



Division of Dockets Management Staff (HFA-105)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 208552

**RE: Docket No. FDA-2022-D-1253: Laser-Assisted In Situ Keratomileusis Lasers—
Patient Labeling Recommendations; Draft Guidance for Industry and Food and
Drug Administration Staff**

The American Academy of Ophthalmology, as the world's largest association of eye physicians protects sight and empowers lives by setting the standards for ophthalmic education and advocating for our patients, appreciates the opportunity to comment upon the draft *Laser-Assisted In Situ Keratomileusis (LASIK) Lasers - Patient Labeling Recommendations Draft Guidance for Industry and Food and Drug Administration Staff*.

We deeply appreciate and understand the motivation and regulatory requirement for FDA to protect patient safety and to promote public health. We share that goal of protecting patient safety and providing treatments to meet public health needs, while responsibly meeting patient demand for elective procedures. In general, we are concerned about three major themes in the draft guidance:

- 1) The checklist appears to be duplicative of already existing informed consent
- 2) Although LASIK has been approved as safe and effective, the balance of the statement is heavily tilted toward potential harms and risks, which does not inform patients well as they try to accurately assess relative risk and benefit in their situation.
- 3) Wherever possible all statements must be evidence-based and have appropriate references

We would very much like to continue to be engaged with the FDA in working to address these issues in a way that meets the need for public information without overburdening and duplicating the responsibilities of the physician.

Existing Informed Consent Practices:

The Academy believes that education about the benefits and risks of LASIK should be and is already routinely being provided within the setting of the physician and patient relationship. Indeed, as per the Academy's Code of Ethics¹, the physician is responsible for obtaining informed consent from the patient in all cases, and thoroughly explaining the benefits and risks of a surgical procedure.

"Informed Consent. Informed consent is the process of shared decision-making between the ophthalmologist and the patient and must precede the performance of medical or surgical procedures. During the informed consent process, pertinent medical and surgical facts, and recommendations consistent with standard of care in medical/surgical practice must be presented in understandable terms to the patient or patient surrogate. Such information should include the indications, benefits, objectives, risks and possible complications of the procedure, alternatives

to the procedure, and the potential consequences of no treatment. The operating ophthalmologist must personally confirm comprehension of this information with the patient or patient surrogate.”

The 2022 Academy’s Refractive Surgery Preferred Practice Pattern® Guideline² has the following section on informed consent:

“Informed Consent”

Although there is a high probability of successful outcomes for keratorefractive surgery, care should be taken to discuss adverse events or complications that may occur and explain which may be transient and which may be permanent. The patient should be informed of the risks, benefits, and alternatives to the different refractive procedures prior to surgery. The informed consent process should be documented, and the patient should be given an opportunity to have all their questions answered before surgery. The surgeon is responsible for ensuring that the patient provides his or her informed consent.^{6,7} Elements of the discussion may include the following:

- ◆ Range of expected refractive outcomes
- ◆ Residual refractive error
- ◆ Reading and/or distance correction postoperatively
- ◆ Loss of or change to uncorrected habitual near vision in myopes
- ◆ Monovision advantages and disadvantages (for patients of presbyopic age)
- ◆ Loss of BCVA
- ◆ Side effects and complications (e.g., microbial keratitis, sterile keratitis, keratoectasia)
- ◆ Changes in visual function not necessarily measured by visual acuity testing, including glare and function under low-light conditions
- ◆ Night-vision symptoms (e.g., glare, haloes) developing or worsening. Careful consideration should be given to this issue for patients with high degrees of ametropia or for individuals who require a high level of visual function in low-light conditions.
- ◆ Effect on ocular alignment
- ◆ Development or exacerbation of dry eye symptoms, neuralgia
- ◆ Recurrent corneal erosion syndrome
- ◆ Possibility that it may influence predictive accuracy of IOL calculations for subsequent cataract surgery
- ◆ Postoperative care plans (setting of care, providers of care)

The Ophthalmic Mutual Insurance Company (OMIC) provides a comprehensive informed consent form for the patient to review and sign in English and in Spanish (<https://www.omic.com/lasik-consent-forms/>).³ This informed consent form is utilized by many ophthalmic practices participating in OMIC to discuss the risks and benefits with their patients.

The Academy encourages the FDA to work with us, as well as other key stakeholders, to eliminate rather than create duplicative activities given the existing guidelines and well-crafted informed consent forms available for patients.

Tone and Balance:

A goal of the document is to aid patients in assessing the risks and benefits of LASIK. However, the general tone and content of the document is focused on the risks and contraindications to LASIK surgery, but the general safety and effectiveness of LASIK is not fully described for the public. The 2016 Modern laser in situ keratomileusis outcomes review of 97 articles concluded the following results⁴: percentage of eyes with uncorrected

distance visual acuity was 99.5%, spherical equivalent refraction was within target refraction of ± 1.0 diopter in 98.6% eyes.

The Patient-Reported Outcomes with LASIK (PROWL) Study⁵ found high rates of satisfaction:

“While most participants were satisfied, the rates of dissatisfaction with vision ranged from 1% (95% CI, 0%-4%) to 4% (95% CI, 2%-7%), and the rates of dissatisfaction with surgery ranged from 1% (95% CI, 0%-4%) to 2% (95% CI, 1%-5%).”

The U.S. military has been and continues to be one of the largest providers of refractive surgery in the country. Studies have described the safety and effectiveness of LASIK in terms of night vision, night driving, flight performance and firing performance.⁶⁻¹⁰ A 2021 study found that both wavefront-guided and wavefront-optimized LASIK provided excellent visual outcomes and were similar to prior reports performed in the military.¹¹

The Academy Refractive Surgery PPP also describes the results of PROWL⁵ as well as a more recent study of 1,800 patients with LASIK and contact lenses, which also found high rates of satisfaction and no increase in night driving difficulty or dry eye symptoms¹²

“The FDA-conducted PROWL studies addressed many of these concerns. Most participants were satisfied with their postoperative vision and surgery; the rates of dissatisfaction with vision ranged from 1% to 4% and the rates of dissatisfaction with surgery ranged from 1% to 2%. Overall, visual and dry eye symptoms decreased with time, although 43% in the PROWL-1 study and 46% in the PROWL-2 study reported new symptoms at 3 months, such as glare and halos. Of those participants who reported visual symptoms at baseline, 46% in the PROWL-1 study and 34% in the PROWL-2 study reported no visual symptoms at 3 months. Double images were the most common complaint to resolve in both studies. With respect to the significance of these visual symptoms, difficulty performing usual activities was reported by less than 1% of the participants in each study.¹⁷⁵

A recent 3-year prospective multicenter survey was conducted on 1800 subjects from age 16 to 60 years to compare contact lens wear with LASIK. The subjects included the control group of 694 (39%) who continued contact lens wear, LASIK group 1 of 819 (45%) wore contacts at baseline and had LASIK, and LASIK group 2 of 287 (16%) wore eyeglasses at baseline and had LASIK. The study found that patients from both LASIK groups (88% group 1, 77% group 2) had greater satisfaction than the control contact lens group (54%) during the 3-year survey period. The LASIK groups did not report a higher rate of night driving difficulty nor a significant increase in dry eye symptoms.²³⁸

The effectiveness of LASIK was described in the Academy’s 2022 Refractive Surgery PPP³, which was based on systematic reviews in the literature and expert consensus, as well as wide review from many related organizations, and included the results of the PROWL Study.²

“Results”

A systematic review of 64 studies of LASIK published since 2000 found 17 studies that reported that 75% to 100% (median, 92%) of eyes with myopia or myopic astigmatism were within 1.00 D of the intended correction. Low to moderate myopia were corrected with a greater degree of predictability than higher degrees of myopia.¹⁶⁴ A study with 10-year follow-up of patients who received LASIK for less than 10.00 D of myopia reported that 73% of eyes were within 1.00 D of the

expected correction and 54.6% of eyes demonstrated an increase in BSCVA.¹⁶⁵ Based on data from 22 studies, the systematic review reported that 94% of eyes had a postoperative UCVA of 20/40 or better. Uncorrected visual acuity of 20/40 or better was achieved in 94% to 100% (median, 98%) of eyes with low to moderate myopia, and in 76% to 97% (median, 89%) of eyes with high myopia. In three studies of myopic astigmatism, 94% to 100% (median, 99%) of eyes achieved UCVA of 20/40 or better. In 25 studies that reported eyes with a loss of two or more lines of BCVA from pre-LASIK values, a median rate of 0.6% (range 0% to 3%) of eyes with myopia or myopic astigmatism lost two or more lines of BCVA.⁴⁰

Laser in situ keratomileusis for hyperopia (preoperative refraction, 0.50 to 6.00 D of hyperopia) was reported to achieve within 1.00 D of the intended refraction in 86% to 91% (median, 88%) of eyes.⁴⁰ In hyperopic eyes, 94% to 100% had a postoperative UCVA of 20/40 or better. For eyes with hyperopic astigmatism, 88% to 89% (median, 88%) were within 1.00 D of the intended correction and 94% had UCVA of 20/40 or better.⁴⁰ A systematic review of LASIK found two studies of eyes with hyperopia or hyperopic astigmatism, and in these reports 2% to 5% (median, 3%) lost two or more lines of BCVA.⁴⁰

Hyperopic LASIK (H-LASIK) has also been used successfully to treat overcorrected myopic LASIK.¹⁶⁶ A study¹⁶⁷ of H-LASIK and H-PRK reported that they were comparable in efficacy and safety for low to moderate hyperopia. However, H-PRK was associated with more postoperative pain, an initial and temporary myopic overcorrection, and delayed refractive stability compared with H-LASIK.

LASIK is associated with more regression in hyperopic procedures than in myopic procedures.¹⁶⁸⁻¹⁷⁰ The mechanisms of H-LASIK regression are not clearly defined, but epithelial hyperplasia and potential biomechanical causes may contribute. Apparent regression after refractive surgery can be due to a natural age-related hyperopic shift, or to the emergence of residual or incompletely treated hyperopia as latent hyperopia becomes manifest.¹⁷¹

As with myopic LASIK, many of the more serious complications of H-LASIK are associated with the creation of the corneal flap. Most microkeratomes are capable of making the larger flaps needed for hyperopic corrections, but thin flaps may be more difficult to create and larger flaps can be associated with more bleeding if limbal vascularization is present.^{172, 173} There is a greater rate of loss of BCVA reported following H-PRK and H-LASIK compared with myopic corrections.⁴⁰ In one study of LASIK for mixed astigmatism, 95% of eyes were within 1.00 D of the intended postoperative refraction and 94% had postoperative UCVA of 20/40 or better.¹⁷⁴

In 2017, the Patient-Reported Outcomes with LASIK (PROWL) studies in the FDA's LASIK Quality of Life Collaboration Project revealed that at 3 months 99% of patients in PROWL-1 (Navy personnel) and 96% of patients in PROWL-2 (general population) had binocular UCVA of 20/20 or better. One eye of the 262 military patients in PROWL-1 and no eyes of the 312 civilian patients in PROWL-2 lost two or more lines of BCVA at 3 months. No eyes had BCVA worse than 20/40 nor more than a 2.00 D increase in cylinder.¹⁷⁵ The Patient-Reported Outcomes with LASIK Symptoms and Satisfaction (PROWL-SS) and Scoring Guide is available from the Academy. (<https://www.aaopt.org/prowl-ss>)”

Evidence Base:

It is important that whenever possible the statements made in the draft guidance must be evidence-based, and if not, marked otherwise for the public's benefit. The Academy has additional detailed edits for the statements and statistics provided in the draft guidance. However, instead of providing suggested line by line revisions of the guidance as is, we urge the FDA to take a step back and reconsider, given that informed consent processes already exist to communicate to patients in a comprehensive and balanced manner, as noted above.

An example of an important issue that is lacking an up-to-date evidence base in the draft guidance is the listing of pupil size as a risk factor for complications. The issue of pupil size has been well studied, and there is little justification to cite it as one of "other things that may increase your risk of LASIK complications" (Precautions) in Table 1 of the draft LASIK – Patient Labeling Recommendations when exhaustive study has indicated that pupil size is in fact not a relevant feature. The Academy's 2022 Refractive Surgery PPP³ concludes the following:

"The data from published studies fail to demonstrate a relationship between pupil size and the quality of postoperative vision. Most studies of conventional and wavefront-guided laser in situ keratomileusis (LASIK) have not shown a relationship between the diameter of the low-light pupil and disturbing visual symptoms postoperatively.⁹⁻¹⁴ Thus, the importance of pupillometry in the preoperative workup remains controversial.⁹ A benefit of more complex aspheric ablations relative to conventional ablations may be found under low-light conditions when the pupil is dilated, because this is when a reduction, or less induction, of high order aberrations (HOAs), particularly spherical aberration, should be most apparent. Some studies comparing conventional and wavefront-guided LASIK have reported fewer postoperative complaints of glare or halo under mesopic conditions with wavefront-guided procedures.^{15, 16} Irrespective of pupil size, it is important for potential patients to understand that there is a risk for night-vision problems after surgery."

Similarly, the Academy's Refractive Surgery PPP³ also lists the contraindications and indications for surgery, which do not include pupil size below, and could possibly be adopted by FDA:

"Contraindications

- ◆ Unstable refraction
- ◆ Abnormalities of the cornea (e.g., keratoconus or other corneal ectasias, thinning, edema, interstitial or neurotrophic keratitis, extensive vascularization)
- ◆ Insufficient corneal thickness for the proposed ablation depth
- ◆ Visually significant cataract
- ◆ Uncontrolled glaucoma
- ◆ Uncontrolled external disease (e.g., blepharitis, dry eye syndrome, atopy/allergy)
- ◆ Uncontrolled autoimmune or other immune-mediated disease
- ◆ Uncontrolled mental illness, including anxiety or depression.
- ◆ Unrealistic patient expectations

Relative Contraindications

- ◆ Functional monocular vision
- ◆ Ocular conditions that limit visual function, such that correction of refractive error would not improve visual function
- ◆ Excessively steep or flat corneas
- ◆ Abnormal corneal topography/tomography indicating possible keratoconus
- ◆ Significant irregular astigmatism

- ◆ Visually significant corneal stromal or endothelial dystrophies
- ◆ History of herpes simplex virus (HSV) or varicella zoster virus keratitis
- ◆ Inadequately controlled dry eye
- ◆ Glaucoma⁵⁹
- ◆ History of uveitis⁶⁰
- ◆ Diabetes mellitus⁶¹
- ◆ Pregnancy or lactation⁶²
- ◆ Autoimmune or other immune-mediated diseases⁶³
- ◆ Certain systemic medications (e.g., isotretinoin, amiodarone, sumatriptan, levonorgestrel implants, colchicine)
- ◆ Age under 21 years (FDA labeling should be consulted for each laser platform)”

The Academy believes an informed patient is a better, more satisfied patient. To that end, the Academy provides extensive educational resources to both ophthalmologists and their patients, including:

- The Academy partnered with the U.S. Food and Drug Administration 10 years ago to produce this patient guide to refractive surgery: [Is LASIK For Me? A Patient's Guide to Refractive Surgery](#)
- The Academy's EyeSmart® program provides the public with the most trusted information about eye health, including vision correction surgeries such as LASIK: [Questions to Ask When Considering LASIK](#)
- The Academy offers [guidelines](#) to assist ophthalmologists in providing, informative advertising for refractive surgery.

The Academy has an extensive record of collaboration with the FDA, and we hope to continue to partner with the FDA on important public health issues. We look forward to further dialogue to accomplish our and FDA's intent to educate the public about LASIK advantages and disadvantages in an evidence-based and balanced approach. Please feel free to contact Scott Haber, Director of Public Health Advocacy, at shaber@aao.org or via phone in the Academy's Washington DC office at 202-737-6662 if we can be of assistance.

Sincerely,



Stephen D. McLeod, MD
 CEO
 American Academy of Ophthalmology

References:

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