Corneal cross-linking (CXL) combined with refractive surgery for the comprehensive management of keratoconus: CXL plus

Vardhaman P Kankariya1, Ankita B Dube, Michael A Grentzelos1,2, George A Kontadakis3, Vasilios F Diakonis4, Myrsini Petrelli, George D Kymionis2

Keratoconus in the past was considered a hindrance to complete visual rehabilitation and surgeons around the world resorted to spectacles, contact lenses and corneal transplantation which were the only options available until recently.[11] Being a non-inflammatory corneal ectatic condition, it is characterized by progressive thinning of corneal stroma and central or paracentral corneal steepening leading to induced regular or irregular astigmatism and decrease in visual acuity.[2,3] The past two decades have witnessed an unprecedented evolution in the management of this disease with the help of advanced diagnostic techniques and newer treatment protocols.[10] The concept of corneal cross-linking (CXL) as a minimally invasive procedure to stabilize corneal ectatic disorders was introduced in the late 1990s.[5] Wollensak et al. in 2003 reported CXL as a potential treatment for halting the progression of keratectasia and alleviating the need for corneal transplantation in keratoconus.[3] CXL constitutes the use of riboflavin and ultraviolet-A (UVA) light to increase the biomechanical corneal stability and halt ectatic progression in keratoconus.[4-11] Numerous studies have reported long-term stabilization of the ectatic cornea, reduction in corneal steepening and regularization of corneal curvature with the use of CXL in keratoconus.[3-11]

Concept of CXL plus

Management of keratoconus demands a holistic approach that comprises of inhibiting the ectatic progression along with visual rehabilitation. Thus, several concerns which need to be sequentially addressed in keratoconus to ensure visual recovery include halting the keratectasia, reducing or rectifying irregular astigmatism and correcting the residual refractive error. CXL as a standalone procedure without subsequent use of contact lenses does not suffice in overcoming the optical inefficiency due to corneal irregularity and achieving a satisfactory visual outcome. Adjunctive use of refractive procedures with CXL was proposed so as to regularize and reshape the cornea and improve functional vision in keratoconic patients.[12,13] The term “CXL plus” coined by Kymionis in 2011 incorporates such adjuvant therapies to CXL which offer both stability and functional vision in keratoconus.[12,14] Various refractive procedures targeting the corneal curvature, corneal irregularity, irregular astigmatism and residual refractive error have been combined with CXL to optimize and enhance the CXL outcome in keratoconus. Combinations of CXL with conductive keratoplasty (CK), photorefractive keratectomy (PRK),

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transtibial phototherapeutic keratectomy (t-PTK), intrastromal corneal ring segments (ICRS) implantation, phakic intraocular lens (PIOL) implantation and multiple other techniques have been studied and suggested. This review aimed to summarize the different protocols of CXL plus, provide guidelines for selection of the optimum CXL plus technique and discuss the future and scope for innovations in keratoconus management. This study attempts to elucidate the rationale and indication for each of the recommended CXL plus techniques and intends to aid in decision-making for the comprehensive management of cases with primary keratoconus while excluding eyes with post-surgical ectasia and other corneal ectatic diseases.

Conductive keratoplasty (CK) with CXL

Conductive keratoplasty (CK) has been described for the treatment of irregular corneas in keratoconus.[15] This non-invasive technique involves no corneal incision.[16,17] It works on the principle of corneal remodeling through heating of collagen fibrils at a specified temperature with radio frequency current (350 kHz) applied to selective spots in the peripheral corneal stroma at a depth of 500 µm in order to achieve the intended correction.[18,19] Kato et al. reported regression of visual acuity and corneal topography to the preoperative state following CK in advanced keratoconus.[19] Kymionis et al. reported the combined effect of CK and CXL procedures in two patients with advanced keratoconus.[19] Conductive keratoplasty was applied on topographically more flattened areas of the corneal periphery to steepen them and decrease the irregular astigmatism.[19] The number of the spots applied in each case depended upon the severity of irregularity and the topography.[19] The CXL procedure was performed 24 hours later in the first patient and immediately after CK in the second patient aiming to stabilize the corneal remodeling effect of CK.[19] Nevertheless, corneal remodeling was found to be temporary despite post-CK application of CXL and regression was noticed 3 months postoperatively.[19] This study concluded that although combining CXL with CK offered theoretical advantage, no added benefit of this combination was observed over CXL alone due to potential regression.[19]

Photorefractive keratectomy (PRK) with CXL

The very first attempt to seek the benefits of CXL plus by conjunction of excimer laser technology with CXL was accomplished by combining topography guided (topo-guided) photorefractive keratectomy (PRK) and CXL [Table 1]. Initially, a two-step sequential approach was presented by Kanellopoulos and Binder.[20] The authors reported a case of keratoconus who was treated with CXL (3 mW/cm², 5.4 J/cm², 30 min) and after one year of corneal stability underwent sequential topo-guided PRK resulting in significant clinical improvement.[20]

Despite the promising results of this case report, there were several limitations with this two-step approach. The ablation rate might be different in a cross-linked than in a non-operated, virgin cornea leading to unpredictable refractive results and possible limited effectiveness of PRK. The risk of post-PRK haze formation is higher as the anterior stroma is repopulated by new keratocytes six months after CXL. Lastly and probably the most significant limitation of this approach is that the second-step PRK removes part of the cross-linked corneal tissue thereby potentially decreasing the stiffening effect of CXL.

On account of these limitations, it was anticipated that simultaneous topo-guided PRK followed immediately by CXL so as to strengthen the cornea at a targeted and uniform depth may be a better approach to optimize the benefits of this combined treatment. This technique was performed for the first time by Kymionis et al. on a contact lens intolerant patient with pellucid marginal corneal degeneration (PMD).[21] Kymionis et al. subsequently applied the simultaneous topo-guided PRK-CXL (3 mW/cm², 5.4 J/cm², 30 min) approach on patients with progressive keratoconus and reported significant improvement in all evaluated parameters including spherical equivalent (SE), defocus, uncorrected and corrected distance visual acuity (UDVA and CDVA) and keratometric values.[22] The PRK treatment was modified (e.g., attempted correction, optical zone, percentage of topographic customization) based on the preoperative corneal thickness (CT), corneal high order aberrations (HOAs) and manifest refraction to limit the maximum ablation depth at 50 µm; expected thinnest pachymetry after PRK was aimed at more than 400 µm.[22]

The simultaneous technique seemed to overcome the drawbacks of the initial two-step CXL-PRK procedure due to its main advantage that laser ablation does not interfere with already cross-linked corneal tissue. This consideration was also confirmed with the comparative clinical study by Kanellopoulos which showed that same-day simultaneous topo-guided PRK-CXL (3 mW/cm², 5.4 J/cm², 30 min) is more effective than sequential CXL with delayed (six months or more) PRK.[23] Kanellopoulos recommended 70% treatment of cylinder and up to 70% treatment of sphere so as not to exceed an ablation depth of 50 µm and achieve an expected CT of no less than 350 µm after PRK.[23] The simultaneous approach was reported to be superior on account of three factors; patients’ comfort, minimization of the potential stromal scarring and preservation of cross-linked corneal stromal tissue.[23] In another case series, Krueger and Kanellopoulos presented two cases of keratoconus who underwent simultaneous topo-guided transepithelial PRK followed by CXL (3 mW/cm², 5.4 J/cm², 30 min) and showed stability and progressive improvement over a long observation period of at least 30 months; the technique was named “Athens protocol” by the authors.[24]

Several other studies confirmed the safety and efficacy of the simultaneous topo-guided PRK-CXL technique in keratoconic patients. Stojanovic et al. performed topo-guided custom surface ablation followed by CXL (3 mW/cm², 5.4 J/cm², 30 min) using transepithelial approach so as to avoid potential custom ablation planning error due to epithelial remodeling observed after traditional manual epithelial debridement.[25] This study recommended the maximum ablation depth of 60 µm with minimum postoperative CT of 400 µm and reported stability over a period of 12 months.[25] Kymionis et al. presented the long-term results of simultaneous topo-guided PRK after epithelial removal with transepithelial phototherapeutic keratectomy (t-PTK) followed by CXL (3 mW/cm², 5.4 J/cm², 30 min) and showed significant topographic and clinical improvement that remained stable throughout the follow-up period.[26] Tuwairqi and Sinjab reported significant visual, refractive and topographic improvement after simultaneous topo-guided PRK-CXL (3 mW/cm², 5.4 J/cm², 30 min) in patients with low grade keratoconus.[27] The ablation depth was targeted to achieve ±1.00 diopter of emmetropia and to preserve 400 µm of stroma before proceeding with CXL, taking into account the normal thickness of corneal epithelium as 50 µm.[27]
| Author                        | Study design                  | Surgical Procedure                                   | Follow-up            | Outcomes                                                                 |
|------------------------------|-------------------------------|------------------------------------------------------|----------------------|--------------------------------------------------------------------------|
| Kanellopoulos and Binder     | Case report                   | CXL followed by topo-guided PRK 12 months later (1)  | 18 months           | Significant clinical improvement and stability; no complications observed |
| Kymionis et al.              | Pilot study (Prospective)     | Simultaneous topo-guided PRK followed by CXL (14)    | 10.69±5.95 months   | Significant improvement in UDVA, CDVA, SE, defocus and keratometry readings; no complications observed |
| Kanellopoulos                | Retrospective, comparative study | Sequential CXL with delayed PRK and simultaneous topo-guided PRK followed by CXL (127 and 198, respectively) | 36±18 months (range: 24 to 68 months) | Simultaneous group performed better in all parameters (UDVA, CDVA, keratometry, SE, corneal haze); significant haze noted in 19 eyes (17 of sequential and 2 of simultaneous group) |
| Krueger and Kanellopoulos    | Case series                   | Simultaneous topo-guided PRK and CXL (2)             | 36 and 30 months    | Reduction of spherocylindrical refraction and improvement in functional vision; no complications observed |
| Stojanovic et al.            | Case series                   | Topography-guided transepithelial custom ablation followed by CXL (7) | 12 months           | Visual, refractive, and topographic improvement; no complications observed |
| Kymionis et al.              | Prospective case series       | Simultaneous topo-guided PRK followed by CXL (31)    | 19.53±3.97 months, (range: 12 to 25 months) | Significant improvement in UDVA, CDVA, SE and keratometry; no progression of keratoconus; 16 of 31 eyes showed posterior linear stromal haze |
| Tuwairqi and Sinjab          | Prospective, non-randomized, non-controlled study | Simultaneous topography-guided PRK and CXL (22)    | 12 months           | Significant improvement in all study parameters (UDVA, CDVA, sphere, SE, manifest and topographic astigmatism, keratometry); no complications observed |
| Alessio et al.               | Prospective, non-randomized clinical trial | Simultaneous transepithelial topo-guided PRK and CXL versus CXL only (17 in each group) | 24 months           | PRK-CXL provided better UDVA/CDVA and lower SE, spherical/cylindrical power and keratometric values than CXL; no complications observed |
| Kontadakis et al.            | Prospective, comparative case series | Simultaneous topo-guided PRK and CXL versus CXL only (60) | 39±11 months        | Significant improvement in UDVA, CDVA, keratometry, SE and defocus equivalent with significant corneal flattening in PRK-CXL group; no complications observed |
| Iqbal et al.                 | Prospective, multicentre, comparative, clinical | Standard CXL (group A) versus non-topo-guided PRK and accelerated CXL (group B) (58/67) | 24 months           | Group B showed significant and early reduction in myopia and astigmatism, Group A showed similar effect on corneal flattening, sphere reduction and equivalent visual outcome at 24 months postoperatively; delayed epithelial healing in 9 eyes and corneal haze in 11 eyes resolved completely; one eye in group B developed stromal scarring |
| Kanellopoulos                | Prospective                   | Simultaneous topo-Guided Partial-Refraction PRK and CXL (144) | 128±4 months (range: 120 to 146 months) | Significant and stable improvement in UDVA, CDVA and keratometry |
| Kanellopoulos and Asimellis  | Case series                   | Simultaneous topo-guided PRK and high-fluence CXL (231) | 36 months           | Visual (UDVA and CDVA) and topographic improvement; no complications observed |
| Kaiserman et al.             | Retrospective, case series    | Epithelial PRK and accelerated CXL (20)             | 822.5±336.7 days (range: 266 to 1,749 days) | Significant improvement in UDVA, CDVA and keratometry; no complications observed |
| Shetty et al.                | Prospective, case series      | Combined same-day topography-guided custom ablation treatment (T-CAT) followed by accelerated CXL (2) | 6 months            | Improvement in UDVA, CDVA and keratometry |

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Significant improvement in visual acuity noticed at the first postoperative year was reported in a ten-year follow-up study. The authors concluded that cone location affected only visual acuity and biomechanics and reported better improvement in CDVA in group 1 than in group 2.\[38\]

Several studies have evaluated the efficacy of PRK (after mechanical epithelial removal) using a non-topo-guided approach combined with CXL and have reported significant visual improvement in patients with early stage keratoconus.\[36,37\] It is also worth noting that the combination of sequential or simultaneous wavefront-guided PRK and CXL has also been studied.\[36-41\]

Two studies evaluated the outcomes of PRK with CXL performed in keratoconic patients as a primary refractive treatment rather than the recommended therapeutic approach, using a high stromal ablation depth determined on the basis of targeted emmetropia and reported a high incidence of complications such as corneal haze and stromal scarring.\[41-43\]

It is palpably clear from the aforementioned studies that several recommendations in the planning of the PRK-CXL technique have been reported regarding the maximal ablation depth and the estimated postoperative CT. However, another issue that still remains a debate is the use of mitomycin C (MMC) after PRK and prior to CXL. In several studies, MMC has not been used (or its use is not mentioned) during PRK-CXL.\[24,27,29,30,34-36\] Kymionis et al. have described a
desolation effect of CXL on the kerocyte population in the anterior stroma with in vivo confocal microscopy. This effect which reduces, at least theoretically, the possibility of haze formation is considered the main reason for avoiding the use of MMC. On the contrary, other studies have described this combined technique with the use of MMC.

Rationale and Indication: Based on the published data, the topo-guided PRK-CXL treatment aims to stabilize the disease progression as well as normalize the corneal surface in keratoconic eyes by reducing the irregular astigmatism and potentially reducing the refractive error. This customized approach; thus, attempts to reverse the impact of corneal irregularity on visual performance of the patient. The combined topo-guided PRK-CXL treatment can be performed in keratoconic patients who have sufficient CT that allows stromal ablation at a depth within the recommended maximum limit of 50 µm. The ablation performed is used for therapeutic correction of corneal topographic irregularities and is not targeted for refractive correction; however, partial correction of refractive error can be attempted based on preoperative CT.

Transepithelial phototherapeutic kerectomy (t-PTK) with CXL (Cretan protocol)

According to the conventional CXL protocol, removal of corneal epithelium is an essential step which is traditionally performed by mechanical debridement. However, corneal epithelium during CXL can also be removed by alternative techniques such as transepithelial phototherapeutic kerectomy (t-PTK) [Table 2]. In 2010, Kymionis et al. were the first to describe the combination of t-PTK and CXL (3 mW/cm², 5.4 J/cm², 30 min) in a keratoconic patient resulting in significant visual and topographic improvement. The aim of t-PTK was not only to remove the corneal epithelium for the following cross-linking process, but also to regularize the anterior irregular cornea. This combined technique of t-PTK-CXL has been called “Cretan protocol”. This protocol constitutes epithelial removal by t-PTK ablation at an intended depth of 50 µm in a 6.5-7.0 mm zone; the de-epithelialized area is then enlarged by mechanical debridement till the targeted diameter of 8.0-9.0 mm followed by CXL.

After the first report, Kymionis et al. compared the two techniques for epithelial removal during CXL (3 mW/cm², 5.4 J/cm², 30 min) between two well-matched groups and showed that t-PTK-CXL resulted in better visual and refractive outcomes than conventional CXL. The improvement in UDVA, CDVA, steep keratometry and corneal astigmatism was reported to be significant in the t-PTK-CXL group at twelve months postoperatively. In a following study, the initial encouraging outcomes of this protocol were confirmed in the long-term and significant improvement was reported at all postoperative intervals.

Several other studies followed and evaluated the combination of t-PTK and CXL. Kapasi et al. in a short-term comparative study showed early results corresponding to the previous studies. Subsequently, another study by the same authors indicated better visual outcome 12 months after treatment with t-PTK-CXL (3 mW/cm², 5.4 J/cm², 30 min) technique. MMC was used following t-PTK ablation in both of these studies.

Gaster et al. on the contrary reported equivalent outcomes up to 24 months with both t-PTK and mechanical debridement during CXL (3 mW/cm², 5.4 J/cm², 30 min). Despite the comparable outcomes, the improvement in CDVA in t-PTK-CXL group was reported to be significant at the last follow-up. Recently, Grentzelos et al. in a prospective comparative long-term study confirmed the outcomes of previously published reports and concluded that t-PTK-CXL (3 mW/cm², 5.4 J/cm², 30 min) is advantageous over mechanical epithelial removal during CXL.

The effectiveness of the Cretan protocol encompassing the combination of t-PTK and accelerated CXL treatment instead of conventional CXL has also been evaluated. Chen et al. confirmed the efficacy of the t-PTK-CXL technique using high intensity CXL (18 or 15 mW/cm², 5.4 J/cm², 5 or 6 min). Moreover, they evaluated the epithelial thickness profile and showed a more uniform regional epithelial thickness distribution after the combined treatment. Shetty et al. reported three cases of keratoconus management using topography-based removal of corneal epithelium (TREK) combined with accelerated CXL (9 mW/cm², 5.4 J/cm², 10 min) and showed promising results. Sarac et al. compared the outcomes of mechanical or t-PTK epithelial removal followed by accelerated CXL (9 mW/cm², 5.4 J/cm², 10 min) in pediatric keratoconus and reported significant visual and topographic improvement at 12 months in the t-PTK group only followed by comparable results between the two groups at 24 and 36 months postoperatively. The overall decrease in HOA RMS and spherical aberration was reported to be significant in the t-PTK group only indicating better visual quality.

Cretan protocol could also be extended and combined with conventional PRK in cases with adequate corneal thickness. Thus, in a procedure called Cretan protocol plus, t-PTK was performed as described previously in the Cretan protocol, whereas conventional PRK was limited to a maximum ablation depth of 50 µm in a maximum zone of 5.5 mm which was immediately followed by CXL. No eye was estimated to have a corneal thickness less than 350 µm after combined t-PTK-PRK. The authors concluded that Cretan protocol plus is a promising alternative surgical approach in keratoconic patients with adequate corneal thickness.

Rationale and Indication: As it has been thoroughly described in the published studies, t-PTK during CXL actually acts as a treatment customized for irregular corneas in keratoconus. Reinstein et al. has shown an epithelial doughnut pattern in keratoconic corneas characterized by localized central thinning surrounded by an annulus of thickened epithelium. Due to the epithelial doughnut pattern, t-PTK in Cretan protocol uses patient’s own epithelium as a masking agent and facilitates removal of small quantity of anterior stromal tissue on the cone apex along with the epithelium. Therefore, t-PTK during CXL additionally targets to smoothen the irregular anterior corneal stroma, decrease the corneal astigmatism and enhance the postoperative outcome. It is also worthwhile to note that Cretan protocol can be performed in any case of CXL, even in those in which combined PRK-CXL procedure could not be an option due to low CT.

Intrastromal Corneal Ring Segments (ICRS) with CXL

Intrastromal corneal ring segments (ICRS) implantation either manual or femtosecond laser assisted, aims for flattening and regularization of central cornea and therefore acts as a potential treatment option for keratoconus. In general, ICRS induce more flattening of the corneal curvature as their thickness increases.
The combination of significant improvement in CDVA in Surgical Procedure (Number of [61,67-74] t‑PTK with topography based ablation UDVA, total RMS and keratometry Visual and topographic improvement; no complications observed Equivalent visual, refractive and keratometric outcomes between the two techniques Significant improvement in CDVA and keratometric values and decrease in corneal HOAs; three eyes lost ≥2 lines of CDVA Significant improvement in CDVA in 2/3 eyes, topography-based t‑PTK technique ablated less stroma and achieved comparable outcomes UDVA, total RMS and keratometry improved significantly in both groups, however, improvement in CDVA, SE, HOA RMS and spherical aberration was significant in only group 2; corneal haze ratio was similar; no complications observed Significant improvement in UDVA, CDVA, keratometric values and corneal astigmatism; no complications observed

and placement gets more proximal to the visual axis.\textsuperscript{[60,61]} Due to the asymmetric cornea commonly present in keratoconus, a combination of thick (placed at the steep areas, usually inferiorly) and thin (placed at the flat areas, usually superiorly) segments may be implanted in order to gain significant corneal surface regularization.\textsuperscript{[62]} On the contrary, equal thickness segments are suggested for managing central cones.\textsuperscript{[30]}

Even though, ICRS may improve corneal irregularity and provide patients with improved visual performance they do not consist of a ‘true’ treatment for keratoconus, as they do not interfere with the pathophysiology of the condition.\textsuperscript{[15]} Hence, combining CXL with ICRS implantation may lead to keratoconic corneal stiffening and inhibition of ectatic progression in addition to improvement of the irregular cornea.\textsuperscript{[13,59-63]}

Several studies have reported the use of ICRS adjuvant to CXL in keratoconic patients [Table 3]. The combination of ICRS implantation and CXL was shown to result in comparable or better refractive and topographic outcomes than ICRS insertion alone.\textsuperscript{[64-66]} The safety and efficacy of CXL and single or paired ICRS used adjunctively was assessed by many studies and significant improvement was reported in UDVA, CDVA, and manifest refraction along with significant reduction in cylinder and keratometry.\textsuperscript{[61,67-74]} A recently published clinical trial reported improvement in anterior corneal HOAs after ICRS implantation and concurrent or sequential CXL.\textsuperscript{[75]} However, no correlation was established between the improvement in HOAs and subjective or objective visual performance.\textsuperscript{[75]}

### Table 2: Summary of Outcomes with Combined t‑PTK and CXL

| Author             | Study design                        | Surgical Procedure (Number of eyes) | Follow-up  | Outcomes                                                                 |
|--------------------|-------------------------------------|-------------------------------------|------------|--------------------------------------------------------------------------|
| Kymionis et al.\textsuperscript{[47]} | Case report                        | t‑PTK followed by CXL (1)            | 6 months   | Visual and topographic improvement; no complications observed           |
| Kymionis et al.\textsuperscript{[47]} | Prospective, comparative, interventional case series | t‑PTK (group 1) and mechanical epithelial debridement (group 2) during CXL (38) | 12 months  | Significant improvement in UDVA, CDVA, steep keratometry and corneal astigmatism with t‑PTK epithelial removal; no complications observed |
| Kymionis et al.\textsuperscript{[48]} | Prospective case series             | t‑PTK followed by CXL (23)          | 33.83±10.82 months (range: 24-56 months) | Significant improvement in UDVA, CDVA, keratometric values and corneal astigmatism; no complications observed |
| Kapasi et al.\textsuperscript{[49]} | Retrospective, comparative          | t‑PTK during CXL (PTK group) and mechanical epithelial removal during CXL (mechanical group) (34) | 1 month   | Significant improvement in SE and astigmatism in PTK group compared to mechanical group; no complications observed |
| Kapasi et al.\textsuperscript{[50]} | Comparative                         | t‑PTK during CXL (PTK group) and mechanical epithelial removal during CXL (mechanical group) (34) | 12 months  | Significant improvement in CDVA and gain of CDVA lines in PTK group; no complications observed |
| Gaster et al.\textsuperscript{[51]} | Retrospective, comparative study    | manual epithelial debridement and ablation via PTK followed by CXL (339) | 24 months  | Equivalent visual, refractive and keratometric outcomes between the two techniques |
| Grentzelos et al.\textsuperscript{[52]} | Prospective, comparative, interventional case series | t‑PTK (Cretan protocol group) and mechanical epithelial debridement (Dresden protocol group) during CXL (30) | 4 years    | Significant and faster improvement in visual, refractive and keratometric values in Cretan protocol group; no complications observed |
| Chen et al.\textsuperscript{[54]} | Retrospective case series           | t‑PTK followed by high intensity CXL (46) | 21.0±7.6 months (range: 10-43 months) | Significant improvement in CDVA and keratometric values and decrease in corneal HOAs; three eyes lost ≥2 lines of CDVA |
| Shetty et al.\textsuperscript{[55]} | Case report                         | t‑PTK with topography based ablation followed by accelerated CXL (3) | 3 months   | Significant improvement in CDVA in 2/3 eyes, topography-based t‑PTK technique ablated less stroma and achieved comparable outcomes |
| Sarac et al.\textsuperscript{[56]} | Retrospective, comparative case series | mechanical (group 1) and t‑PTK (group 2) based epithelial removal followed by accelerated CXL in pediatric population (40) | 36 months  | UDVA, total RMS and keratometry improved significantly in both groups, however, improvement in CDVA, SE, HOA RMS and spherical aberration was significant in only group 2; corneal haze ratio was similar; no complications observed |
| Grentzelos et al.\textsuperscript{[57]} | Prospective case series             | t‑PTK followed by simultaneous PRK and CXL (55) | 12 months  | Significant improvement in UDVA, CDVA, SE and keratometry; no complications observed |

t‑PTK=Transepithelial phototherapeutic keratectomy; CXL=Corneal cross‑linking; UDVA=Uncorrected distance visual acuity; CDVA=Corrected distance visual acuity; SE=Spherical equivalent; HOAs=Higher order aberrations; RMS=Root mean square
Several other studies with conflicting data have also been published, with respect to the optimal sequence and timing of ICRS and CXL, with the main argument being which combination may achieve superior outcomes in terms of maximizing corneal flattening.\textsuperscript{[66-69,76-79]} It seems that ICRS implantation followed by same-session or delayed CXL offers superior corneal flattening, whereas ICRS implantation following CXL (two-step procedure) limits the flattening

| Table 3: Summary of Outcomes with Combined ICRS Implantation and CXL |
|-----------------------------|------------------|---------------------------|-------------------|-----------------------------|-----------------------------|
| Author                      | Study design     | Surgical procedures (Number of eyes) | Follow-up         | Outcomes                                                                 |
| Chan et al.\textsuperscript{[64]} | Retrospective, comparative | Intacs alone/Intacs and CXL (12/13) | 102±39 days/97±38 days | Intacs with CXL showed significantly greater reduction in cylinder, topographic lower - upper ratio and steep and average keratometry, no complications observed |
| Renesto et al.\textsuperscript{[65]} | Randomized clinical trial with 2 groups | Riboflavin only and ICRS 3 months later/CXL followed by ICRS 3 months later (19/20) | 24 months | No significant difference was identified between groups in UDVA, CDVA, SE, and spherical or cylindrical components; no complications observed |
| Legare et al.\textsuperscript{[66]} | Retrospective, comparative | ICRS and same day CXL/ICRS alone (66) | 12 months | Significant improvement in UDVA, CDVA, sphere, cylinder, SE, keratometry and total HOAs in both the groups; no complications observed |
| Hersh et al.\textsuperscript{[61]} | Prospective randomized clinical trial | ICRS with concurrent CXL/ICRS followed by CXL 3 months later (104/94) | 6 months | Substantial improvement in corneal topography with no significant difference between the sequential and concurrent groups, thicker segment size and single segment placement showed greater topographic improvement; No increase in the complication rate in comparison to each procedure alone; infectious keratitis in 2 eyes, inflammation around ICRS in 3 eyes (ICRS explanted in 2 eyes), glare symptoms in one eye (ICRS was explanted) |
| Henriquez et al.\textsuperscript{[67]} | Prospective | CXL followed by Ferrara ICRS 6 months later (9) | 6 months | Significant visual improvement, reductions in SE and keratometry readings; no complications observed |
| El-Raggal\textsuperscript{[68]} | Prospective, Comparative | KeraRing insertion followed by CXL with a 6-month interval/2 step same day procedure (9/7) | 12 months | No significant differences in UDVA, CDVA, refractive error; however keratometric values showed greater reduction in the same day group; no complications observed |
| Saelens et al.\textsuperscript{[69]} | Case series | Same-day Ferrara ICRS implantation and CXL (7) | 12 months | Significant improvement in SE and keratometry; inferior ring had to be removed in 1 patient because of implant migration |
| Ertan et al.\textsuperscript{[70]} | Case series | ICRS followed by tranepithelial CXL 3.98 month interval (25) | 3 months | Additional improvement in UDVA, CDVA, sphere, cylinder and keratometry; no complications observed |
| El‑Awady et al.\textsuperscript{[71]} | Prospective | KeraRing implantation followed by CXL at least 3 months later (21) | 5.67±1.89 months | All outcome measurements (UDVA, CDVA, SE, cylinder, and keratometry readings) were improved after KeraRing implantation and showed further improvement after CXL; no complications observed |
| Sharma et al.\textsuperscript{[72]} | Prospective randomized | CXL alone/CXL combined with simultaneous ICRS implantation (20/18) | 12 months | CXL with ICRS yielded additional improvement in UDVA with significant reduction in cylinder and SE; no complications observed |
| Yeung et al.\textsuperscript{[73]} | Retrospective comparative case series | Single or paired ICRS implantation with CXL (85) | 12 months | Outcomes were equivalent with single and paired implantation; no complications observed |
| Saleem et al.\textsuperscript{[74]} | Retrospective, multicentre clinical | Paired KeraRing implantation with same session epithelium-on accelerated CXL (43) | 36 months | All outcome measurements (UDVA, CDVA, cylinder and keratometry readings) significantly improved; significant reduction in corneal thickness at the thinnest location was noted; 6 eyes showed progression who underwent standard CXL; 1 eye had exposure of ICRS but was stable after a repeat procedure 3 months later |
| Greenstein et al.\textsuperscript{[75]} | Prospective, randomized clinical trial | Same session Intacs and CXL/sequential, Intacs followed by CXL 3 months later (158) | 6 months | Total anterior corneal HOA including vertical and horizontal coma significantly improved, spherical anterior corneal HOAs increased postoperatively with no change in trefoil |

Contd...
Although channel for ICRS can be created after CXL, studyd Case series Study design Outcomes Surgical procedures (Number of eyes) Follow-up

Collamer lens (ICL) implantation 12 months after CXL. Significant improvement was noticed in UDVA and CDVA three months postoperatively and the short-term results of this combined approach were reported to be encouraging. Two studies reported the outcomes of iris-fixed PIOL implantation following CXL. Izquierdo et al. studied the safety and efficacy of foldable anterior iris-claw PIOL implanted 6 months after CXL in eyes with progressive keratoconus. Güell et al. also performed toric Artiflex/Artisan PIOL implantation following CXL and confirmed the long-term stability of this combined treatment. Other studies reported short to long-term outcomes of Visian ICL implantation following CXL. Kurian et al. reported that although it is possible to safely correct the refractive error in keratoconus with posterior chamber PIOL, the aberrations associated with it are uncorrected by the PIOL. Antonios et al. evaluated the long-term clinical outcome of Visian toric ICL insertion after CXL in progressive keratoconus. Although significant visual improvement was maintained throughout the follow-up, a small hyperopic shift was observed at 2 years which did not affect the visual outcome. Shafik et al. evaluated the predictability, efficacy and long-term stability of toric Visian ICL implanted 12 months after CXL and reported significant visual improvement. None of the eyes needed explantation or repositioning of the ICL during the 3-year follow-up. The decrease in endothelial cell count that was observed in the long-term studies was not significant. However, yearly monitoring of endothelial cell count has been recommended.

ICRS=Intrastromal corneal ring segments; CXL=Corneal cross-linking; CDVA=Corrected distance visual acuity; SE=Spherical equivalent; UDVA=Uncorrected distance visual acuity; HOAs=Higher order aberrations. The Intacs and Intacs SK are manufactured by Addition Technology, Lombard, IL. The Ferrara ICRS is manufactured by Ferrara Ophthalmics Ltda, Belo Horizonte, Brazil. The KeraRing is manufactured by Mediphacos, Belo Horizonte, Brazil.

### Table 3: Contd...

| Author       | Study design            | Surgical procedures (Number of eyes) | Follow-up | Outcomes                                                                 |
|--------------|-------------------------|-------------------------------------|-----------|--------------------------------------------------------------------------|
| Nicula et al. | Retrospective, comparative | KeraRing implantation followed by CXL 6 months later (group 1)/CXL followed by KeraRing implantation 6 months later (group 2) (41/30) | 12 months | Group 1 showed more significant improvement in SE, keratometry and cylinder compared to group 2; no complications observed |
| Coskunseven et al. | Prospective, comparative, randomized | CXL followed by ICRS (group 1)/ICRS followed by CXL (group 2); mean interval: 7±2 months (48) | 13±1 months | Group 2 showed more improvement in CDVA, SE and mean keratometry than group 1; 8 eyes had slight corneal edema with stromal opacities, which disappeared within 3 months |
| El-Ragga | Comparative case series | Femtosecond-mediated channel creation using 1.5, 1.6, and 1.7 mJ power setting for ICRS insertion 6 months after CXL (15) | 6 months | Although channel for ICRS can be created after CXL by modifying the femtosecond laser power, channel dissection and ICRS implantation should be performed before or concurrent with CXL; corneal haze in all eyes resolved within 6 weeks |
| Kilic et al. | Case series | Same-day combined ICRS and transepithelial CXL procedure, with 20% alcohol application and riboflavin injection into the corneal channel (131) | 7.07±4.66 months (range: 1 to 25 months) | Refractive and keratometric measurements improved in all cases; no complications observed |
| Alió et al. | Retrospective, comparative, nonrandomized | ICRS followed by CXL (3 to 12 months later) either with epithelial debridement (classic group) or intrastromal pocket for riboflavin delivery (pocket group) (16/11) | 12 months | No statistically significant differences between the 2 groups in any of the parameters measured (UDVA, CDVA, sphere, cylinder, and keratometry values, corneal aberrations, and corneal pachymetry); significant corneal haze in all cases which resolved over time |

### Phakic Intraocular Lens (PIOL) Implantation with CXL

Studies have reported the use of phakic intraocular lens (PIOL) following CXL as an alternative approach for the correction of moderate-to-high refractive error in patients with progressive keratoconus intolerant to contact lenses. The types of PIOL that have been implanted in keratoconic patients include both iris-fixated and posterior chamber. This two-step approach was reported for the first time in 2011 by Kymionis et al. in a 29-year-old woman with progressive keratoconus and high myopic astigmatism who underwent toric implantable Collamer lens (ICL) implantation 12 months after CXL. Significant improvement was noticed in UDVA and CDVA three months postoperatively and the short-term results of this combined approach were reported to be encouraging. Two studies reported the outcomes of iris-fixed PIOL implantation following CXL. Izquierdo et al. studied the safety and efficacy of foldable anterior iris-claw PIOL implanted 6 months after CXL in eyes with progressive keratoconus. Güell et al. also performed toric Artiflex/Artisan PIOL implantation following CXL and confirmed the long-term stability of this combined treatment.

Other studies reported short to long-term outcomes of Visian ICL implantation following CXL. Kurian et al. reported that although it is possible to safely correct the refractive error in keratoconus with posterior chamber PIOL, the aberrations associated with it are uncorrected by the PIOL. Antonios et al. evaluated the long-term clinical outcome of Visian toric ICL insertion after CXL in progressive keratoconus. Although significant visual improvement was maintained throughout the follow-up, a small hyperopic shift was observed at 2 years which did not affect the visual outcome. Shafik et al. evaluated the predictability, efficacy and long-term stability of toric Visian ICL implanted 12 months after CXL and reported significant visual improvement. None of the eyes needed explantation or repositioning of the ICL during the 3-year follow-up. The decrease in endothelial cell count that was observed in the long-term studies was not significant. However, yearly monitoring of endothelial cell count has been recommended.
Rationale and Indication: After achieving stability of ectatic progression with CXL, PIOL implantation can be performed in selective keratoconic patients having good or acceptable spectacle-assisted CDVA in addition to high refractive error with or without anisometropia. All of the aforementioned studies have reported PIOL implantation after a minimum of 3 months following CXL.\cite{76-82}

**Combination of Multiple Techniques**

The combination of CXL with a single refractive procedure may sometimes lead to partial gain of functional vision. Therefore, surgeons have proposed combinations of two or more of the above mentioned modalities with CXL so as to maximize the visual outcome. A multimodal approach serves to combine the desirable attributes of each of the included procedures while minimizing their individual limitations. The following combinations of multiple procedures have been reported Table 5 –

1. CXL with PRK and ICRS implantation
2. CXL with PRK and PIOL implantation
3. CXL with ICRS and PIOL implantation
4. CXL with t-PTK and ICRS implantation
5. CXL with ICRS, PIOL and PRK (Quadruple approach).

The combination of ICRS and PRK incorporates the synergistic use of a tissue-sparing and a tissue-removing procedure with CXL. PRK and CXL may be performed either sequentially or simultaneously with ICRS implantation to address the mild residual refractive error encountered following ICRS insertion in keratoconic patients.\cite{95-96} Despite the variations in the timing and the interval between each of the three procedures, this technique has been reported as safe and effective in providing functional visual acuity to patients with low to moderate keratoconus,\cite{95-96}

Another study evaluated the combination of Athens protocol (PRK with CXL) followed by PIOL implantation to treat the high residual refractive error and reported improved and stabilized visual performance in keratoconic patients.\cite{97}

Several studies have confirmed the safety, efficacy and long-term stability of PIOL implantation following sequential ICRS insertion and CXL in patients with moderate to severe keratoconus.\cite{96-100} PIOL implantation was targeted to correct the moderate to severe ametropia persistent after the initial procedures and improve the visual outcome.\cite{96-100}

The combination of ICRS implantation with CXL and t-PTK performed on the same day has been shown as safe, effective and predictable in patients with moderate keratoconus.\cite{101,102}

A recent retrospective interventional study evaluated a four-stage combined treatment comprising of ICRS, CXL, PIOL and PRK performed sequentially in the same order and confirmed the safety and efficacy of this combined approach in suitable keratoconic patients.\cite{103} All eyes in this series had low preoperative spectacle-assisted CDVA which improved significantly after ICRS implantation compared to improvement in UDVA.\cite{103} The patients underwent CXL treatment followed by PIOL implantation with an interval of 6 months between each of the procedures to correct the high residual refractive error which led to a significant improvement in UDVA and SE.\cite{103} The eyes were later subjected to topo-guided PRK treatment which resulted in added improvement in these parameters.\cite{103} The end result after the four-stage procedure showed significant improvement in visual acuity, with all eyes achieving better postoperative UDVA than preoperative spectacle-assisted CDVA.\cite{103}

**LASIK Xtra, SMILE Xtra and PRK Xtra**

*Laser in situ* keratomileusis (LASIK) Xtra is a modified procedure that combines LASIK with prophylactic accelerated CXL for the correction of refractive error in an attempt to decrease the risk of postoperative corneal ectasia. Similarly, the combination of small incision lenticule extraction (SMILE) and PRK with CXL...
Table 5: Summary of Outcomes with Combinations of Multiple Techniques and CXL

| Author           | Study Design       | Combined procedures (number of Eyes) | Order of the procedures (Duration of follow-up)                                                                 | Outcomes                                                                 |
|------------------|--------------------|--------------------------------------|---------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Kremer et al.    | Case series        | ICRS, PRK, and CXL (45)              | ICRS implantation followed by (6 months later) simultaneous wavefront-guided PRK and CXL (12 months)         | Significant improvement in UDVA, CDVA, and keratometry values; no patient lost any line of CDVA; no ECD changes; Epithelial hyperplasia in 4 of 45 eyes |
| Coskunseven et al. | Prospective        | ICRS, CXL and PRK (16)               | ICRS implantation followed by CXL followed by transepithelial topography-guided PRK with an interval of 6 months between each procedure (6 months) | UDVA, CDVA, SE, and keratometry values showed significant improvement; no eye lost any line of CDVA; no complications observed |
| Dirani et al.    | Retrospective      | ICRS, CXL and PRK (17)               | ICRS implantation followed by CXL with a 4-week interval followed by non-topography-guided PRK 6 months later (6 months) | UDVA, CDVA, SE, and keratometry values showed significant improvement; no complications observed |
| Al-Tuwairqi et al. | Prospective        | ICRS, CXL and PRK (41)               | ICRS implantation followed by (6 months later) simultaneous topography-guided PRK and CXL (12 months)          | Significant improvement in UDVA, SE and keratometry values, 85% of eyes maintained or gained multiple lines of CDVA; no complications observed |
| Lee et al.       | Retrospective      | ICRS, PRK, and CXL (23)              | ICRS implantation followed by combined corneal WFG-PRK (transepithelial) and high-fluence accelerated CXL 1 month later (6 months) | Significant improvement in UDVA, CDVA, SE, keratometry values and HOAs; no complications observed |
| Koh et al.       | Prospective        | ICRS, PRK, and CXL (30)              | ICRS implantation followed by (3 months later) simultaneous wavefront-guided PRK and CXL (12 months)          | UDVA, CDVA, SE, and keratometry values improved with reduction in HOAs; no complications observed |
| Assaf et al.     | Prospective        | CXL, PRK, PIOL (22)                  | Topography-guided PRK followed by same day CXL (Athens protocol), followed by iris claw or angle-supported PIOL implantation 2–4 months later (6 months) | Significant improvement in CDVA, SE and keratometry values; no complications observed |
| Coskunseven et al. | Case series        | ICRS, CXL and PIOL (14)              | ICRS implantation followed by CXL (>6 months) and then toric PIOL implantation (>6 months) (12 months)      | Significant improvement in UDVA and CDVA in keratoconic eyes with high refractive error; no complications observed |
| Dirani et al.    | Retrospective      | ICRS, CXL and PIOL (11)              | ICRS implantation followed by CXL (4-week interval) and then toric PIOL implantation 6 months later (12 months) | Significant improvement in UDVA, CDVA, SE and keratometry; no complications observed |
| Abdelmassih et al. | Consecutive case series | ICRS, CXL and PIOL (16)             | ICRS implantation followed by CXL (4-week interval) and then toric PIOL implantation 6 months later (24 months) | Significant improvement in UDVA, CDVA, SE and keratometry; no complications observed |
| Yeung et al.     | Retrospective      | t-PTK, ICRS and CXL (16)             | Same-day t-PTK followed by single ICRS implantation and CXL (6.9±4.6 months)                                | Significant improvement in UDVA, CDVA and mean and steep keratometry values; no complications observed |
| Rocha et al.     | Prospective        | t-PTK, ICRS and CXL (55)             | ICRS implantation, followed by CXL and PTK (6 months)                                                        | Significant improvement in UDVA, CDVA sphere and cylinder; no complications observed |
| Coskunseven et al. | Retrospective      | ICRS, CXL, PIOL, PRK (11)            | ICRS implantation, followed by CXL followed by topography-guided PRK with interval of 6 months between each procedure (12 months) | Significant improvement in UDVA, CDVA, SE and astigmatism; no complications observed |

CXL=Corneal cross-linking; ICRS=Intrastromal corneal ring segments; PRK=Photorefractive keratectomy; UDVA=Uncorrected distance visual acuity; CDVA=Corrected distance visual acuity; PIOL=Phakic intraocular lens; SE=Spherical equivalent; ECD=Endothelial cell density; t-PTK=Transepithelial phototherapeutic keratectomy; HOAs=Higher order aberrations; WFG=Wavefront-guided

termed as SMILE Xtra and PRK Xtra, respectively, has also been reported with the same rationale. These procedures are mainly used in patients with high refractive error or borderline corneal parameters seeking refractive correction and therefore, have not been extensively discussed as it is beyond the scope of this study. Several studies reported comparable results in terms of safety, efficacy and predictability between LASIK Xtra and conventional LASIK [Table 6]. Despite the initial supportive evidence, long-term studies are required to determine whether LASIK Xtra is beneficial in preventing...
postoperative keratectasia.\[106,108\] Tomita et al. showed insignificant changes in corneal biomechanics after LASIK Xtra as compared to LASIK.\[104\] Kohnen et al. reported topographic and refractive stability with no signs of keratectasia at 12 months postoperatively in both LASIK Xtra and conventional LASIK groups and showed no advantage of LASIK Xtra over LASIK.\[107\] Taneri et al. reported a case of unilateral corneal ectasia that developed 2 years after LASIK Xtra.\[109\]

Studies have evaluated the initial safety and efficacy of SMILE Xtra at 1-2 years postoperatively.\[110-112\] In a comparative study, a slight trend towards myopic shift after SMILE Xtra has been reported.\[111\] Although SMILE Xtra has been safely used in forme-fruste keratoconus, authors have mentioned the need for longer duration of follow-up and larger sample size to fully confirm these findings.\[113\]

Sachdev et al. showed the initial safety and efficacy of PRK Xtra in myopic eyes with thinner pachymetry and tomographic abnormalities at one year postoperatively.\[114\] Ohana et al. reported that although the improvement in visual outcome was significant after PRK Xtra in eyes with thin or irregular cornea, the refractive outcome was less accurate compared to the published results of PRK-only procedure.\[115\]

Rationale and indication: Although the use of adjuvant accelerated CXL after LASIK, SMILE and PRK in eyes with thin corneas, borderline topography and high refractive error has been presented in several aforementioned studies, there is no long-term evidence supporting their role in the prevention of keratectasia. As a result, due to paucity of long-term studies and lack of conclusive evidence regarding the efficacy of these protocols in preventing ectasia, currently, PIOL implantation may be preferred over corneal procedures in such susceptible eyes for refractive correction.

**Guidelines for Selection of CXL Plus Technique**

In patients with documented keratoconus progression, CXL is required in order to increase the corneal biomechanical
Figure 1: Proposed algorithm to aid in decision-making for the comprehensive management of keratoconus. After diagnosing the disease, the treatment is planned after taking into consideration the stage of keratoconus, disease stability or progression, functional vision, preoperative corneal irregularity and astigmatism, corneal thickness and patient’s willingness or tolerance towards contact lenses. VA = Visual acuity; RGP-CL = Rigid gas-permeable contact lens; DALK = Deep anterior lamellar keratoplasty; PKP = Penetrating keratoplasty; CXL = Corneal cross-linking; t-PTK = Transepithelial phototherapeutic keratectomy; PRK = Photorefractive keratectomy; ICRS = Intrastromal corneal ring segments; PIOL = Phakic intraocular lens; CT = Corneal thickness.
stability and thus halt the ectatic process. Although CXL alone might improve the vision and few corneal parameters to some extent, the majority of patients, with moderate to advanced keratoconus, will still require adjunctive refractive therapies for resolving the corneal irregularities and enhancing the visual outcome. For this reason, combined CXL treatments (CXL plus) are gaining more ground and popularity in order to provide a better quality of life to keratoconic patients.

To date, no algorithm exists for determining the most efficient and effective CXL plus protocol for each individual patient. The treatment needs to be planned and customized after taking into consideration many parameters such as patient’s age, refractive status, personal needs, stage of keratoconus, disease progression rate, corneal irregularity and willingness or tolerance towards spectacle and contact lenses.[116] Combined CXL treatment protocols are indicated in patients with documented progression of the disease showing unsatisfactory visual function or aversion/intolerance towards contact lenses and spectacles [Fig. 1]. In eyes with cones located within the central 2-mm zone, the combination of CXL with topo-guided PRK and/or t-PTK appears to be the most appropriate treatment approach in an attempt to both stabilize keratoconus progression and regularize the anterior corneal surface. The prerequisites for combining CXL with laser ablation techniques are maximum stromal ablation depth up to 50 µm and predicted postoperative thinnest pachymetry of more than 400 µm.[22,23] In more advanced cases where the safety requirements regarding CT are not met and in eyes with cones located outside the central 2-mm zone, simultaneous ICRS implantation and CXL seems to provide satisfactory results in terms of disease stabilization, corneal reshaping and reduction of irregular astigmatism. Additionally, the two-step approach of CXL followed by PIOL implantation after an interval of 3-6 months offers a promising alternative for patients with high residual refractive errors (myopia and regular astigmatism) and ectatic progression. The aforementioned combined treatment techniques may also be used in stable keratoconic cases or keratoconus suspects without non-satisfactory visual function (contact lens/spectacle intolerance, irregular astigmatism, high refractive error etc.) in order to improve their refractive profile without causing biomechanical destabilization of the cornea. Lastly, in order to further enhance refractive outcomes of CXL plus, a triple or quadruple approach can also be performed by combining multiple refractive techniques with CXL. Nevertheless, further studies are required in order to draw definite conclusions regarding their safety, efficacy and long-term stability.

Conclusion

Although CXL remains the gold standard for halting the ectatic process, it does not offer the advantage of fully addressing the refractive component of keratoconus. For this reason, a plethora of combined treatment protocols, as presented above, have been introduced in clinical practice, but no definitive management strategy has been described yet. Several parameters need to be further explored in order to standardize treatment planning and improve predictability, especially that of combined CXL and laser ablation techniques. Till date, no algorithm has been developed that takes into account all the possible factors (patient’s age, refractive status, personal needs, keratoconus stage etc.) affecting the final refractive outcome of combined CXL protocols. The future aim is to develop nomograms that can incorporate all the aforementioned parameters and help in achieving highly accurate and predictable refractive results. Further prospective long-term randomized controlled studies are required for the development of customized CXL plus techniques that can be individualized as per each patient’s status and needs.

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Conflicts of interest

There are no conflicts of interest.

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