AMERICAN ACADEMY OF OPHTHALMOLOGY®

Evidence-Based Guidelines for Keratorefractive Lenticule Extraction Surgery

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Topic: Development of evidence-based guidelines for keratorefractive lenticule extraction (KLEx).

Clinical Relevance: Keratorefractive lenticule extraction refers to various corneal refractive procedures involving removal of refractive lenticules of intrastromal corneal tissue, typically through a small incision, eliminating creation of a corneal flap. This technique has gained popularity rapidly; however, no clinical practice guidelines exist.

Methods: These evidence-based guidelines were developed following the World Health Organization guidebook using the Appraisal of Guidelines for Research and Evaluation II tool and adhering to the Reporting Items for Practice Guideline in Healthcare statement. The body of evidence was drawn from 8 literature databases, 5 clinical guideline databases, and 2 academic organizations. Recommendations were developed via a Delphi consensus of 44 global experts in refractive surgery, cornea, retina, glaucoma, and optometry. The certainty of evidence, balance of benefits and harms, patient preferences and values, and economic evaluations were considered fully. The Grading of Recommendations Assessment, Development, and Evaluation approach was used to assess evidence quality and recommendation strengths.

Results: From 385 initial clinical questions, 15 were identified, prompting a review of 250 717 studies, with 609 included for conducting and updating 26 and 2 systematic reviews, respectively. Subsequently, consensus was reached on 38 recommendations for preoperative screening, candidate selection, intraoperative quality control, operating principles, postoperative monitoring, and complication management. For KLEx, an effective and accurate refractive correction is attributed to various factors such as corneal thickness, degree of myopia, treatment nomogram, and optical zone. For complications that could affect vision, comprehensive and effective management strategies were proposed, particularly for wrong-plane dissection and difficult lenticule removal, suction loss, and perioperative infection. Customized surgical planning protocols and operative techniques were analyzed. Among all recommendations, 29 (76%) were labelled as strong, each externally reviewed. The corneal biomechanical properties may help to improve safety and predictability, although they need further validation. Several research gaps for enhancing KLEx safety were also revealed.

Conclusions: These guidelines provide evidence-based recommendations for KLEx in clinical practice, such as for preoperative screening for keratoconus, surgical planning, and management and prevention of complications and infection. The guidelines are expected to minimize the complications and achieve better outcomes.

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Keratorefractive lenticule extraction (KLEx) is a novel laser corneal refractive procedure that has gained popularity in recent years.[1,2] The initial technique of femtosecond lenticule extraction (FLEx), also known as refractive corneal lenticule extraction, was developed into the now commonly used small-incision lenticule extraction (SMILE) surgery. Further developments of the technique included cornea lenticule extraction for advanced refractive correction, smooth incision lenticule keratomileusis, small incision-guided human-cornea treatment, and other available lenticule extraction-based procedures.[2−7] Keratorefractive lenticule extraction has been used to correct myopia, hyperopia, and astigmatism.[1,8−11] The main advantage of lenticule extraction over traditional refractive surgeries lies in the lack of need for a corneal flap and subsequent flap-related complications. It also provides better protection to the corneal nerves and maintains good corneal biomechanical properties.[12−18] Since the introduction of refractive

https://doi.org/10.1016/j.ophtha.2024.11.016
ISSN 0161-6420/24

lenticule extraction in 2008,[19] > 8 million procedures had been performed globally by the end of 2023, with > 5 million occurring in China. Studies have established its surgical safety and efficacy.[20–22] However, intraoperative complications such as suction loss, black spots, opaque bubble layer (OBL), and lenticule remnants, as well as postoperative complications such as corneal ectasia, have been reported.[23–28] Moreover, because of a long learning curve and distinct differences to previous surgical methods used in corneal refractive surgery, KLEx presents new challenges in clinical practice, especially for inexperienced surgeons.[27] No clinical practice guidelines for KLEx procedures have been published.

Evidence-based guidelines are crucial for improving clinical diagnosis and treatments.[29] With the rapid evolution of KLEx techniques, an urgent need exists for guidelines on its performance, minimizing surgical failures and enhancing safety. Furthermore, numerous perspectives from different studies require evidence-based guidance for unification and endorsement.[30] Therefore, we assembled a working group, led by global experts in corneal refractive surgery, aimed at proposing guidelines using evidence-based methodology and procedures. The final document is expected to provide guidance on surgical indications, procedure design, operative technique, and complication management for KLEx procedures, helping to standardize surgical specifications and to promote further development.

Methods

These guidelines were sponsored by the Refractive Surgery Group of Chinese Ophthalmologist Association, in collaboration with the International Society of Refractive Surgery. Methodologic support was provided by the World Health Organization (WHO) Collaborating Centre for Guideline Implementation and Knowledge Translation and the Lanzhou University Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Center. These guidelines were registered initially on the Practice Guideline Registration for Transparency registry (identifier, PREPARE-2022CN624) and were developed based on the WHO guidebook published in 2014,[31] while referring to the definition of clinical practice guidelines proposed by the American Academy of Medical Sciences.[32] We adhered to the Appraisal of Guidelines for Research and Evaluation II tool[33] and the Reporting Items for Practice Guideline in Healthcare statement.[34] The study was deemed exempt from human subjects' research by the Institutional Review Board. All research adhered to the tenets of the Declaration of Helsinki. The requirement for informed consent was waived because of the retrospective nature of the study.

Scope of the Guidelines

In the present guidelines, the KLEx procedure comprises various forms of lenticule extraction surgeries using different technologies, rather than being specific to any particular device. Because early FLEx procedures were reformed from large-incision to small-incision techniques, these guidelines predominantly discuss small incision-based KLEx applications, including SMILE surgery.

These guidelines briefly summarize the state of the art of KLEx technology, mainly covering 3 domains: indications, surgical planning and technique, and complications. Specifically, preoperative screening and candidate selection, intraoperative quality control and operating principles, and postoperative monitoring and complication management are highlighted. Preoperative screening includes topics such as early detection of keratoconus, risk assessment, and the application of corneal biomechanical measurements. Intraoperative quality control includes topics such as safe lenticule removal, thresholds for remaining corneal tissue, and appropriate ranges of astigmatism correction. Key parameter settings and nomogram adjustment, as important elements of quality optimization, also are addressed. Prevention and treatment of KLEx-related complications such as suction loss, black spots, retained lenticule fragments, diffuse lamellar keratitis (DLK), and corneal ectasia, are specified in these guidelines.

Target Audience and End Users

These international guidelines apply to all health care settings that allow the implementation of KLEx surgery. The targeted users are health care professionals involved in this surgery, including physicians, optometrists, clinical pharmacists, and nurses. Patients who undergo KLEx surgery comprise the end users of these guidelines.

Development of the Guidelines

The development process of the guidelines is presented in Figure 1.

Organization of the Guideline Working Groups. Five groups were established to develop these guidelines. All members provided information on potential conflicts of interest before joining the guideline development panel. No relevant financial conflicts of interest were identified.

The Guideline Steering Committee included 1 refractive surgery specialist with extensive experience in KLEx surgery (Y.Wang), 2 corneal specialists (L.Xie and V.Jhanji), 1 cataract surgery specialist (K.Yao), and 1 methodologist (K.Yang). Their responsibilities were (1) to define the scope of the guidelines, (2) to organize other working groups and manage the disclosure of their conflicts of interest, (3) to lead and oversee the guideline development process and approve recommendations, and (4) to monitor and assess the need for updating the guidelines.

The guideline consensus panel included 44 global ophthalmologists (Walter Sekundo, Jorge L. Alió, Jod S. Mehta, Sanjay Goel, Ahmed Elmassry, Julie Schallhorn, Tatiana Shilova, Changbin Zhai, Chenjiu Pang, Dan Wen, Fan Lv, Fengju Zhang, Gang Liang, George P. M. Cheng, Henan Bai, Hua Gao, Ji Bai, Juan Wu, Keming Yu, Liang Hu, Likun Xia, Lingling Wu, Min Chen, Pirong Lin, Qin Liu, Rui He, Shihao Chen, Wei Han, Weiyun Shi, Wenfang Zhang, Wenxiu Lu, Xianglong Yi, Xingtao Zhou, Xingwu Zhong, Xue Li, Ye Shen, Ying Li, Yingping Deng, Yabo Yang, Yan Zhang, Yueguo Chen, Zheng Wang, Zhengzheng Wu, and Zhiyu Du). The selection process for guideline consensus panel members involved the following criteria: (1) specialty representation comprised experts with more than 10 years of experience in corneal refractive surgery, and those specializing in corneal diseases, retinal diseases, glaucoma, and optometry; (2) regional representation comprised experts from various regions within China and other countries; and (3) academic achievements and influence comprised experts with significant contributions to the field, as evidenced by their published scientific papers. Their responsibilities were to (1) formulate the clinical questions and outcomes that were included in the guidelines, (2) reach a consensus on the recommendations, and (3) provide input throughout all stages of the guideline development process.

The guideline secretary group included 6 members from the sponsoring organization. Their responsibilities were to (1) investigate and collect the clinical questions expected to be included in the guidelines, (2) initiate every round of the Delphi questionnaires on clinical questions and recommendations and to summarize the results, (3) organize and record the daily work

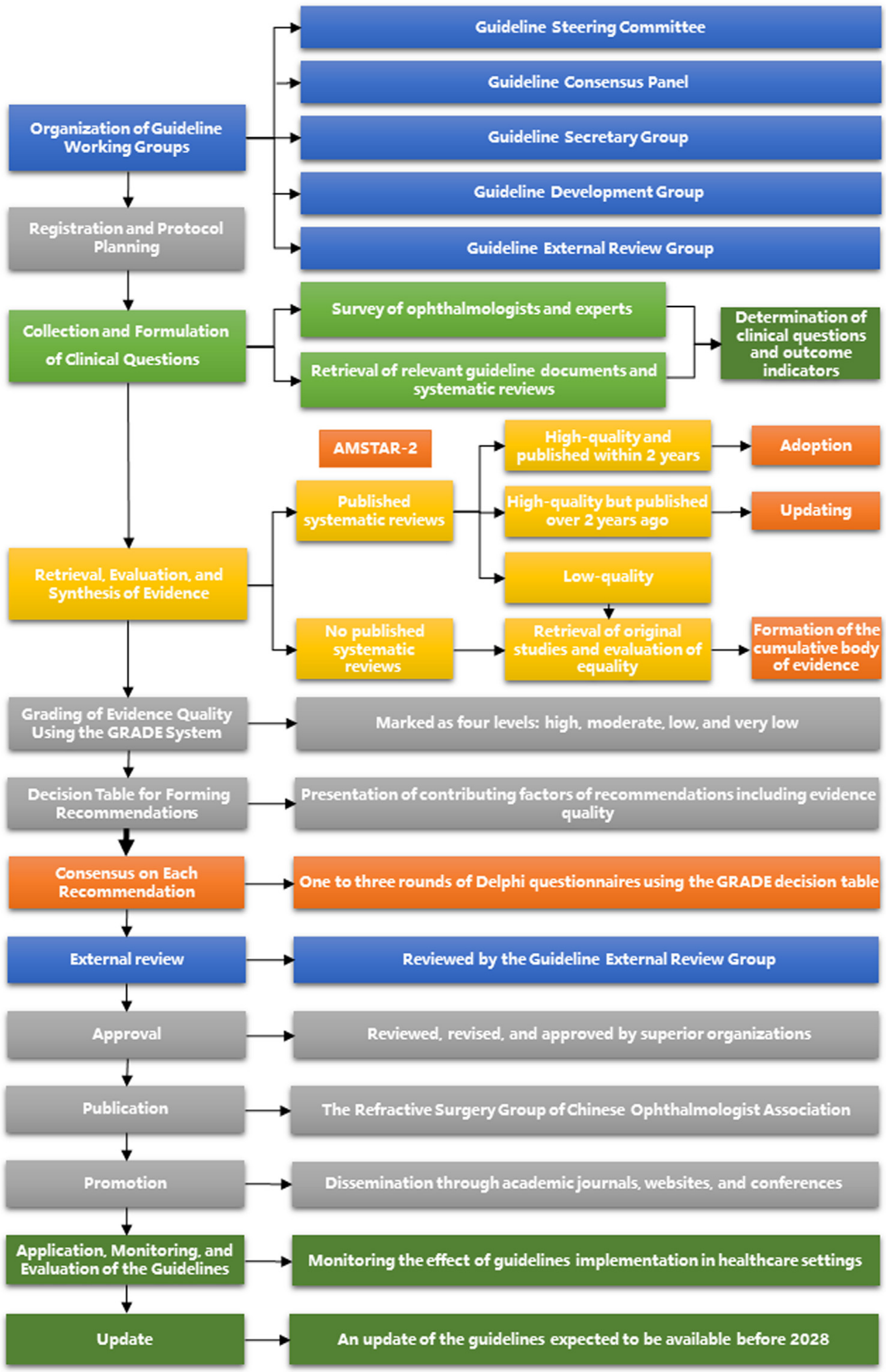

Figure 1. Diagram showing the development process of the guidelines. AMSTRAT-2 = A Measurement Tool to Assess Systematic Reviews-2; GRADE = Grading of Recommendations Assessment, Development, and Evaluation.

arrangements of the guidelines, and (4) communicate with expert panels and coordinate all groups and guideline developers. The head of the secretary group was also the coordinator of the guidelines.

The guideline development group (GDG) included 24 members with previous experience in evidence-based medicine, ophthalmology, and corneal refractive surgery. Their responsibilities were to (1) retrieve, evaluate, and synthesize the evidence related to the guidelines; (2) conduct a systematic review; (3) perform evidence grading; and (4) draft the initial manuscript of the guidelines.

The guideline external review group included 6 members, comprising 2 ophthalmologists (John Chang and Renyuan Chu), 1 journal editorial reviewer (Yibin Huang), 1 evidence-based medicine methodologist (Yaolong Chen), 1 legal adviser (Hongjie Liu), and 1 patient representative (Yi Hua). Their responsibilities were to (1) assess the applicability of the recommendations and (2) review the manuscript and provide comments and suggestions.

Collection and Formulation of Clinical Questions. The formulation of the clinical questions was based on the retrieval of existing evidence from systematic reviews and original studies related to KLEx procedures, combined with patient preferences and values and in-depth interviews with stakeholders. A total of 385 questions were collected from nationwide frontline ophthalmologists in China. After classifying and merging these concerning questions, the Population, Intervention, Comparison, and Outcome principle was used to develop clinical questions. The final questions were identified by the guideline consensus panel using the Delphi method, in which each question was scored on a scale of 1 through 7 reflecting its importance, and only questions with scores of 6 or 7 from $\geq$ 75% of panelists were included. For each question, outcome indicators and economic evaluations were proposed based on literature retrieval and assessment, evidence review, in-depth interviews, and patient preferences and values, after several rounds of discussion.

Patient Preferences and Values. The GDG conducted a cross-sectional study involving 149 patients from 7 Chinese hospitals who underwent KLEx surgery to assess their values and preferences regarding surgical safety and efficacy. The hospitals were selected based on regional distribution, and the patients were selected through convenience sampling. A 5-minute video was shown to patients, providing background information for the questionnaire (i.e., explanations of medical terminology, potential benefits and risks of KLEx, and costs). All research results were presented to the guideline consensus panel for full consideration while formulating recommendations.

Evidence Synthesis. The following electronic databases were searched: PubMed, Web of Science, Cochrane Library, Embase, China National Knowledge Infrastructure, China Biology Medicine Disc, Wanfang Data, and VIP Database. Clinical guideline websites included the National Guideline Library, International Guideline Collaboration Network, Inter-School Guideline Network in Scotland, National Institute for Clinical Excellence, and WHO. Official academic organization websites included the American Academy of Ophthalmology and the International Council of Ophthalmology. The search strategy used a combination of subject and free-text terms and was reviewed by the guideline steering committee, guideline methodologists, and information scientists to ensure it covered all relevant databases and appropriate search terms. The retrieval period spanned from the inception of database through May 10, 2023. No language restrictions were applied, and references in the included literature were reviewed thoroughly. The retrieved studies were screened based on their title, abstract, and full text in that order, covering systematic reviews, randomized controlled trials, cohort studies, case-control studies, cross-sectional studies, case series, and case reports. Screening and data extraction from each study were performed independently by 2 professionals, with a third party involved in cases of disagreement. Statistical analyses were performed using RevMan software version 5.4. (Cochrane Collaboration) and Stata software version 17.0 (StataCorp). A random-effects model was used to calculate the effect estimate and 95% confidence interval (CI). Statistical heterogeneity among studies was assessed using I^2 statistic, with values of 0%, 25%, 50%, and 75% indicating no, low, moderate, and high heterogeneity, respectively. To verify the stability of the results, sensitivity analyses were performed by omitting each study individually.[35] Studies were subgrouped to analyze the reasons for heterogeneity.[36] Publication bias was assessed statistically using Begg and Egger tests.[37] For all analyses, a 2-tailed P value of < 0.05 was considered statistically significant. The keywords and retrieval schema of the PubMed search are presented in Supplemental Digital Content 1 (available at www.aaojournal.org), and similar retrieval strategies were used for other databases. The information on the authors who contributed to each step of the evidence synthesis for each clinical question is presented in Supplemental Digital Content 2 (available at www.aaojournal.org).

Consensus on Recommendations and External Review. The guideline consensus panel voted on the proposed recommendations considering the balance of benefits and harms, quality of evidence, clinical practicality, and patient welfare. A strong recommendation required an affirmative vote of $\geq$ 70% for strongly recommended plus conditionally recommended and an affirmative vote of $\geq$ 50% for strongly recommended. The percentage threshold for opposing a consensus recommendation was set at $\leq$ 20%.[38] After approval from the guideline steering committee, the drafted recommendations were submitted to the guideline external review group for further review and revision, and the final version was formulated, approved, and published by the Refractive Surgery Group of Chinese Ophthalmologist Association.

Updates. As new evidence is published, the guideline steering committee will collect and analyze it continuously to determine how it might supplement and update the recommendations. Updated guidelines will adhere to the Checklist for the Reporting of Updated Guidelines.[39] The updated guidelines are expected to be available before 2028.

Evidence Quality and Recommendation Strength

A Measurement Tool to Assess Systematic Reviews-2 (AMSTAR-2),[40] Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2),[41] Cochrane risk-of-bias assessment tool,[42] Newcastle-Ottawa scale,[43] and Joanna Briggs Institute critical appraisal checklist[44] were used to evaluate the methodological quality of the corresponding studies. The GRADE and GRADE-Confidence in Evidence from Reviews of Qualitative Research (CERQual) methods were used to assess the quality of corresponding evidence, with 4 levels in decreasing order (A, B, C, and D).[45,46] Evidence quality ratings were assigned to recommendations, identifying the strength of the cumulative body of evidence supporting each recommendation. A good practice statement was made when they were perceived to be necessary to help clinicians to take appropriate actions in areas of uncertainty.[47] Following the GRADE system for recommendation grading, the recommendation strengths were quantified as 2, 1, 0, −1, and −2.[45,48,49] Different grades represent different trade-offs between advantages and disadvantages and whether this is recommended in the present guidelines. The grading schemes for evidence and recommendations are shown in Table 1.

Results

In these guidelines, 15 clinical questions were determined through a 2-round Delphi method. Regarding these questions, a total of 250 717 studies were retrieved, and 609 were included for quality evaluation and data analysis through a full-text review; 26 systematic reviews were conducted and 2 were updated further. Thirty-eight recommendations were formulated, and all reached consensus through a 1-round Delphi questionnaire. The search process is presented in Supplemental Digital Content 3 (available at www.aaojournal.org). The GRADE evidence profiles, and

Table 1. Grading of Evidence Quality and Recommendation Strength

Grading	Detailed Description
Evidence quality	
High (A)	The estimated effect is close to the real effect
Moderate (B)	The estimated effect is probably close to the true effect, but also may be different
Low (C)	The estimated effect is different from the true effect
Very low (D)	The estimated effect is extremely different from real values
Recommendation strength	
Strongly recommended (2)	Advantages significantly outweigh the disadvantages
Conditionally recommended (1)	Advantages probably outweigh the disadvantages
Without recommendation (0)	Equivalent or uncertain of advantages over disadvantages
Conditionally not recommended (−1)	Disadvantages likely outweigh the advantages
Strongly not recommended (−2)	Disadvantages significantly outweigh the advantages

Delphi questionnaire results are shown in Supplemental Digital Contents 4 and 5 (available at www.aaojournal.org), respectively.

Domain 1: Indications

Clinical Question 1. Clinical question 1 investigated the influence of corneal biomechanical properties on the surgery (preoperative screening of keratoconus, selection of surgical options, surgical plans, and postoperative outcomes).

Recommendations. Recommendation 1: Keratoconus is contraindicated for corneal refractive surgery; preoperative screening of keratoconus and risk assessment are required; given the current technologies, assessment of corneal morphologic features combined with biomechanics is feasible to detect subclinical or forme fruste keratoconus; tomographic and biomechanical index (TBI), Corvis biomechanical index (CBI), and corneal resistance factor (CRF) currently are sensitive corneal biomechanical parameters (evidence quality: D; strong recommendation).

Recommendation 2: This surgery can preserve biomechanical properties after surgery (evidence quality: B; conditional recommendation).

Recommendation 3: The thickness of the removed corneal tissue directly affects the corneal biomechanical strength, and lower thickness of removed corneal tissue is recommended; postoperative corneal biomechanical properties are associated with the optical zone diameter, and unreasonable expansion of the optical zone is not recommended (evidence quality: D; strong recommendation).

Recommendation 4: Corneal biomechanical properties influence the surgical predictability of refractive outcomes (evidence quality: D; conditional recommendation).

Summary of the Evidence.

1. Diagnostic efficiency of corneal biomechanics for early detection of keratoconus: Using the network meta-analysis method, the diagnostic efficiency of 10 well-known corneal morphologic indices for the identification of subclinical and forme fruste keratoconus, including Ambrósio relational thickness to the horizontal profile (ARTh), central astigmatism from the anterior corneal surface, Belin−Ambrósio enhanced ectasia total deviation index, inferior−superior difference value, index of surface variance, keratoconus index, maximum keratometry from the anterior corneal surface, posterior corneal elevation, average pachymetric progression index, and the thinnest corneal thickness, were compared with 10 corneal measurements of biomechanical response via air-puff deformation ranked by initials, including the first applanation velocity (A1V) and the second applanation velocity (A1V), CBI, corneal hysteresis (CH), CRF, the maximal value of the ratio between the deformation amplitude at the apex and at 1 mm from the corneal apex (DA ratio), central curvature radius at the highest concavity, integrated radius (IR), stiffness parameter at the first applanation (SP-A1), and TBI. The Belin−Ambrósio enhanced ectasia total deviation index achieved the best diagnostic performance (surface under the cumulative ranking curve [SUCRA], 92.1), followed by TBI (SUCRA, 88) and ARTh (SUCRA, 77.2). To determine the diagnostic potential of corneal biomechanical evaluation further, rank the effectiveness of each indicator, and identify the best ones, 15 well-known measurements (the first [A1T] and the second [A2T] applanation time, A1V, A2V, ARTh, CBI, CH, CRF, DA ratio, central curvature radius at the highest concavity, IR, inverse concave radius, peak distance, SP-A1, and TBI) were included for analysis. For early detection of keratoconus, TBI had the best accuracy (SUCRA, 96.2), followed by CBI (SUCRA, 83.8) and CRF (SUCRA, 66.4).
2. Effects of different corneal refractive surgeries on corneal biomechanical strength: The corneal biomechanical properties after SMILE surgery were compared with those after LASIK, laser-assisted subepithelial keratectomy, and FLEx. In the early postoperative period, no significant difference was noted between SMILE surgery and femtosecond laser-assisted LASIK groups ($P > 0.05$ for all). However, at 6 and 12 months, the CRF changes after SMILE surgery were less than after femtosecond laser-assisted LASIK (mean difference [MD], −0.51 [95% CI, −0.98 to −0.04; $P = 0.03$]; MD, −1.13 [95% CI, −1.36 to −0.9; $P < 0.001$]; respectively). In addition to CRF, SMILE surgery resulted in fewer CH decreases compared with LASIK (MD, −1.17 [95% CI, −1.45 to −0.89;

$P < 0.001$]). In the meta-analysis conducted by the GDG, SMILE surgery exhibited comparable biomechanical influence with that of laser-assisted subepithelial keratectomy ($P > 0.05$ for all) and FLEx ($P > 0.05$ for all).

3. Effects of different surgical plans on corneal biomechanical strength in KLEx: For the surgical design, the meta-analysis revealed that the lenticule thickness (LT) was correlated negatively with the postoperative DA ratio (1 mm; summary r, −0.45; $P < 0.001$), DA ratio (2 mm; summary r, −0.39; $P < 0.001$), and IR (summary r, −0.54; $P < 0.001$), whereas this was not the case for biomechanical-corrected intraocular pressure, SP-A1, or the stress−strain index ($P > 0.05$ for all). No significant differences were noted in postoperative CH among surgeries with different optical zones at 1 week, 1 month, and 3 months after surgery ($P > 0.05$ for all). However, the CRF change in the large optical zone group (≥ 6.5 mm) was significantly greater (MD, 0.58 [95% CI, 0.28−0.88; $P < 0.001$], 0.31 [95% CI, 0−0.62; $P = 0.05$], and 0.81 [95% CI, 0.35−1.27; $P < 0.001$] at 1 week, 1 month, and 3 months, respectively). As for the corneal cap, comparable biomechanical strength, indicated by A1T, A2T, biomechanical-corrected intraocular pressure, CH, CRF, deformation amplitude, DA ratio, IR, and peak distance, was observed between thicker (≥ 120 μm) and thinner ($P > 0.05$ all) caps.

Rationale.

1. Corneal biomechanical measurement improving the accuracy of keratoconus detection: No endorsed criteria exist for the identification of early keratoconus.[50] In the initial phase of keratoconus, a decrease in the focal elastic modulus is linked to the breakdown and degeneration of corneal collagen fibers, initiating a biomechanical decompensation cycle, where stress levels rise and redistribute, resulting in corneal steepening and thinning.[50] The current evidence emphasizes the important role of corneal biomechanical evaluation in the detection of keratoconus, especially in early and uncertain cases. To avoid false-negative findings resulting from a single index and to improve diagnostic accuracy, conducting preoperative keratoconus screening through a comprehensive assessment combining corneal tomography (such as Scheimpflug imaging or OCT) with biomechanic evaluation is recommended. The TBI, CBI, and CRF are promising corneal biomechanical indicators. The A1V and A2V currently are considered suboptimal biomechanical indices and require further investigations.
2. Corneal biomechanical properties as a key basis for selection of surgical options and planning of surgical protocol: The design of corneal refractive surgery mainly includes the selection of surgical options and the planning of surgical protocols. Compared with other surgeries, KLEx maximally preserves the structural integrity of the anterior cornea, which is helpful for maintaining corneal biomechanical stability.[13,16,51−53] Lenticule thickness, cap thickness, and optical zone diameter are important for KLEx planning. Based on the current evidence, different surgical plans manifested different influences on corneal biomechanical stability.[15] For example, lower thickness of removed lenticular tissue was associated with smaller biomechanical changes; a larger setting of the optical zone diameter led to a greater decrease in CRF, indicating a stronger reduction in biomechanical strength after KLEx and suggesting that the optical zone should not be expanded unreasonably. Thus, regarding parameter settings, aside from the consideration of corneal morphologic features, determining the effects of removed thickness, residual thickness, and the optical zone diameter on postoperative biomechanical strength also is necessary.
3. Corneal biomechanical assessment probably improving surgical predictability: The assessment of corneal biomechanical properties may help to improve the predictability of refractive outcomes. This was documented by Wang et al,[54] who showed that combining biomechanical indicators with corneal topographic parameters improved the predictability of KLEx by more than 25% from its original level. The predictive value of corneal biomechanics for KLEx also has been described in a few recent studies. For example, patients with less stiff corneas have been reported to have a 2-fold to 3-fold increased risk of residual refractive error after KLEx.[55] Enhancing surgical accuracy through the measurement of corneal biomechanics thus may hold significant value. Because of the limited time frame for evidence retrieval in the guidelines, more prospective investigations are warranted.

Domain 2: Surgical Planning and Technique

Clinical Question 2. Clinical question 2 investigated safe ranges of corneal thicknesses in surgical planning (central corneal thickness [CCT], cap thickness, maximum LT, and residual stromal thickness [RST]).

Recommendations. Recommendation 5: The calculation of the percentage of tissue altered (PTA) for such procedures mainly is based on the removed corneal tissue (LT) (evidence quality: C, conditional recommendation).

Recommendation 6: The exact cause leading to postoperative corneal ectasia remains unclear; however, when considering corneal thickness settings, an RST of ≥ 280 μm and LT index (ratio of maximum LT to CCT) of 28% or less could be used as reference values; caution should be taken when the RST is insufficient (< 280 μm), commonly seen in thin corneas (< 500 μm) and eyes with very high myopia (less than −9 diopters [D]); the procedure should be performed on the premise of much stricter preoperative screening and more diligent postoperative monitoring; given measurement error, an RST of less than 250 μm should not be allowed (evidence quality: C; strong recommendation).

Recommendation 7: As appropriate, surgeons could reduce the cap thickness to ensure a sufficient RST in surgical planning; however, an extremely thin corneal cap (< 100 μm) is not recommended (evidence quality: B; strong recommendation).

Summary of the Evidence.

1. Safety thresholds for removal and remaining of corneal tissue in KLex: The exact safety thresholds for corneal tissue removal and residual stroma in KLEx procedures remain unclear. From a corneal biomechanical view, as indicated by multiple measurements (DA ratio, IR, CH, and CRF), the weakening of corneal biomechanical properties after KLEx was more accelerated when the RST was low or the LT index was high.[56,57] Specifically, the postoperative variation in the DA ratio was much more dramatic with an RST of less than 280 μm or an LT index > 28%[56]; the variety rate of CH and CRF changes was much higher when the LT was > 140 μm, and this borderline 140-μm LT indicated a 28% LT index for a normally 500-μm cornea.[57] From the perspective of posterior corneal elevation, eyes with thinner corneas, higher myopia requiring greater LT, and a lower RST exhibited greater predispositions toward posterior protrusion[58]; the limited LT index (< 27%) showed no effect on the changes in posterior corneal elevation.[59] Two studies reported thresholds for preventing forward posterior corneal displacement of an LT index of 26.9% to 28.3% and an RST of 255.5 to 263.5 μm.[58,59] In consensus files published in 2016 and 2018, a planned RST of ≥ 280 μm was recommended conservatively and an RST of < 250 μm was not allowed.[60,61]
2. Effects of different thickness planning protocols on corneal stability: In the systematic review and meta-analysis conducted by the GDG, no intragroup differences were noted between thin and thick corneas or among different surgeries ($P > 0.05$ for all). For cap thickness, 10 corneal biomechanical parameters, including A1T, A2T, biomechanical-corrected intraocular pressure, CH, CRF, deformation amplitude, DA ratio, IR, peak distance, and SP-A1, all were comparable in thin cap groups (cap thickness, 100−120 μm) and thick cap groups (cap thickness, 130−160 μm; $P > 0.05$ for all).

Rationale.

1. Determination of safe residual stromal bed thickness over the corneal biomechanical and posterior corneal stability: Although a minimal RST (also known as residual bed thickness) of 250 μm is reported as the threshold for safe LASIK procedures,[62] determining the exact limit for corneal tissue removal remains an extremely critical clinical issue that requires more rigorous and objective exploration. For KLEx, literature suggests that the presence of the cap may lead to different biomechanical effects compared with LASIK on the cornea.[13,63] Regardless of whether the cap contributes to corneal biomechanical strength, the minimum RST for KLEx should not be < 250 μm, as supported by the evidence.[13,63] However, determining the exact threshold requires further evidence, including randomized controlled trials, longer-term observations, and experimental studies. In the extant literature, most studies reported that the weakening of corneal biomechanical properties after KLEx was much more accelerated with an RST of < 280 μm or an LT index of > 28%, indicated by multiple measurements such as DA ratio, CH, and CRF.[56,57] These are in accordance with consensus statements.[60,61] Given that iatrogenic keratectasia after refractive surgery may be attributed mainly to lowered corneal biomechanical strength below the level for maintaining corneal stability,[64] an LT index of 28% and an RST of 280 μm are the suggested thresholds for KLEx.

Observation of the posterior corneal surface further validated the aforementioned recommendations. Posterior corneal elevation is not only an early indicator of corneal ectasia, but also is a major factor representing corneal stability.[65−68] A forward shift in posterior elevation indicates cornea instability that predisposes patients to a high risk of ectasia.[69,70] The reported thresholds of the LT index and RST for preventing forward posterior corneal displacement were approximately 28% and 260 μm, respectively.[58,71]

2. Calculation of PTA for KLex and the biomechanical support of caps: The use of the PTA was proposed to determine the risk of ectasia after LASIK, defined as the sum of the ablation depth and the flap thickness divided by the CCT.[72] A PTA value of 40% of more was associated significantly with the development of corneal ectasia.[72] For KLEx, the controversy in PTA calculation lies in whether the corneal cap should be regarded as an altered tissue. If using cap thickness to replace the flap depth in the PTA formula, a cutoff value of 40% will never be practical for KLEx, because a large proportion of eyes (31.9%) had PTA of ≥ 40%, but no observed postsurgical ectasia at more than 3 years of follow-up.[73,74] Furthermore, a novel thickness planning protocol of increasing cap thickness to retain additional uncut stroma in the stronger anterior stromal fibers achieved good safety, with a minimum 220-μm RST and 300-μm total uncut stromal thickness.[8] These findings have been supported by mathematical models as well as finite element analysis[75−78] and have demonstrated that caps may provide a certain degree of biomechanical strength in corneas after KLEx, which might be an essential difference from LASIK.

Nonetheless, long-term observations in clinical practice and more studies are needed to clarify the contribution of the cap to corneal strength.

To determine the biomechanical differences between thin and thick caps further, the GDG conducted a meta-analysis and found that cap thickness has no robust effect on postoperative biomechanical strength. Surgeons thus could reduce the cap thickness appropriately to ensure preferentially an adequate RST in surgical planning. However, it must be noted that extremely thin corneal caps are not recommended.

3. Considerations for extreme cases: Performing laser ablation on thin corneas and correcting extremely high myopia remains challenging for surgeons, because such conditions indicate a very low RST, damage to corneal stability, and an increased risk of iatrogenic ectasia.[79] Although this important topic has been discussed in several studies in which KLEx has achieved relatively ideal outcomes in thin corneas (< 500 μm) and in cases of high myopia (less than −9 D), with the lowest RST of 250 μm, the absolute safety of KLEx in these cases has not been confirmed.[8,80,81] Because insufficient RST may accelerate disease progression as soon as postoperative ectasia has developed and may revert the effects of treatment, extra precaution is still needed for such conditions, including much stricter preoperative screening and more diligent postoperative monitoring.

Clinical Question 3. Clinical question 3 investigated the setting ranges of the optical zone.

Recommendations. Recommendation 8: Large optical zones may result in less undercorrection after surgery, especially in patients with high myopia, and small optical zones may increase the risk of refractive regression after surgery (evidence quality: D; conditional recommendation).

Recommendation 9: Larger optical zones are associated with fewer surgery-induced higher-order aberrations, and a large optical zone is recommended if the corneal thickness is sufficient (evidence quality: D; conditional recommendation).

Recommendation 10: Smaller optical zones have a smaller effect on postoperative corneal biomechanical strength (evidence quality: B; conditional recommendation).

Recommendation 11: For patients with thinner corneas or higher degrees of myopia, if the pupil size is small, an appropriate reduction in optical zone size (≥ 6.0 mm, except in exceptional cases) is recommended to prioritize adequate RST (Good Practice Statement; conditional recommendation).

Summary of the Evidence. The meta-analysis showed no significant differences in corrected distance visual acuity (CDVA) or spherical equivalent (SE) between a large optical zone group (6.5−6.8 mm) and a small optical zone group (6.0−6.4 mm) 3 months after surgery ($P > 0.05$ for both). However, the uncorrected visual acuity was significantly better in the large optical zone group than in the small optical zone group (MD, −0.08 [95% CI, −0.1 to −0.6; $P < 0.001$]). In terms of visual quality, the large optical zone group (≥ 6.5 mm) showed comparable total higher-order aberrations, spherical aberration, and trefoil with the small optical zone group (< 6.5 mm; $P > 0.05$ for all), with lower coma than the small optical zone group (MD, −0.03 [95% CI, −0.04 to −0.01; $P = 0.008$]). Moreover, postoperative changes in CRF in the large optical zone group (6.5−6.6 mm) were significantly greater than those in the small optical zone group (6.0−6.2 mm; MD, 0.81 [95% CI, 0.35−1.27; $P < 0.001$]).

Rationale. Patients with an insufficient surgical optical zone may be at increased risk of night vision disturbances, halos, or glare under certain circumstances, although more evidence-based support is needed. However, current literature suggests that the importance of pupil diameter is now considered to be less significant.[82,83] For KLEx, the optical zone diameter is generally set at 6 to 7 mm. A small optical zone may increase the risk of postoperative refractive regression.[84,85] For every 1-mm increase in optical zone diameter, the postoperative undercorrection decreased by 8.13% (0.39 D).[85] In a clinical trial supported by the United States Food and Drug Administration, a large optical zone increased patient satisfaction with night vision from 65% to 86%.[86] Other studies have reported that an optical zone exceeding the pupil size by 15% could reduce postoperative higher-order aberrations effectively, in which a 7-mm optical zone setting could achieve almost no increased higher-order aberrations for a myopia correction of −3.50 D. However, the association between these changes in higher-order aberrations and the subjective visual experience of patients has not been well estabilished.[87] A difference between the optical zone and the scotopic pupil size within 0.2 mm did not have an evident impact on visual quality.[88] Increasing the optical zone implies that more corneal tissue must be removed, which influences biomechanical stability.[89] This indicates that enlarging the optical zone may be not advisable in all patients. In fact, for surgical planning, the optical zone should be adjusted while considering refraction, corneal thickness, pupil size, and biomechanical properties to ensure safety and improve postoperative visual quality.

Clinical Question 4. Clinical question 4 investigated astigmatism correction ranges and auxiliary positioning technique.

Recommendations. Recommendation 12: To date, the correction of astigmatism ranges from −0.25 D to −5.00 D; the higher the target astigmatism, the weaker the effects of correction after surgery (evidence quality: B; conditional recommendation).

Recommendation 13: Correcting astigmatism with axis alignment and cyclotorsion compensation achieves better results after surgery than without the use of the auxiliary positioning technique; when a large cyclotorsion angle is present, corresponding compensation is recommended to minimize alignment error and to improve the accuracy of astigmatism correction (evidence quality: D; conditional recommendation).

Supplementary Information. The current axis alignment and cyclotorsion compensation methods for astigmatism correction mainly include limbal horizontal marking, triple centration, and the use of limbal vascular imaging-guided systems.

Summary of the Evidence. The reported factors affecting outcomes after astigmatism correction with KLEx technology include eye laterality, ocular residual astigmatism, corneal curvature, cap thickness, degree of ametropia, laser energy, cyclotorsion error, rinsing with a balanced salt solution, incision position, number of incisions, incision size, optical zone diameter, age, ablation ratio (defined as LT index herein), chosen surgery protocol for astigmatism correction, decentration, astigmatism type, and procedure learning curves. In our meta-analysis using the vector method, the corrective effects of KLEx were better in a low-astigmatism group (< 2.0 D) than in a high-astigmatism group (> 2.0 D); for example, higher postoperative residual astigmatism was found in the high-astigmatism group than in the low-astigmatism group (high group: effect size, −0.33 [95% CI, −0.42 to −0.23]; low group: effect size, −0.22 [95% CI, −0.26 to −0.17]). Cyclotorsion compensation significantly improved postoperative outcomes with lower indices of success (MD, −0.05 [95% CI, −0.08 to −0.03; $P < 0.001$]) and residual astigmatism (MD, −0.16 [95% CI, −0.27 to −0.05; $P = 0.004$]).

Rationale. Because of astigmatism's vectorial nature, both its magnitude and axial direction should be determined during surgical planning of laser procedures. For KLEx, the range of astigmatism correction approved by the United States Food and Drug Administration is up to −3.0 D (SMILE surgery), whereas the surgical device allows an astigmatic correction setting up to −5.0 D.[90] Because the astigmatism is examined in a sitting position before surgery and the surgery is performed with the patient lying down, this change in body position induces cyclotorsion and may reduce the surgical accuracy.[91−93] For these patients, compensating for cyclotorsion error to align the axis is essential for accurate correction of astigmatism.[94,95] This has been well described by the current evidence, in which cyclotorsion compensation such as limbal horizontal marking, triple centration, and using a limbal vascular imaging-guided system effectively minimize this axial shift and improve postoperative outcomes.[96−98] Given that accurate astigmatism correction is affected by multiple factors in addition to axis alignment, surgeons should customize surgical design based on comprehensive considerations.

In the guidelines, most included studies adopted technology without an eye-tracking system. For the latest technologies and equipment, such as those with automatic cyclotorsion compensation and automatic centration systems, currently evidence is limited because of its recent introduction. As time progresses, more evidence will be incorporated into the updated guidelines.

Clinical Question 5. Clinical question 5 investigated the relationship between decentration and postoperative visual quality.

Recommendations. Recommendation 14: The centration locations used in clinical practice are mainly the coaxially sighted corneal light reflex (CSCLR) and entrance pupil center (EPC); both approaches have been found to achieve acceptable postoperative outcomes. However, CSCLR-centered procedures might be associated with better postoperative visual acuity, lower residual refractive error, and fewer induced higher-order aberrations, particularly coma (evidence quality: D; strong recommendation).

Recommendation 15: Some decentration within 0.2 mm will not cause a significant decrease in postoperative visual acuity and quality; in some cases, decentration within 0.5 mm has little impact on postoperative vision. As the amount of decentration further increases, visual acuity and quality are affected, even with decreased vision quality and increased residual astigmatism; therefore, accurate centration is crucial for surgery (evidence quality: C; strong recommendation).

Recommendation 16: The presence of a large-angle κ value may lead to impaired postoperative visual acuity or visual quality; in this case, a corresponding adjusted centration is recommended during surgery to improve visual outcomes (evidence quality: B; strong recommendation).

Summary of the Evidence.

1. Comparison among centration strategies: In our meta-analysis, postoperative decentration was significantly less in a CSCLR-centered group than in an EPC-centered group (MD, −0.21 [95% CI, −0.33 to −0.09; $P < 0.001$]), and postoperative CDVA was significantly better in the CSCLR-centered group (MD, −0.13 [95% CI, −0.21 to −0.05; $P = 0.001$]), with no difference in uncorrected visual acuity and residual astigmatism ($P > 0.05$ for both). A further subgroup analysis showed that for myopic correction, the postoperative SE in the CSCLR-centered group was lower than that in the EPC-centered group (MD, −0.05 [95% CI, −0.10 to 0.00; $P = 0.04$]), whereas no significant difference was found between the groups for hyperopic correction ($P > 0.05$). Furthermore, the CSCLR-centered group included a higher proportion of eyes that achieved a target refractive error within 0.50 D (odds ratio, 1.49 [95% CI, 1.11−1.77; $P = 0.005$]) and showed less coma (MD, −0.06 [95% CI, −0.08 to −0.04; $P < 0.001$]) than the EPC-centered group.
2. Performance of centration in KLEx procedure: In our systematic review, good centration in KLEx could be achieved manually, and postoperative decentration was comparable with that of other flap-based surgeries and surface ablation techniques. Furthermore, some studies have demonstrated that individualized procedures, such as topography-guided LASIK, have less postoperative decentration than KLEx. Regarding the relationship between decentration after KLEx and postoperative visual quality, our systematic review showed that the cutoff for the modulation transfer function remained unaffected; however, residual astigmatism, total higher-order aberrations, spherical aberrations, and coma increased as decentration increased. Moreover, associations have been made between horizontal decentration and induced horizontal coma as

well as between large-angle κ value and increased decentration.

3. Tolerance to decentration in KLEx: Studies regarding tolerance to decentration in corneal refractive surgery have shown that (1) ensuring that the decentration distance does not exceed 0.2 mm is crucial for achieving good visual quality, (2) a small degree of decentration (0.5 mm) will not have a significant effect on postoperative refractive power, and (3) decentration of more than 0.6 mm may lead to impaired visual outcomes. For KLEx, 0.335 mm was reported as the cutoff for inducing obvious postoperative corneal aberrations, which is related to the optical zone size and aberration analysis diameter.

Rationale.

1. Ablation center for laser corneal refractive surgery: Centration in corneal refractive surgery long has sparked debate because of the cornea's multiple anatomic and optical centers with varying positions. The visual axis, defined as the line between the macula and the fixation point of the eye, theoretically intersects with the cornea at the optimal ablation center. However, it is challenging to determine this precise location clinically, often leading to the use of nearby markers such as the CSCLR, corneal apex, or EPC as ablation centers. The relationships among these centers are illustrated in Figure 2. The CSCLR is the image point formed by a point light source reflecting off the anterior corneal surface when the patient fixes their gaze on a coaxial fixation object. The line connecting the CSCLR with the light source (the optical axis of the laser device) intersects with the anterior corneal surface, and this intersection point is known as the corneal vertex. The CSCLR is the closest point to the visual axis ($<$ 0.02 mm), and it coincides with the vertex point when the fixation point is on the optical axis of the device (Fig 2). Because the position of the CSCLR is unaffected by changes in pupil size and the pupil center, it is considered an ideal ablation center for refractive surgery, commonly used to locate the visual axis.[99] The corneal apex is the highest point on the anterior surface of the cornea. In corneal topography, the corneal apex typically is used as a reference point for CSCLR. The EPC is the geometric center of the pupil. Because the pupil boundary can be determined easily, this method has been adopted most commonly for corneal refractive surgeries. However, the EPC has limited stability, because changes in light intensity or pupil dilation can lead to variations in pupil size, which may cause a shift in the position of the center.[100,101] The angle κ value is the angle between the visual axis and the pupillary axis, which is usually assessed as the angle between CSCLR and the EPC in clinical practice.
2. Difference between centration strategies: In the synthesis of the current evidence, although both CSCLR-centered and EPC-centered corneal refractive surgical approaches could achieve good efficacy and safety, the CSCLR-centered approach led to less decentration, better CDVA, lower SE, and less induced coma after surgery. In addition to subjective centration, some objective methods such as the triple marking centration method in KLEx surgery can reduce the possibility of decentered ablations and the induction of total higher-order aberration.[102]
3. Influence of angle κ value on centration and corresponding adjusting strategies: The angle κ value is a key factor that might affect the accuracy of different centration methods. In individuals with myopia, an angle κ value of $\leq$ 0.4 mm did not cause intraoperative decentered ablation, postoperative reduced vision, or increased residual refraction, whereas a large angle κ value was associated with more higher-order aberrations, with those of $>$ 0.6 mm potentially affecting postoperative visual performance.[103–105] In a modeling study, when the angle κ value was $<$ 5°, centration on the EPC was more effective, whereas when the angle κ value was $<$ 5°, centration on the CSCLR was more advantageous.[106] In the current evidence from refractive surgery, compensation for the angle κ value helped to optimize surgery and to improve surgical accuracy, and complete compensation was superior to incomplete compensation and resulted in fewer HOAs.[104,105,107–109] A typical example for angle κ value compensation is seen in preoperative corneal limbal marking to compensate for axial changes

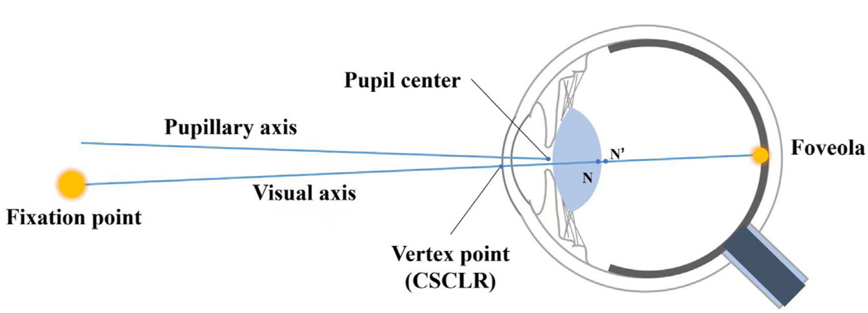

Figure 2. Diagram showing various ablation center markers of the cornea. CSCLR = coaxially sighted corneal light reflex.

(described in the rationale of clinical question 4 and during surgery adjusting the angle κ value; KLEx was shown to achieve equivalent correction in patients with high astigmatism when compared with wavefront-guided LASIK.[110] Given the complexity of visual quality and the fact that objective examination findings are sometimes inconsistent with subjective perception, owing to varying sensitivities among individuals, the effect of compensation for axial changes and the angle κ value for astigmatism correction on visual quality can be taken only for reference.

Clinical Question 6. Clinical question 6 investigated factors influencing the accuracy of preoperative refraction measurement.

Recommendations. Recommendation 17: Multiple factors can affect preoperative refraction, such as functional abnormalities (accommodation or binocular vision anomalies, visual fatigue, and inappropriate prescriptions for spectacles), organic diseases (nystagmus, strabismus, and corneal clarity), objective factors (optometrist experience), and subjective factors (repeatability of specific equipment), and all these factors are worth considering in preoperative refraction measurements (evidence quality: B; strong recommendation).

Recommendation 18: Accommodation is one of the most important factors affecting the precision of refraction measurement; the decision to perform a cycloplegic examination depends on a combination of factors, such as accommodative status and binocular visual function; when possible, cycloplegic refraction is recommended (evidence quality: B; strong recommendation).

Summary of the Evidence. Reported factors affecting the accuracy of refraction measurement include binocular vision and accommodative function; examination equipment, environment, and repeatability; professional quality, skill level, clinical experience, and reproducibility of the optometrist; and the cooperation level of the patient.

Rationale. Cycloplegic refraction, commonly known as mydriatic refraction, is the accepted gold standard for the diagnosis of myopia, because it eliminates the ocular accommodation induced by relaxation and contraction of the ciliary muscle and more closely reflects the true refractive status.[111] The optometric examination for corneal refractive surgery requires a precise determination of the magnitude and axis of existing astigmatism, which is commonly more stringent than those required for diagnosis and prescription spectacles. Accommodation is one of the most important factors that affects optometric accuracy. Because of the strong accommodative capabilities of the ciliary muscle in children, cycloplegic refraction is suggested. In adults, however, the change in refraction status after cycloplegia is small. Thus, in clinical decision-making, refraction examination with or without cycloplegia depends on multiple factors such as accommodative status and binocular vision function. It has been reported that optical fogging is effective to relax ocular accommodation.[112] This method may prevent further overestimation of myopia and underestimation of hyperopia in refractive examination.

Other factors influence refraction as well. Good binocular function can equate the accommodation stimuli of both eyes and minimize the accommodation response.[112] Mood swings, stress, and anxiety may affect brain function and cause changes in the ocular refractive status. In these cases, the refractive prescription should not be made, and psychological counseling or supportive psychotherapy is recommended.

Clinical Question 7. Clinical question 7 investigated factors related to nomograms and adjusting strategies.

Recommendations. Recommendation 19: Nomogram adjustment is an essential part of the laser surgery procedure that directly affects surgical precision and predictability; the major factor related to nomogram settings is preoperative SE (or simple spherical values), whereas others include age, eye laterality, corneal curvature, diameter, biomechanical properties, cap thickness, LT, CCT, RST, optical zone diameter, accommodation, and laser energy (evidence quality: B; strong recommendation).

Recommendation 20: The nomogram should be adjusted for multiple factors related to the patient, surgeon, and surgical environment; at present, adjusting strategies mainly include simple spherical and cylindrical modification, multivariable regression analysis, and artificial intelligence-based personalized adjustments (evidence quality: C; strong recommendation).

Summary of the Evidence.

1. Factors to be considered in nomogram settings: Reported factors associated with nomogram values include preoperative SE, spherical values, cylindrical values, astigmatism axis, uncorrected visual acuity, LT, cap thickness, RST, CCT, age, eye laterality, corneal diameter, optical zone diameter, corneal curvature, anisometropia, relative accommodation, and corneal biomechanical properties.
2. Strategies for nomogram adjustment: The current strategies to adjust nomogram values remain controversial. For spherical correction, previous studies applied a 10% overcorrected nomogram for low to moderate myopia, which yielded an average undercorrection of -0.09 ± 0.37 D after KLEx.[113] In comparison, 7% overcorrected nomograms showed better refractive outcomes for myopia of between -1.00 and -3.00 D, and 12% overcorrected nomograms were better for myopia of more than -7.00 D.[113] For astigmatism correction, an approximately 13% undercorrection has been observed in patients with low to moderate astigmatism (< 2.00 D), with 16% undercorrection in high astigmatism (> 2.00 D).[114] Alió et al[115] proposed that surgeons should increase nomogram values by 10% for the target cylinder treatment, especially in the presence of preoperative astigmatism of > 0.75 D. This 10% increased nomogram also has been recommended by Pedersen et al[116] and Ivarsen and Hjortdal.[114]

Rationale. The nomogram is a designed value generated by a precise analysis of a series of patient variables to improve surgical precision and to reduce the possible necessity for retreatment of refractive regression. Previous studies have determined the factors (described above) contributing to nomogram settings and reported improved predictability and excellent outcomes after nomogram-optimized KLEx; this provides crucial evidence for adjusting nomograms in surgical design and preventing undercorrection and overcorrection.[117,118] For the current KLEx procedure, an approximately 10% increase in nomogram values at the original refraction level might be required.[113,114,116] However, because of limited sample sizes and follow-up durations, further validation is needed for these results. For astigmatism correction, in addition to nomogram adjustments, standardizing the refraction process, manually compensating cyclotorsion error, and aligning the axis are noteworthy methods.[115] It should be noted that, although a nomogram adjustment is necessary, it cannot currently be predetermined in general for both sphere and cylinder because some surgical platforms have preadjusted nomogram. Differences between early-generation and latest-generation devices may be another important consideration because earlier instruments often led to more undercorrection, whereas the latest machines have adjusted their aims to address this issue. Future nomogram adjustment strategies should rely on effective algorithms and multimodal data from patients, and personalized nomograms must be updated constantly based on advancements in surgical techniques as well as the wide application of artificial intelligence.

Domain 3: Complications

Clinical Question 8. Clinical question 8 investigated the prevention and management of intraoperative adverse events (difficult lenticule dissection, wrong plane dissection and difficult lenticule removal, incision tearing, and cap perforation).

Recommendations. Recommendation 21 (preventive measures): Difficult lenticule dissection, improper laser energy, and severe OBL and black spots should be prevented and avoided. Additionally, inexperienced surgeons should avoid performing procedures on corneas with very low myopia or should increase the minimum LT as appropriate. To prevent wrong plane dissection, the upper and lower planes should be differentiated first at the incision site before lenticule dissection; surgeons also should be familiar with the signs of unintended posterior plane dissection and should make prompt corrections when detecting abnormalities. To prevent cap perforation or tears, excessively thin caps should be avoided, and surgeons should ensure good intraoperative fixation by requesting the patient's cooperation to avoid sudden eye movements (evidence quality: C; strong recommendation).

Recommendation 22 (management principles): The lenticule should be identified and dissected carefully; if the lenticule cannot be found, a relatively sharp dissector should be used to search for the edge of the lenticule, and the magnification of the microscope should be increased, or the built-in slit lamp should be used to identify the lenticule. OCT also can be applied when necessary; if the lenticule still cannot be found, the procedure should be postponed. In the event of cap perforations or tearing, the cornea must be tightly aligned, and a bandage contact lens is recommended (evidence quality: B; strong recommendation).

Summary of the Evidence. Common adverse events in the KLEx procedure include epithelial defects and abrasion at the incision site (incidence, 13.6% [95% CI, −0.035% to 0.306%]), OBL (incidence, 5.7% [95% CI, 0.042%−0.073%]), unintended posterior plane dissection and difficulty in identifying intrastromal lenticule (incidence, 5.5% [95% CI, −0.05% to 0.16%]), corneal epithelial damage (incidence, 2.8% [95% CI, 0.018%−0.037%]), interface debris (incidence, 2.8% [95% CI, −0.003% to 0.059%]), incision tearing (incidence, 2.6% [95% CI, 0.017%−0.035%]), difficult lenticule dissection (incidence, 2.2% [95% CI, 0.011−0.03]), lenticule decentration (incidence, 1% [95% CI, 0.001%−0.019%]), incisional or subconjunctival hemorrhage (incidence, 0.9% [95% CI, 0.005%−0.012%]), incomplete lenticule extraction (incidence, 0.9% [95% CI, 0.002%−0.016%]), cap perforation or tearing (incidence, 0.5% [95% CI, 0.002%−0.009%]), and lenticule tearing (incidence, 0.3% [95% CI, 0.002%−0.004%]).

Rationale.

1. Difficult lenticule dissection: Possible causes of difficult lenticule dissection and extraction include improper laser energy, black spots, or abnormal corneal tissue structures. Novice surgeons should avoid performing procedures for very low myopia. Because excessively thin corneal caps may increase the risk of difficult lenticule dissection, a cap thickness of 120 μm is recommended for surgical planning.[60,61] When dealing with difficult lenticule dissection, surgeons should be patient and exercise caution to avoid damage to the cap and lenticule while also ensuring a complete dissection of the lenticule edges. During dissection, excessive uptilting of the dissector should be avoided, and the dissection should be performed at a slow speed. In the event of lenticule dehiscence, the direction of dissection should be changed to avoid retained lenticules. The lenticule can be extracted using forceps or can be flushed out through irrigation. If uncertainty over the completeness of the extracted lenticule exists, the lenticule tissue should be distended to confirm its completeness, and the extraction should be repeated to remove any remnants. If the dissection is expected to be hard and tissue structures cannot be identified, postponement of procedure is recommended.
2. Wrong plane dissection and difficult lenticule removal: The main causes of unintended posterior plane dissection and difficult lenticule identification include excessively thin lenticules, surgeon inexperience, and abnormal dissection. The following management methods are recommended: (1) using a relatively sharp dissector to search for the edge of the lenticule, (2) increasing the magnification of the microscope or switching on the built-in slit lamp to

identify the lenticule, (3) using anterior segment OCT to measure corneal thickness and to observe traces from the laser scans to identify the lenticule, and (4) if the lenticule is still not identified, temporarily closing the incision, smoothing any dissected tissue, and returning it to its original position. After a few months, other surgeries can be performed, such as photorefractive keratectomy or femtosecond laser-assisted LASIK.[60,61] Patients should be given a trial with full spectacle correction to ensure that no diplopia caused by the partial residual lenticule is present before the surgical correction is attempted.

3. Cap perforations or tearing: Possible causes for cap perforations or tearing include excessively thin caps, excessively small incisions, and sudden eye movements. Furthermore, surgical instruments may perforate the corneal cap if it is very thin or in cases of difficult lenticule dissection. The recommended management principles are as follows: (1) minor tears at the edge of the incision should be smoothed and aligned with no special treatment needed; (2) more severe tears should be closed tightly to prevent epithelial ingrowth, and bandage contact lenses are suggested after the surgery if necessary; and (3), if the corneal epithelium is defective, it should be smoothed and returned to its original position at the end of the procedure, and bandage contact lenses are needed to prevent epithelial ingrowth.
4. Opaque bubble layer: Opaque bubble layer is caused by the accumulation of water vapor and carbon dioxide at the interlamellar space or extending deeper into the posterior corneal stroma. Its occurrence is associated with the stability of the laser procedure platform. Thus, the recommended temperature and humidity of the operating room are 18° to 25° C and 30% to 70%, respectively. Severe OBL indicates that the laser energy setting is too high and needs adjustment. Furthermore, excessively thin corneal caps are prone to OBL; at this point, a cap thickness of 120 μm might be recommended. The prevention and management principles include the following: (1) lenticule dissection should be performed with great caution and care; (2) excessively sharp instruments and excessive force should be avoided to prevent dissection in the wrong plane; (3) unnecessary manipulations should be minimized to prevent excessive tissue disruption, which would delay postoperative recovery; and (4) care should be taken regarding lenticule remnants when OBL appears at the edge of the lenticule.

Clinical Question 9. Clinical question 9 investigated prevention and management of suction loss.

Recommendations. Recommendation 23 (preventive measures): Before surgery, patient education and fixation training should be reinforced; during the procedure, the patient's head and eye positions should be adjusted appropriately, and patients should be instructed to remain relaxed and to maintain fixation; during suction, conjunctival tissue trapping and excess water on the ocular surface and conjunctival sac should be avoided, factors that may distract the patient's attention should be eliminated, and the laser scanning mode should be modified by increasing spot and track separation to shorten the operative time (evidence quality: A; strong recommendation).

Recommendation 24 (management principles): If suction loss occurs during laser scanning at the periphery of the lower lenticule plane (< 10%), the original parameters should be retained, and redocking and reinitiating the procedure should be performed; if at the near-central region (> 10%) or central region of the lower plane, KLEx should be rescheduled or converted to other procedures. For suction loss during the side cut, redocking and reinitiation should be performed with the option to increase the incision depth (e.g., 10 μm) or decrease the lenticule diameter (e.g., 0.2 mm). For suction loss during upper scanning (cap cutting) and incision creation, the original parameters should be retained, followed by redocking and continuing with the procedure; experienced surgeons could create the incision manually (evidence quality: B; strong recommendation).

Summary of the Evidence. The overall incidence of suction loss is 0.5% (95% CI, 0.004%−0.006%). The reported risk factors for suction loss include patient anxiety, eyelid squeezing, Bell reflex, poor fixation, conjunctival ingress, eye pain, sudden intraoperative head or eye movements, excessive secretions (e.g., oil) or water on the ocular surface, surgeon inexperience, small corneal diameter, excessively large cap diameter, and conjunctivochalasis.

Rationale. Based on the known causes and risk factors for suction loss, preventive measures should be adopted to avoid such events, including patient education and intraoperative specifications. Because suction loss may occur during any stage of the surgical procedure (with an incidence during laser cutting at the periphery of the lower lenticule plane [< 10%], near or at the central region of the lower plane [10−100%], during the side cut, at the cap cut, and during incision creation accounting for 10%, 25%, 5%, 45%, and 15%, respectively) different management strategies are recommended at different stages.[119] These recommendations are applicable mainly to SMILE surgery, but maybe not be relevant for other surgical platforms, such as cornea lenticule extraction for advanced refractive correction, when a lenticule cannot be recut after suction loss.[120] Regardless of the technology, the management principles are to minimize interference in the central optical zone, reduce repeated laser scanning, and avoid false paths or abnormal separation caused by multilayer scanning.

Clinical Question 10. Clinical question 10 investigated prevention and management of black spots.

Recommendations. Recommendation 25 (preventive principles): Prevention is primary, including strict adherence to patient selection, maintenance of a clean and properly humidified ocular surface and suction ring and patient interface, avoidance of repeated suction procedures, selection of appropriate laser energy (not too low) and scanning modes, and avoidance of abnormal laser output (evidence quality: B; strong recommendation).

Recommendation 26 (management principles): For small or peripheral black spots in the nonoptical zone, the procedure should be continued with cautious dissection; for larger black spots, the procedure should be suspended, and the causes should be determined. When necessary, reschedule the procedure or convert to other surgeries (evidence quality: B; strong recommendation).

Summary of the Evidence. The overall incidence of black spots is 0.3% (95% CI, 0.001%−0.004%). Factors contributing to this include laser settings (e.g., energy and spot spacing), secretions on the ocular surface (e.g., oil), repeated suctioning, residual dust on the suction ring surface or laser emission port, and surgeon inexperience.

Rationale. Black spots refer to points where the femtosecond laser fails to produce effective cutting action on the corneal tissue during KLEx. Insufficient energy is a risk factor for black spots. As reported in the literature, the risk of black spots increased by 18% with a 5-nJ reduction of laser energy.[121] The main strategy for managing black spots is prevention, such as strict preoperative screening to exclude corneal opacities, an appropriate laser energy and scanning mode, and regular maintenance and cleaning of the equipment. For small or peripheral black spots, careful dissection is recommended to avoid fragmentation of the lenticule or upper corneal tissue.[25,28] For large black spots, the procedure should be postponed to a later date or converted to another surgery type.[28]

Clinical Question 11. Clinical question 11 investigated prevention and management of retained lenticule fragments.

Recommendations. Recommendation 27 (prevention measures): Standard surgical procedures are recommended; before surgery, laser energy, surgery-related parameters, and temperature and humidity of the operating room should be set; after lenticule extraction, complete removal must be confirmed. After surgery, physicians should be vigilant for symptoms indicating retained lenticule fragments, such as poor visual acuity, severe irregular astigmatism, or abnormal corneal topography (evidence quality: B; strong recommendation).

Recommendation 28 (management principles): When retained lenticular tissue is discovered, it should be removed thoroughly, especially when in the optical zone; the minimal residual tissue in the peripheral areas that does not affect visual acuity can be followed up (evidence quality: B; strong recommendation).

Summary of the Evidence. The overall incidence of 0.3% (95% CI, 0.001%−0.005%) for retained lenticule fragments is relatively low. In our systematic review, related factors included thin lenticules, inappropriate laser energy and cutting mode, black spot development, surgeon experience, patient cooperation, corneal stroma opacity, and irregular corneal astigmatism.

Rationale. Retained lenticule fragments are attributed to lenticular tearing or incomplete extraction resulting from a thin lenticule, inappropriate laser energy settings, or nonstandard surgical procedures.[60,61] Inexperienced surgeons should avoid procedures in patients with very low myopia, should increase the lenticule substrate thickness or enlarge the optical zone, and should dissect the lenticule during the procedure carefully and adequately. Furthermore, because more stromal bridge-like connections will create more dissection resistance, optimal laser energy and scanning cutting parameter settings (such as spot and line space) are recommended. When uncertain about the completeness of the removed lenticule, the extracted tissue should be examined for confirmation. If any residual fragments remain, a repeat extraction should be performed. For cases where identification is difficult, masked removal should be avoided. To prevent irreversible medical hazards, rescheduling the procedure or converting to other surgeries is recommended. After surgery, surgeons should be vigilant for symptoms related to retained lenticule fragments. As soon as retained tissue is discovered, especially in the optical zone, it should be removed in principle. If only a very small strip of tissue remains at the periphery (e.g., length of 1−2 mm and width of < 1 mm) outside the optical zone, it can be observed and followed up at the surgeon's discretion. However, because large, retained fragments may cause elevations in the corneal surface and increased curvature, even if the patient's vision is not affected, visual quality may have been affected. Thus, as much of this retained tissue as possible should be removed. Finally, microsurgical skills are required for lenticule dissection and extraction.

Clinical Question 12. Clinical question 12 investigated prevention and management of perioperative infections.

Recommendations. Recommendation 29 (preventive measures): Before surgery, surgeons should follow surgical indications strictly, should administer antimicrobial drugs prophylactically, and should treat and control actively ocular surface diseases that may predispose patients to infection. During surgery, they should comply with aseptic practices strictly and avoid excessive manipulation. After surgery, they should pay attention to ocular hygiene, administer drugs rationally with close follow-up, and attempt to detect and treat any infections promptly (evidence quality: B; strong recommendation).

Recommendation 30 (management principles): Physicians should identify the cause and the pathogen as early as possible and adopt anti-infection measures and practice rational administration of drugs to alleviate inflammatory reactions. If the infection is uncontrollable, the incision should be enlarged or opened as soon as possible, and the lesion should be removed in the intrastromal pocket followed by rinsing the pocket with antibiotics (evidence quality: A; strong recommendation).

Summary of Evidence. The overall incidence of perioperative infections is 0.1% (95% CI, 0%−0.002%). The main contributing factors include excessive intraoperative manipulation, keratoconjunctivitis, blepharitis, dacryocystitis, entropion, trichiasis, corneal epithelial defects caused by long-term wear of contact lenses, dry eyes, or inappropriate use of antibiotics and glucocorticoids.

Rationale. Perioperative infection is a serious complication after corneal refractive surgery despite its exceptionally low incidence. Because an open corneal flap is not created in KLEx procedures, the infection can spread rapidly within a relatively enclosed pocket, and it is difficult to administer topical medication directly to the lesion, making treatment more challenging. For the management of infection, prevention is primary, and the key anti-infection measure is based on pathogen identification and differentiation. For example, bacterial infections have a rapid onset, usually within 1 to 3 days after surgery.[122–125] However, nontuberculous mycobacterial infection can have an onset as late as 1 week after surgery.[126,127] Broad-spectrum antibiotics usually are used for empirical treatment, with fluoroquinolone or aminoglycoside eye drops preferred, and 5% cefazolin eye drops can be added for suspected *Staphylococcus* infection. Fungal infection usually has a slow onset and a long course of development, which is difficult to control with drugs and may require a surgical intervention.[128] Viral infection is cryptic and usually occurs in combination with bacterial or other infections; it should be suspected when empirical antibacterial treatment is ineffective.[129]

The principles of perioperative infection treatment are to identify the cause quickly, to control the infection actively, and to alleviate the inflammatory response. If empirical treatment is ineffective, the incision should be opened as soon as possible, and the corneal pocket should be rinsed with antibiotics. For severe cases, continuous rinsing of the ocular surface or corneal cross-linking for infectious keratitis such as photoactivated chromophore corneal cross-linking can be performed (except for viral infections) to reduce the bacterial load. For cases with a cap damaged by a large ulcer, excision of the cap is recommended. If the infection causes corneal perforation, then penetrating keratoplasty is required.

Clinical Question 13. Clinical question 13 investigated prevention and management of postoperative diffuse lamellar keratitis.

Recommendations. Recommendation 31 (preventive measures): Before surgery, the external eye should be examined carefully, the operative eye should be strictly cleaned and disinfected, disinfection methods for medical apparatus and instruments should be improved, and residual disinfectant should be avoided. During the procedure, physicians should select and set an appropriate laser energy, improve surgical skills with gentle operative manipulation, avoid repeated insertion and removal of instruments, change the incision position to prevent bleeding if necessary, and should avoid oil and tear accumulation. After surgery, prophylactic glucocorticoids should be applied, with regular follow-up (evidence quality: B; strong recommendation).

Recommendation 32 (treatment principles): First, infection should be differentiated from inflammation, and routine local treatments should be applied, combined medications or interlamellar steroid rinsing should be used for patients with severe symptoms, and caution should be taken for interlamellar rinsing in late-onset and atypical cases (evidence quality: A; strong recommendation).

Summary of Evidence. The overall incidence of DLK is 0.84% (95% CI, 0–0.03%), with an incidence of stage I, II, III, and IV DLK of 1.42% (95% CI, 0–0.04%), 0.29% (95% CI, 0–0.01%), 0.08% (95% CI, 0–0.01%), and 0.02% (95% CI, 0–0.01%), respectively. Related factors and causes for DLK are listed as follows: before surgery, meibomian gland secretions, dry eye, meibomian gland dysfunction, inadequate sterilization of surgical instruments, and soaking and washing surgical instruments with multienzyme detergents; during surgery, excessively high laser energy, epithelial defects, chemical substances, glove talcum powder, irrigation fluid, insufficient conjunctival sac irrigation, oily secretions, metal fragments, bacterial endotoxins, thin lenticules or larger optical zones, repeated suction, longer lenticule dissection durations, repeated operative manipulations, and lack of interlamellar rinsing. Furthermore, DLK can be caused by trauma.

Rationale. Diffuse lamellar keratitis commonly is characterized by noninfectious diffuse cellular infiltration beneath the corneal cap, manifesting as small white granular turbidity.[130,131] It is often observed within 1 week after surgery; in the current synthesis of evidence, it was most common on the first day and occurred 1 month after surgery when combined with interlamellar corneal vacuolation, whereas trauma-related cases were reported with an onset of as late as 4 years later.[132,133] For the treatment of typical DLK, the continuous use of local glucocorticoid drugs has been suggested, such as prednisolone acetate once every hour, tobramycin dexamethasone 6 to 8 times daily, or fluorometholone 6 to 8 times daily; for severe symptoms, oral steroids can be used, and the dosage can be reduced gradually as symptoms improve. For DLK grade II and higher, early high-dose glucocorticoid therapy should be administered, and interlamellar rinsing should be used when necessary to prevent the formation of corneal scars that can affect visual acuity and quality. Severe DLK, such as grade IV, requires steroid interlamellar rinsing. For atypical cases, the treatment is basically the same as that for typical ones, with local or systemic glucocorticoids.[134]

Appropriate treatment of DLK results in good outcomes. The lesions improve within 1 week with resolved intrastromal inflammatory reactions in most cases, and symptoms improve completely in approximately 3 weeks. Visual acuity is not affected for most patients with DLK grades I through III. However, the recovery time is longer, and the prognosis may be worse in patients with atypical and severe cases. For example, in 1 patient with trauma-induced DLK, vision began to recover after treatment for 2 weeks and stabilized after 15 months, with residual corneal scars.[130] In patients with multifocal DLK, vision had recovered 6 months after treatment, and infiltration of both eyes regressed successfully,[130,135] whereas the recovery of vision in atypical concentric ring DLK remained unsatisfactory at 5 months.[134]

Clinical Question 14. Clinical question 14 investigated the causes, prevention, and treatment principles of delayed visual recovery and poor visual acuity after surgery.

Recommendations. Recommendation 33 (causes): Individual differences among patients, the occurrence of various intraoperative conditions, excessive manipulation, and poor laser stability can induce early postoperative corneal edema and healing reactions (evidence quality: A; strong recommendation).

Recommendation 34 (preventive measures): Before surgery, surgical protocols must be planned carefully, especially for older patients and those with high myopia or unstable visual function. During surgery, laser energy must be set appropriately, and excessively thin caps and excessive corneal manipulation should be avoided (evidence quality: A; strong recommendation).

Recommendation 35 (treatment principles): Visual acuity often improves gradually over time and with the subsiding of tissue edema. Corticosteroid or nonsteroidal anti-inflammatory eye drops should be used in cases with obvious corneal edema. Visual function training should be provided to patients with abnormal visual function; if their vision does not recover for a prolonged period with the identified cause of residual postoperative refractive error, enhancement surgery can be performed after ensuring a stable refraction status (evidence quality: A; strong recommendation).

Summary of Evidence. The overall incidence of delayed visual recovery and poor visual acuity is 1.5% (95% CI, 0.004%−0.026%). Possible reasons for delayed visual recovery and poor visual acuity in the early postoperative period are as follows. (1) Patient-related factors such as older age, high myopia, eye fatigue, dry eye, and individual differences can lead to this; high myopia may be associated with a higher incidence of refractive regression resulting from postoperative overgrowth of the corneal epithelium. (2) Intraoperative parameter settings such as laser energy, incision size, and cap thickness also can cause delayed recovery. Higher laser energy can cause inflammatory reactions, leading to poor visual recovery. Excessively thin caps may result in a high risk of OBL and may impair visual recovery. Smoother lenticules lead to better visual recovery. As the incision size is reduced, corneal stability may increase and the epithelium may heal rapidly, which helps in faster visual recovery. (3) Intraoperative adverse events such as black spots, loss of suction, interface debris, and incision tears also can impede recovery and can impair visual acuity. Crude manipulations during lenticule dissection and removal may cause stromal edema. Incision tearing increases damage to the surrounding stromal tissue. Lenticule decentration can lead to poor visual outcomes.

Rationale. For the prevention of delayed visual recovery and poor visual acuity, preoperative optometric examinations should be avoided with unstable refractive status and during eye fatigue. Surgical techniques should be improved to reduce intraoperative corneal damage. For surgical planning, optimal parameter settings are beneficial for improving postoperative vision. After surgery, changes in refractive status should be followed up closely with the option of visual function training for suitable individuals. In cases of residual refractive error, an enhancement surgery could be considered. For enhancement options, besides surface ablation, surgeons can create a corneal flap using a femtosecond laser at the original cap plane and can proceed with enhancement surgery using the excimer laser.[60,61] During the procedure, cap fitting and repositioning can reduce the pocket gap, which can reduce microfolds and can facilitate visual recovery.[136] Another option is thin-flap femtosecond LASIK, which creates a new flap on the original cap, but only for cases in which a thick cap was created during the original procedure.[137]

Clinical Question 15. Clinical question 15 investigated early diagnosis, prevention, and management of postoperative corneal ectasia.

Recommendations. Recommendation 36 (early diagnosis): For suspected postoperative corneal ectasia with visual decline and newly detected refractive errors, surgeons should examine and monitor the corneal thickness and posterior corneal elevation promptly with a close follow-up; early identification of postoperative ectasia is similar to that for subclinical or forme fruste keratoconus (described in Recommendation 1) (evidence quality: B; strong recommendation).

Recommendation 37 (preventive measures): Surgeons should avoid performing procedures on corneas with abnormal morphologic features with a close follow-up; after surgery, patients should avoid eye rubbing, and physicians should pay attention to changes in posterior corneal elevation and evaluate long-term safety (evidence quality: B; strong recommendation).

Recommendation 38 (treatment principles): For corneal ectasia with a definite diagnosis with signs of progression and visual decline, timely interventions such as corneal cross-linking are recommended to halt disease progression; rigid contact lens can be used to improve vision (evidence quality: B; strong recommendation).

Summary of Evidence. In a systematic review,[26] the global incidence of corneal ectasia following KLEx was 0.02%. Among these cases, approximately 30% were found within 1 year after surgery, and approximately 70% occurred within 2 years. No concentrated distribution was found in age, SE, or corneal thickness, indicating that ectasia after KLEx can occur in all age groups (< 20 years, 20−30 years, 30−40 years, and > 40 years), all degrees of myopia (low, moderate, and high), and with any corneal thickness (< 510 μm, 510−550 μm, and > 550 μm). No significant differences were found between sexes (male:female, 4:3). Further analysis showed that 65.5% of patients showed suspicious or abnormal preoperative corneal topography, and 52.3% of patients had an RST of < 280 μm. In 3 studies (6 eyes)[138−140] reporting preoperative corneal biomechanical data, all eyes had a CBI of > 0.5, and 4 eyes (66.7%) had a TBI of > 0.29. All patients underwent corneal cross-linking treatment, after which a CDVA of 20/20 or better was achieved in 9 patients (45%) and a CDVA of 20/25 or better was achieved in 13 patients (59.1%).

Rationale.

1. Predictors for postoperative ectasia: Corneal ectasia is one of the most severe complications after corneal refractive surgery.[26] Although abnormal preoperative corneal topography and insufficient RST have been identified as the two most important contributing factors for corneal ectasia after LASIK,[140,141] the risk factors after KLEx remain unclear. In the current evidence, suspicious corneal topography was defined using the criteria of Brar et al[140]: (1) Orbscan (Bausch & Lomb, Orbtek Inc.) criteria: irregularity index > 1.5 within 3 mm and > 2.5 within 5 mm, ratio of

preoperative to postoperative best fit sphere > 1.21; (2) Pentacam (Oculus GmbH) criteria: Belin−Ambrósio enhanced ectasia total deviation index > 1.65. For ectasia detection after KLEx, the sensitivity of abnormal corneal topography and RST as an independent risk factor did not exceed 70%, suggesting that the risk of postoperative ectasia cannot be predicted by a single characteristic or indicator; instead, it may require a comprehensive evaluation combined with multimodal data from patients. Furthermore, according to the criteria of Brar et al,[140] the biomechanical criteria for suspicious eyes were defined as (1) CBI > 0.5 and (2) TBI > 0.29. Preliminary results (described above) showed that corneal biomechanical evaluation may be an effective way to prevent postoperative corneal ectasia.

2. Management and treatment of ectasia after KLex: Given that a significant proportion of cases of ectasia after KLEx develop > 2 years after surgery, long-term follow-up and monitoring are recommended to ensure long-term safety after surgery. For treatment, corneal cross-linking currently is recommended in a timely manner to prevent disease progression. Different forms have been reported in the literature such as conventional corneal cross-linking, pocket cross-linking, and accelerated cross-linking.[26] Uncorrected visual acuity can be improved by wearing rigid corneal contact lenses.

Discussion

Concerns about the safety and efficacy of KLEx surgery have been expressed, and to the best of our knowledge, these are the first evidence-based guidelines for KLEx surgery. In strict accordance with WHO guideline formulation specifications and international standards, the guideline working group surveyed frontline surgeons and experts, investigated patient preferences and values, determined the 15 most important clinical questions from 385 collected questions, reviewed 250 717 studies from 15 databases and websites, built a cumulative body of evidence with 609 studies, conducted 26 systematic reviews and updated 2 systematic reviews, and proposed 38 detailed recommendations covering preoperative, intraoperative, and postoperative key points in KLEx surgery; of them, 29 are considered strong. The present guidelines possess strengths and uniqueness when compared with existing consensus documents because of the application of evidence-based methods. The comprehensive retrieval strategy used to identify the largest number of relevant studies possible laid a foundation for the credibility of the guidelines. The GRADE system and the Delphi consensus method gave this process transparency and efficiency. Each recommendation was based on published literature and was reviewed externally by physicians, methodologists, legal advisers, and patients, and feedback was received from target audiences and end users. Applying these recommendations does not need much resource input except for treatment instruments in clinical use, training, and health care professionals involved in this surgery.

The guidelines offer evidence-based solutions to long-standing clinical dilemmas, such as the permissible range of refractive correction, parameter adjustment for optimization, and the prevention and management of complications. These recommendations are crucial for improving the learning curves for inexperienced surgeons and minimizing surgical risks for patients. Additionally, the development of these guidelines revealed several gaps in research aimed at enhancing the safety of KLEx. These improvements could involve establishing preoperative screening criteria for suspected keratoconus, defining safety thresholds for corneal tissue removal and retention, and accurately predicting and assessing the risk of postoperative ectasia. Well-designed, high-quality research exploring the potential of corneal biomechanics may address these issues effectively. Furthermore, large-scale studies in a clinical setting that integrate multiple disciplines and leverage advanced technologies, including artificial intelligence and big data, will highlight new insights and will aid in surgical advancement. Because most of the included evidence was gathered through a comprehensive literature search and the recommendations were developed by experts from various regions of the world with multispecialty and regional representation, the guidelines are expected to be helpful to eye care providers globally in ensuring the safety and efficacy of KLEx procedures.

The term *KLEx* refers to a type of corneal refractive surgery, rather than being specific to any commercial brand or any particular device. The significance of the recommendations lies in their reliable evidence and emphasis on surgical principles and operative specifications, aimed at improving applications. From this perspective, the present guidelines are applicable to nearly all lenticule extraction procedures. Given the differences between various technologies and devices, the guidelines used SMILE surgery technology as a typical example to propose effective recommendations for managing complications such as suction loss, because it has been used widely for a relatively long time. With the development of future advanced devices, KLEx surgery is expected to mature and new recommendations will be incorporated in updated guidelines. Meanwhile, with the growing adoption of evidence-based practices among surgeons, these high-quality evidence-based guidelines will be needed urgently. A pared-down version of the guidelines and recommendations may be helpful for use in clinical settings.

There are some limitations to these guidelines. First, although 76% of the recommendations were deemed strong, some remained weak because of the novelty of this technique, highlighting the necessity of more direct and high-quality evidence. Second, the comprehensive effect of surgery results from various factors, each with distinct limitations across different clinical scenarios. Therefore, evidence-based conclusions may not be applicable universally, yet they offer valuable insights for clinical practice. Third, KLEx is still an evolving technique, and our understanding of it remains somewhat limited because of its relatively short clinical application history. Although these guidelines are based on the best available evidence to date, their conclusions may not be definitive and may require further investigation and validation. The evidence search was conducted through May 2023, implying that some studies were not included such as on corneal biomechanics (e.g., SMILE surgery has a comparable corneal biomechanical influence as LASIK).[142] Future updates to the guidelines will incorporate new studies to supplement and refine the findings.

In summary, these inaugural evidence-based guidelines for KLEx surgery systematically elaborate on many aspects of candidate selection, quality control, protocol optimization, risk aversion, and complication management. Its broad applicability aims to provide a reference for KLEx in clinical practice, improving safe and effective implementation. As further studies emerge and our understanding of the surgical principles deepens, the guidelines will undergo continuous refinement. It is important to note that these guidelines were developed entirely based on existing literature and published data. They are not legally binding and are not intended for commercial promotion or publicity. Their primary objectives are to enhance surgical quality and to maximize patient benefit.

Acknowledgment

The authors thank all the members who participated in developing the guidelines and all the reviewers for their comments on the guidelines; Wenjuan Wan, Wenbo Cheng, Jing Li, and Jie Hou for clinical question collection; Yongji Liu for figure production; Haohan Zou for seminar organization; Mingdong Zhang, Yuting Tang, and Shuangcheng Li for literature retrieval and evidence evaluation; and Meixuan Li and Yanfei Li for manuscript revision.

Footnotes and Disclosures

Originally received: April 2, 2024.
Final revision: November 13, 2024.
Accepted: November 14, 2024.
Available online: November 21, 2024. Manuscript no. OPHTHA-D-24-00663.

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Disclosure(s):

All authors have completed and submitted the ICMJE disclosures form.

The author(s) have made the following disclosure(s):

S.G.: Consultant, Lecturer, and Financial and nonfinancial support − Carl Zeiss Meditec

Supported by the National Natural Science Foundation of China (grant no.: 82271118); the National Program on Key Research Project of China (grant no.: 2022YFC2404502); and Tianjin Key Medical Discipline (Specialty) Construction Project (grant no.: TJYXZDXK-016A). The funding organizations had no role in the design or conduct of this research.

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HUMAN SUBJECTS: No human subjects were included in this study. The study was deemed exempt from human subjects' research by the Institutional Review Board. All research adhered to the tenets of the Declaration of Helsinki. The requirement for informed consent was waived because of the retrospective nature of the study.

No animal subjects were included in this study.

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Abbreviations and Acronyms:

ARTh = Ambrósio relational thickness to the horizontal profile; **A1T** = the first applanation time; **A1V** = the first applanation velocity; **A2T** = the second applanation time; **A2V** = the second applanation velocity; **CBI** = Corvis biomechanical index; **CCT** = central corneal thickness; **CDVA** = corrected distance visual acuity; **CH** = corneal hysteresis; **CI** = confidence interval; **CRF** = corneal resistance factor; **CSCLR** = coaxially sighted corneal light reflex; **D** = diopter; **DA ratio** = ratio between the deformation amplitude at the apex and at 1 mm from the corneal apex; **DLK** = diffuse lamellar keratitis; **EPC** = entrance pupil center; **FLEx** = femtosecond lenticule extraction; **GDG** = guideline development group; **GRADE** = Grading of Recommendations Assessment, Development, and Evaluation; **IR** = integrated radius; **KLEx** = keratorefractive lenticule extraction; **LT** = lenticule thickness; **MD** = mean difference; **OBL** = opaque bubble layer; **PTA** = percentage of tissue altered; **RST** = residual stromal thickness; **SE** = spherical equivalent; **SMILE** = small-incision lenticule extraction; **SP-A1** = stiffness parameter at the first applanation; **SUCRA** = surface under the cumulative ranking curve; **TBI** = tomographic and biomechanical index; **WHO** = World Health Organization.

Keywords:
Complication, Corneal biomechanics, Refractive surgery, Keratorefractive lenticule extraction, Small-incision lenticule extraction.

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