), English, French, Polish, and Farsi. He is married to Nikki Hafezi and has three daughters, Leilah Alina (2008), Lilian Malaya (2010), and Lola Alexandra (2016).

Professor Hafezi's clinical focus are the cornea and complication management after complicated refractive laser surgery. Being part of the team around Theo Seiler that translated cross-linking from experimental research into the clinical application, he was instrumental in implementing corneal cross-linking technology in ophthalmology.

From 2010 to 2014, Farhad Hafezi was Professor and Chairman of the Department of Ophthalmology of the Geneva University Hospitals, Geneva, Switzerland. Currently, Dr. Hafezi holds the following positions: Professor at the Faculty of Medicine, University of Geneva, Switzerland; Clinical Professor of Ophthalmology, Department of Ophthalmology USC Los Angeles, USA; Medical Director, The ELZA Institute, Zürich, Switzerland; Research Group Leader, Center for Applied Biotechnology and Molecular Medicine (CABMM), University of Zürich, Switzerland; and Visiting Professor, Faculty of Medicine, University of Wenzhou, China.

As of March 2017, Professor Hafezi has published more than 160 scientific articles, his scientific work has been cited more than 5700 times, his total impact factor is 510, and his h-index is 39.

He is an Associate Editor for the *Journal of Refractive Surgery* and is on the Editorial Boards of *TVST*, the *International Journal of Keratoconus and Ectatic Corneal Disease*, *Eye and Vision* and the *Iranian Journal of Ophthalmology*. Professor Hafezi is also a member of the Advisory Board of "Global ONE," the educational network of the American Academy of Ophthalmology (AAO).

Professor Hafezi has received 22 national and international awards and distinctions, both for his scientific work and for the development of new technologies (innovation awards). Awards include, among others, the ARVO Foundation/Carl Camras Translational Research Award (USA) 2014, as well as the highest distinctions in ophthalmology from Switzerland and Belgium.

In 2014, Professor Hafezi was voted by peers onto the "PowerList," a list of the 100 most influential international personalities in ophthalmology. In April 2016, he was again voted onto the PowerList.

For more information, please visit: https://en.wikipedia.org/wiki/Farhad_Hafezi or <http://www.elza-institute.com>

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Dr. Randleman has been awarded the Claus Dohlman Fellow Award, the inaugural Binkhorst Young Ophthalmologist Award from the American Society of Cataract and Refractive Surgery, the Kritzing Memorial Award, the Inaugural ISRS Recognition Award, the Secretariat Award, Achievement Award, and Senior Achievement Award from the American Academy of Ophthalmology.

Dr. Randleman has served as Editor-in-Chief for the *Journal of Refractive Surgery* since 2011. He has authored more than 120 peer-reviewed publications in leading ophthalmology journals in addition to 30 book chapters on refractive surgery evaluation, corneal cross-linking, and management of complications with IOLs, and has authored two additional textbooks, *Refractive Surgery: An Interactive Case-Based Approach* (2014), and *Intraocular Lens Surgery: Selection, Complications, and Complex Cases*.

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Dr. Khandelwal's clinical research interests include keratoconus, ocular surface diseases, and optimizing outcomes in cataract surgery. She has published numerous book chapters and peer-reviewed articles, and her extensive research has been presented nationally and internationally.

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FOREWORD

Since the publication of the first edition of this book in 2013, our knowledge of corneal cross-linking (CXL) has again significantly increased, both scientifically and clinically. The sheer number of publications, reviews, and meta-analyses on the technique demonstrate this growth and its versatility. As many experts recognize but often criticize CXL, the technique was adopted and adapted from other medical disciplines (eg, dentistry) and translated into clinical practice relatively rapidly based on empirical knowledge and without a lot of basic knowledge supporting the principles of cross-linking.

For example, CXL inspired basic researchers to explore the biochemical and morphological relationships by investigating new highly sensitive methods of ultrastructural analysis. During this time period, the discovery that oxygen significantly influenced the CXL effect marked a milestone. As a result, the strong reduction of treatment time, which was once considered a significant progress, is now considered disadvantageous. Now, the possibilities and also limitations of this method become more evident. The clinical practice also showed that some applications, such as CXL for bullous keratopathy, did not meet the high expectations regarding the long-term effect.

Iontophoresis still serves as a promising method for riboflavin application because it may eliminate the biggest risk of CXL, corneal infection by penetrating through the epithelium. However, the first clinical results on this method showed rather disappointing results. This book attempts to demonstrate what was learned from these trials and possibly how to overcome these obstacles (ie, by respecting the need for sufficient oxygen diffusion).

From a clinical perspective, the criteria for progression of keratoconus were also precisely formulated during this time period. Today, concise recommendations (guidelines for cross-linking) help the clinician to select patients, make decisions, and provide optimal treatment.

Based on this new knowledge and respecting the criteria for safety, CXL has become a routine method accepted in ophthalmology in most countries. However, there are plenty of other unexplored areas of research, including (but not limited to) scleral cross-linking, other cross-linking methods, and cross-linking for the stabilization of artificial collagen implants and corneas. One particular area that has already created a major impact, interest, and research momentum is CXL for the treatment of corneal infections (also referred to as PACK-CXL). This area is quite promising because it addresses a major medical need in both developed and developing countries.

In such a still-developing field, an actualization of the knowledge and experiences is necessary. Therefore, on behalf of the editors and authors of this second completely revised and updated edition of *Corneal Cross-Linking*, we hope that you will continue your interest and dedication in this promising treatment modality.

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INTRODUCTION

When we published the first edition of this book in 2013, we knew that this field was dynamic and quickly moving. However, who knew that things would move so quickly as to require a second edition (and new title) so soon!

The first change that readers will notice is the shift in title for the second edition (*Corneal Cross-Linking*). In 2012, Zhang and colleagues proved that the actual cross-links are not formed between and within the collagen fibers, but rather between the amino terminals of the collagen side chains and the proteoglycans of the extracellular matrix. This is a fundamental difference. Therefore, the term collagen cross-linking is misleading and should be avoided. More and more scientific articles have adopted this position over time, and we felt compelled to change the title of our book to reflect that fundamental change in our understanding of the cross-linking process.

Many other changes are immediately noticeable. Sections on imaging have expanded as our understanding of these fields related to corneal cross-linking (CXL) has grown. The use of cross-linking protocols for infectious keratitis was an important chapter in the first edition; photoactivated chromophore for infectious keratitis CXL is now a significant section in the current edition. And many topics included in the first edition as “future hot topics” are now chapters unto themselves.

Among the biggest changes since the first edition is the US Food and Drug Administration (FDA) approval of CXL in the United States for the treatment of both keratoconus and ectasia after LASIK surgery. This has opened the door to finally treating US patients using the same protocols that have been available for almost 20 years throughout the rest of the world. This has also opened the floodgates for combination therapies, as everything that has developed over time in other areas, such as combining CXL with topography-guided excimer laser ablations, with phakic intraocular lenses, or with intracorneal ring segments, is now available all at once in the US market. Further, various protocols are available throughout the world, including accelerated and transepithelial protocols, that are not currently FDA approved. Some of these techniques, however, have been in practice in the United States even without FDA approval. Time will tell what processes and procedures remain viable here and abroad.

Finally, in this edition you will see the addition of another colleague, Sumitra S. Khandelwal, as Associate Editor. Sumitra has worked tirelessly on this project and has been instrumental in bringing this second edition to fruition.

We hope that you will enjoy reading this book as much as we enjoyed putting it together.

Farhad Hafezi, MD, PhD
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