September 2022

evolve medical education

A CE activity administered by Evolve Medical Education LLC.
This activity is supported by an unrestricted educational grant from Dompé.

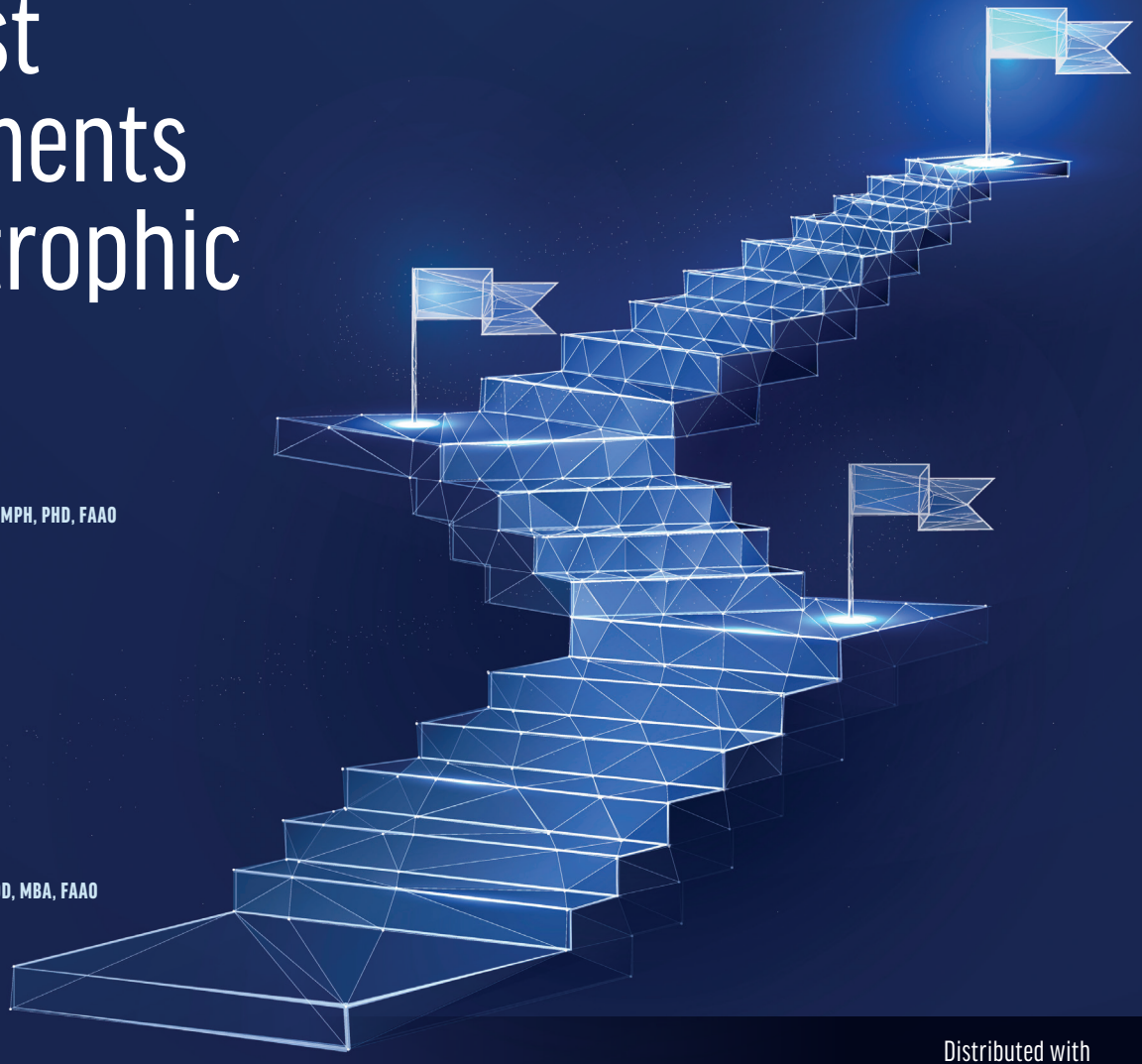
Sponsored by
UAB SCHOOL OF OPTOMETRY
The University of Alabama at Birmingham

# A Step Forward: The Latest Developments in Neurotrophic Keratitis

KELLY K. NICHOLS, OD, MPH, PHD, FAAO
PROGRAM CHAIR

FRANCIS S. MAH, MD

WALTER O. WHITLEY, OD, MBA, FAAO



Distributed with
MODERNOPTOMETRY

COPE Release Date: September 1, 2022
COPE Expiration Date: September 30, 2023

# A Step Forward: The Latest Developments in Neurotrophic Keratitis


## Faculty

**Kelly K. Nichols, OD, MPH, PhD, FAAO**
Program Chair
Dean, School of Optometry
University of Alabama at Birmingham
Birmingham, AL

**Francis S. Mah, MD**
Director of Corneal and External Disease
Co-Director of Refractive Surgery
Scripps Clinic
La Jolla, CA

**Walter O. Whitley, OD, MBA, FAAO**
Director of Professional Relations and Education
Virginia Eye Consultants
Norfolk, VA


## Content Source

This continuing education (CE) activity captures content from a live virtual symposium.

## Activity Description

Neurotrophic keratitis (NK) is a rare, degenerative corneal disease characterized by decreased or absent corneal sensation, which can lead to epithelial breakdown, impairment of healing, and ultimately to the development of corneal ulceration, melting, and perforation. Trigeminal nerve damage causes this loss of corneal sensitivity. The well-known faculty summarizes the best approaches to diagnosing NK and the latest information on classifying the condition, plus advancements in treatment.

## Target Audience

This certified CE activity is designed for optometrists.

## Learning Objectives

Upon completion of this activity, the participant should be able to:

- **Summarize** the etiologies of neurotrophic keratitis (NK) and how to differentiate it from similar diseases
- **Recognize** the newly proposed stages of NK
- **Describe** the stepwise approach to therapy and determine when to refer patients
- **Review** clinical data on new and emerging treatments for NK

## Grantor Statement


This activity is supported by an unrestricted educational grant from Dompé.


## Accreditation Statement

Evolve is a COPE-accredited administrator.

This activity, COPE Activity Number 124429, is accredited by COPE for continuing education for optometrists. This course is approved for 1.25 hours of CE.

Course #79489-TD
Activity #124429

## To Obtain Credit

To obtain credit for this activity, you must read the activity in its entirety and complete the Pretest/Posttest/Activity Evaluation/Satisfaction Measures Form, which consists of a series of multiple-choice questions. To answer these questions online and receive real-time results, please visit https://evolvemeded.com/course/2221-supp. Upon completing the activity and self-assessment test, your certificate will be available. Alternatively, please complete the Posttest/Activity Evaluation/Satisfaction Form and mail or fax to Evolve Medical Education LLC, 353 West Lancaster Avenue, Second Floor, Wayne, PA 19087; Fax: (215) 933-3950.

## Disclosure Policy

It is the policy of Evolve that faculty and other individuals who are in the position to control the content of this activity disclose any real or apparent financial relationships relating to the topics of this educational activity. Evolve has full policies in place that will identify and mitigate all financial relationships prior to this educational activity.

The following faculty/staff members have the following financial relationships with ineligible companies:

**Francis S. Mah, MD,** has had a financial agreement or affiliation during the past year with the following ineligible companies in the form of *Consultant*: Alcon, Allergan/AbbVie, Dompé, Johnson & Johnson Vision, Kiova, Novartis, Santen, and Sun Pharmaceutical Industries. *Speaker's Bureau:* Dompé, Johnson & Johnson Vision, Santen, Sun Pharmaceutical Industries, and Tarsus Pharmaceuticals.

**Kelly K. Nichols, OD, MPH, PhD, FAAO,** has had a financial relationship or affiliation with the following ineligible companies in the form of *Consultant*: Aerie Pharmaceuticals, Allergan/AbbVie, Axim, Bausch + Lomb, Bruder Healthcare, Dompé, HanAll Bio, Kala Pharmaceuticals, Novartis, Osmotica/RVL, Oyster Point Pharma, Sight Sciences, Tarsus Pharmaceuticals, Tear Film Innovations/Alcon, TearSolutions, Thea,TopiVert, Visionology, and YuYu Pharma. *Grant/Research*: Allergan, Kala Pharmaceuticals, and Tear Science.

**Walter O. Whitley, OD, MBA, FAAO,** has had a financial agreement or affiliation with the following ineligible companies in the form of *Consultant*: Aerie Pharmaceuticals, Alcon Vision, Allergan/AbbVie, Astareal, Bausch + Lomb, Bruder Healthcare, BMC, Dompé, Eyevance, Heru, Horizon Therapeutics, Johnson & Johnson Vision, Kala Pharmaceuticals, Novartis, Oyster Point Pharma, Quidel, RegenerEyes, RVL Pharmaceuticals, ScienceBased Health, Sun Pharmaceutical Industries, Tarsus Pharmaceuticals, ThermaMEDx, and Visus. *Speaker's Bureau:* Aerie Pharmaceuticals, Alcon Vision, Allergan/AbbVie, Bausch + Lomb, Kala Pharmaceuticals, Oyster Point Pharma, ScienceBased Health, and Sun Pharmaceutical Industries. *Share/Stockholder:* MediPrint Pharma.

## Editorial Support Disclosures

The Evolve staff, planners, reviewer, and writers have no financial relationships with ineligible companies.

## Off-Label Statement

This educational activity may contain discussion of published and/or investigational uses of agents that are not indicated by the FDA. The opinions expressed in the educational activity are those of the faculty. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

## Disclaimer

The views and opinions expressed in this educational activity are those of the faculty and do not necessarily represent the views of Evolve, *Modern Optometry*, or Dompé.

## Digital Edition

To view the online version of the material, log in to your Evolve account and go to https://evolvemeded.com/course/2221-supp or scan the QR code with your smartphone's camera.

To view the webinars associated with this supplement, log in to your Evolve account and go to: https://evolvemeded.com/course-group/a-stepwise-approach-to-recognizing-and-managing-neurotrophic-keratitis.

# PRETEST QUESTIONS

Please complete prior to accessing the material and submit with Posttest/Activity Evaluation/Satisfaction Measures for credit.

**1. Please rate your confidence in your ability to describe the stepwise approach to neurotrophic keratitis (NK) therapy and determine when to refer patients (based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).**

a. 1
b. 2
c. 3
d. 4
e. 5

**2. Endogenous nerve growth factor helps preserve and restore the ocular surface by which of the following mechanisms?**

a. Strengthening tight junctions between epithelial cells to enhance corneal epithelial barrier functions
b. Providing nutrition to conjunctival goblet cells and eyelid tear glands in order to increase tear production and improve tear quality
c. Stimulating limbal stem cells to generate new epithelial cells.
d. Increasing tear production at the lacrimal gland, stimulating nerve regeneration, and supporting epithelial cell proliferation and differentiation

**3. A 54-year-old patient presents to your office for routine evaluation. He is a contact lens wearer with a history of visually significant cataracts, severe primary open-angle glaucoma on maximal medical drop therapy, and dry eye disease (DED). On exam, you note loss of corneal sensation bilaterally and diagnose him with NK. All of the following conditions may have led to his condition, EXCEPT:**

a. DED
b. Contact lens-related disorders
c. Cataracts
d. Topical drug toxicity

**4. All of the following statements about NK are true, EXCEPT:**

a. NK is a degenerative corneal disease
b. NK results from damage to cranial nerve VII
c. NK results in loss of corneal sensation
d. NK causes impaired corneal healing

**5. Corneal innervation is essential for good epithelial health. How do corneal nerves maintain a healthy corneal surface?**

a. Provide stromal, epithelial, and Bowman's structural support
b. Maintain sensory functions that are essential to tear film maintenance
c. Facilitate protective functions of blinking and tear production as well as trophic support
d. Provide key nutrients to the epithelium while also serving as a physical barrier to microbes

**6. A 69-year-old man presents to your office for routine eye examination. He has a history of LASIK OU. On slit lamp examination, you note an inferior, oval-shaped corneal epithelial defect with smooth and rolled edges. However, the patient does not report any pain. What is the next best diagnostic step to aid in this patient's diagnosis?**

a. Dilated fundus examination
b. Corneal sensitivity testing
c. Corneal pachymetry
d. Corneal hysteresis measurement

**7. A 56-year-old patient presents to your office with evidence of NK. On exam, you note a persistent oval-shaped epithelial defect with smooth, rolled edges and stromal haze. According to the Mackie Severity Classification, what stage of NK does this patient have?**

a. Stage 1
b. Stage 2
c. Stage 3
d. Stage 4

**8. All of the following are examples of QUALITATIVE corneal sensitivity testing, EXCEPT:**

a. Cotton swab testing
b. Cotton wisp testing
c. Cochet-Bonnet esthesiometer
d. Dental floss testing

**9. What is a benefit of the proposed new 7-step clinical staging system for NK?**

a. To allow for earlier diagnosis of NK
b. To differentiate between NK and infectious keratitis
c. To determine which patients with NK need surgical therapy
d. To determine systemic risk factors for NK

**10. A 79-year-old patient presents to your office for routine evaluation. Slit lamp examination reveals a normal anterior segment examination. Corneal sensation testing reveals absent corneal sensation. According to the staging system proposed by the NK Study Group, what stage of NK does this patient have?**

a. Stage 0
b. Stage 1
c. Stage 2
d. Stage 3

**11. A 46-year-old contact lens wearer presents to your office for routine examination. On exam, you note diffuse punctate epitheliopathy with no other significant findings on slit lamp exam and dilated fundus exam. What test might determine whether this patient has NK or DED?**

a. Tear film breakup time
b. Meibography
c. Corneal sensitivity testing
d. Schirmer testing

**12. The Mackie Neurotrophic Keratitis Classification System breaks NK into three stages. Recently, the Neurotrophic Keratitis Study Group has developed a new 7-step staging system. The purpose for this new system is:**

a. To replace an outdated system
b. To allow for more accurate monitoring of progression of the disease as well as delineate which patients may respond well to particular therapies and evaluate response to treatment
c. To better educate patients about their disease and help them understand the prognosis and possible consequences of the condition
d. To determine which patients need amniotic membrane grafting

**13. You are evaluating a patient in your office with stage 2 NK. All of the following treatments are reasonable therapies for this patient, EXCEPT:**

a. Amniotic membrane
b. Scleral lens
c. rhNGF
d. Keratoplasty

**14. NK is a rare disease with fewer than _____ affected in the United States.**

a. 25,000
b. 65,000
c. 105,000
d. 250,000

# A STEP FORWARD: THE LATEST DEVELOPMENTS IN NEUROTROPHIC KERATITIS

*Neurotrophic keratitis (NK) is a degenerative corneal disease caused by damage to the trigeminal nerve.[1] Patients have decreased or no corneal sensation, which results in corneal epithelium breakdown, poor corneal healing, and the eventual development of corneal ulceration, melting, and perforation if left untreated.[1] Due to the desensitization of the corneal nerves, patients don't experience pain and are likely unware of their disease beyond minor complaints of vision fluctuation. It is therefore critical that eye care clinicians are proactive in screening for, recognizing, and managing NK. Until 2017, there was no specific treatment for NK. That changed with the Food and Drug Administration (FDA) approval of cenegermin. As our experience with cenegermin has deepened, new data on long-term efficacy has also emerged. A modern-day NK classification system has been proposed that outlines the clinical signs and symptoms of early stage disease, empowering clinicians to intervene early on in the disease process when NK is most treatable. The following content summarizes a presentation by experts in NK who discussed clinical evidence on how to differentiate NK from other masquerading ocular surface diseases (OSDs) as well as pearls on diagnosis and management.*

**— Kelly K. Nichols, OD, MPH, PhD, FAAO, Program Chair**

## AN INTRODUCTION TO NEUROTROPHIC KERATITIS

**Dr. Nichols:** NK is considered an orphan disease, which allows new treatments to advance through the FDA approval process a bit more rapidly.[2] Prevalence is difficult to estimate, and estimations are largely based on other conditions that have NK associated with them. As of right now, we say that there are fewer than 65,000 cases in the United States.[3] Some conditions that are associated with NK include herpes simplex keratitis and herpes zoster. About 6% and 12% of patients with herpes simplex and zoster, respectively, will develop NK.[3] With zoster, specifically, you'll see some postsurgical nerve damage. It's important to note that some of these conditions can overlap making NK much worse.

In terms of differential diagnosis, it's important to focus on pain and not stain. NK affects the nerves of the eye, and patients experience a loss of corneal sensation. Their clinical presentation may not match their pain level.[1-3] That is very different from neuropathic pain, in which a patient has excessive pain with no clinical signs, like corneal staining.

NK is a degenerative corneal disease where there's damage to the trigeminal nerve, cranial nerve 5, and the loss of corneal sensation, which, through feedback loop and regulation of the ocular surface, results in a breakdown of corneal epithelium. It can then impact the stroma. You can have stromal melting and a persistent epithelial defect that doesn't seem to clear or keeps returning.[1]

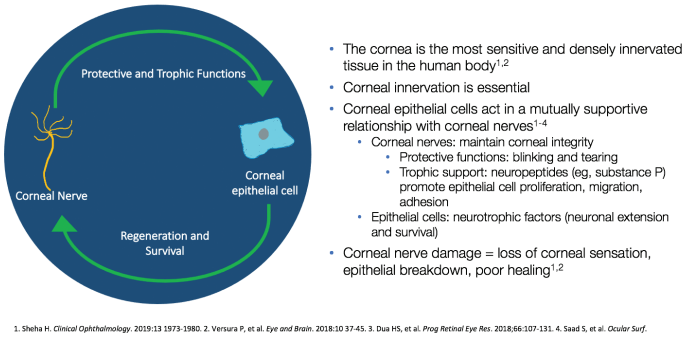



**Figure 1. Corneal innervation.[2-5]**

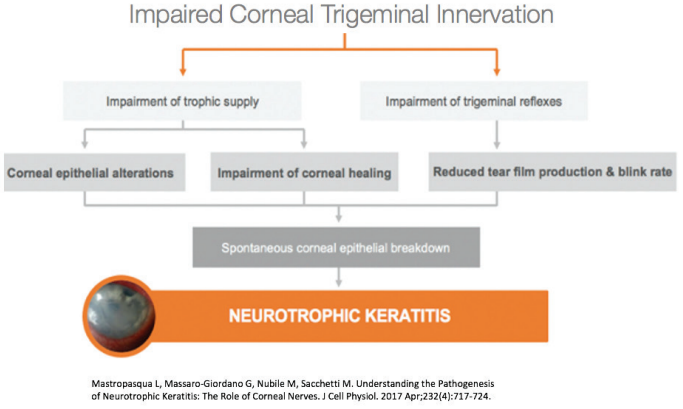



**Figure 2. Nerve malfunction is central to NK.[1]**

Figure 1 illustrates the feedback loop. When the nerves are damaged, the feedback loop is broken, and the system slowly unravels. There are protective and trophic functions of nerves beyond just sensation that support the epithelial cells and their growth, regeneration, and survival. With a loss of sensation, the cells stop communicating.[2-5]

There are also factors associated with neuropeptides, like substance P, that are released when the corneal nerves are normal. This is part of the feedback loop that results in epithelial cell proliferation and migration, allowing them to communicate and touch one another. Blinking also occurs through the nerves, and normal corneal innervation patterns keep the ocular surface healthy. Any breakdown, even if it slowly occurs over time, causes

**TABLE 1. NK ETIOLOGY[2]**

| INFECTIOUS | TOXIC | IATROGENIC | SYSTEMIC DISEASE |
|---|---|---|---|
| • Herpes (simplex, zoster)<br>• Leprosy | • Chemical burns<br>• Carbon disulfide exposure<br>• Hydrogen sulfide exposure | • Trauma to ciliary nerves by laser treatment and surgery<br>• Corneal incisions<br>• LASIK | • Diabetes<br>• Multiple sclerosis<br>• Vitamin A deficiency |
| **TOPICAL MEDICATIONS** | **FIFTH-NERVE PALSY** | **CORNEAL DYSTROPHIES** | **OTHER** |
| • Anesthetics (abuse)<br>• Timolol<br>• Betaxolol<br>• Sulfacetamide<br>• Diclofenac sodium<br>• Ketorolac | • Trigeminal neuralgia surgery<br>• Neoplasia (acoustic neuroma)<br>• Aneurysms<br>• Facial trauma<br>• Congenital<br>• Riley-Day syndrome<br>• Goldenhar-Gorlin syndrome<br>• Möbius syndrome<br>• Familial corneal hypesthesia | • Lattice<br>• Granular | • Contact lenses<br>• Increasing age<br>• Dark eye color<br>• Adie syndrome<br>• Limbal stem cell failure (chronic) |

this to worsen with poor healing.[1] Figure 2 shows how impaired corneal trigeminal innervation leads to NK.

Systemic conditions that are associated with NK don't stop with herpes simplex and herpes zoster. There are many, including diabetes, listed in Table 1. A diet high in sugar and certain medications can also lead to NK. Chronic comorbidities—such as dry eye, blepharitis, exposure keratitis, topical drug toxicity, contact lens-related disorder, and others—can also cofound the diagnosis of NK, increasing the need for a thorough diagnostic workup, including a confirmatory test.[2] It's unclear if comorbidities are more likely to result in a recurrence even with treatment, but I would suspect that's the case.

If you see a nonhealing wound, it's important to ask yourself if there is an association with herpetic corneal disease. Is there damage due to a stroke or a brain injury? Has there been a history of recent surgery or repetitive surgery? Have they had longstanding contact lens wear? Maybe they wore rigid lens for a number of years. Do they use chronic topical medications for glaucoma? When you see something on the cornea that isn't resolving, you need to be asking these questions and thinking of NK, especially if more than one is present in the patient.

## DIAGNOSING NEUROTROPHIC KERATITIS

**Walter O. Whitley, OD, MBA, FAAO:** Patients with NK have decreased sensation or decreased or no pain whatsoever.[6] The cornea epithelium will have some irregularities, which you can have with or without an epithelial defect. Is the stroma involved? If it is, it's usually oval shaped. Patients may also have a corneal ulcer that has led to melting as well as perforation.

When it comes to diagnosing NK, taking a complete history is crucial. Ask patients directly if they've had a herpetic eye infection. Ask them about their contact lens wear, if they take glaucoma medication, and if they are on multiple medications. We know

**TABLE 2. DIAGNOSTIC CONSIDERATIONS FOR NK[6]**

| |
|---|
| Clinical History |
| Corneal sensitivity testing |
| Complete eye exam (eg, slit lamp, rule out diabetic retinopathy) |
| Corneal staining (eg, fluorescein, lissamine green) |
| Schirmer test (can be impaired as a result of reduction in corneal sensitivity) |
| Corneal cultures (rule out secondary infection) |
| In vivo confocal microscopy (affected sub-basal nerves) |
| Evaluation for systemic immune disorders |

preservatives in eye drops can cause toxicity and accumulate within that corneal epithelium leading to dysfunction.[7] Corneal sensitivity testing is also essential and should be included in every OSD workup. Drs. Mah and Nichols, do you routinely check corneal sensitivity?

**Francis S. Mah, MD:** Yes. I include corneal sensitivity testing in all my ocular surface referrals and consults. I assess corneal sensitivity on every patient who comes in with any type of OSD.

**Dr. Whitley:** Corneal sensitivity assessment is part of our workup when someone comes in for dry eye as well. If you see any significant or chronic staining or epithelial defects, you should have NK as a potential differential. You should also be suspicious for NK in patients with diabetes, which we know can overlap with dry eye

disease and occurs in about 54% of patients.[8] Diabetes also affects the peripheral nerve endings, and we know that there are significant nerve endings within the cornea itself. Does the patient have diabetic retinopathy? There are various reports looking at patients with proliferative diabetic retinopathy who had a vitrectomy and also had concurrent NK.[9,10] Table 2 lists diagnostic considerations for NK.

Staining is definitely underutilized, and you want to make sure you're looking at this—whether it's fluorescein, lissamine green, or whatever stain you feel most comfortable with—because if you don't use stain, you will miss some of the subtle clinical findings that are common within NK. Dr. Nichols, how often do you use the Schirmer test?

**Dr. Nichols:** I think it is important to measure tear production on all new dry eye patients to understand their baseline. For example, could they be at risk for Sjögren syndrome?

**Dr. Mah:** I'm not doing a whole lot of Schirmer tests. I'll do them for rheumatology workups, for Sjögren syndrome, and for clinical trials.

**Dr. Whitley:** In addition to corneal sensitivity testing, I often use Schirmer when I suspect a patient has NK and when I am trying to get medications approved to show insurance a clinical finding. If you're concerned about an epithelial defect or if the patient has an infectious ulcer, corneal cultures would be indicated. Additionally, in a cornea clinic, we can utilize confocal microscopy and evaluate the sub-basal corneal nerves to see how those have been impacted.

If a patient has nocturnal lagophthalmos, for example, we can put drops on there all day long, but if we're not finding the underlying etiology and treating that first, it's not going to get better. In these cases, exposure keratitis as well as NK is going to be our differential. We have to make sure we're remembering that list whether it's dry eye, contact lens wear, or chronic medication with preservatives—could this patient have NK?

## HOW TO CONDUCT CORNEAL SENSITIVITY TESTING

**Dr. Whitley:** Corneal sensitivity testing is critical to diagnosing NK. Does the patient have normal or reduced sensitivity or is it completely absent? Typically, the greatest sensitivity will be in the central cornea, but in older adults the cornea will be more sensitive in the periphery. Corneal sensation does drop rapidly as the distance increases from the limbus and falls with increasing age. It's not affected by iris color. Testing can be done with a cotton wisp from a cotton swab, unwaxed dental floss, or tissue tip.[5] Of course, don't put anesthetic in the eye beforehand because you want to see how sensitive, not sensitive, or desensitized that cornea is.

I find that tissue paper is easier and quicker than a cotton wisp. I twist the tissue and touch it to the cornea. I always start with the right eye, touching the tip of the twisted tissue to the central, superior, temporal, inferior, and nasal cornea. I record the findings, classifying the corneal sensitivity as normal, reduced, or absent, and then move on to the other eye afterward with a new tissue.

If you want a quantitative number, you can also use the Cochet-Bonnet esthesiometer. If you're using the Cochet-Bonnet, you extend the retractable nylon monofilament to full length of 6 cm. You then retract that filament incrementally in 0.5 cm steps until the patient feels contact. It will give you a number of how sensitive or desensitized that cornea is, with shorter length indicating decreased sensation. It's primarily used in clinical research, but you can use it in the clinic as well.

Dr. Mah, what is your corneal sensitivity testing technique?

**Dr. Mah:** Similarly, I take my cotton wisp and do each eye. Sometimes the cotton wisp will soak up some of the tears if you do it too far inferiorly or if the patient blinks in the middle, especially if they have normal sensation, then you have to start over. It's not perfect. But again, it's not quantitative; it's more qualitative. Then I'll use a new cotton swab on the other eye. I also record the sensitivity as normal, reduced, or absent.

**Dr. Whitley:** Do you test various regions or are you only focused on the central cornea?

**Dr. Mah:** That's a great question. In our fellowships, we teach testing the central area and the four quadrants. Historically, the reason to check the four quadrants is because of conditions like herpes simplex or zoster, which can have sectoral corneal hypoesthesia or anesthesia. First and foremost, the key is remembering to test. But I do test central as well as the four quadrants.

**Dr. Nichols:** I focus on the central cornea unless it looks like there is a lesion somewhere. In that case, I test around the cornea or in other areas for comparison.

**Dr. Whitley:** I agree that the main focus needs to be on testing in the first place. However, as we get used to sensitivity testing, it's important to test those various areas because it helps narrow down the underlying cause.

**Dr. Nichols:** As you treat and the patient improves, you might see a different result if you test the four regions. It's certainly peripherally where you might see some nerve regeneration and then sensation improves. Testing the four quadrants and being able to compare to future tests is valuable.

**Dr. Mah:** You also need to test the fellow eye, especially in the beginning, to get an idea of what is normal and what is abnormal. Being able to compare eyes is critical.

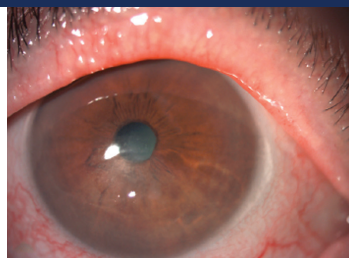
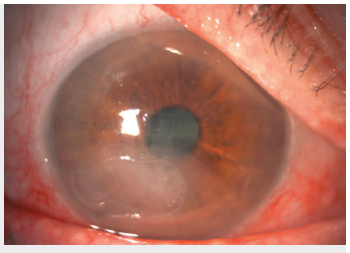
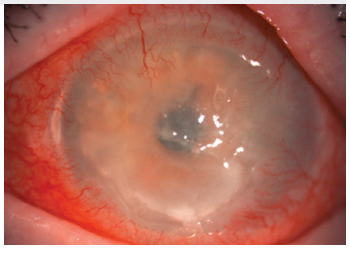
## TRADITIONAL AND MODERN CLASSIFICATIONS OF NK

### Mackie Severity Classification

**Dr. Whitley:** The Mackie Severity Classification of NK was developed several decades ago. It has three stages (Table 3).[2,11]

Thankfully, I see a lot of stage 1 patients in my clinic. Patients

**TABLE 3. MACKIE SEVERITY CLASSIFICATION FOR NK[11]**

| STAGE | CLINICAL FEATURES | PRESENTATION |
|---|---|---|
| 1 | • Punctate epitheliopathy (punctate corneal fluorescein/lissamine green staining)<br>• Decreased tear breakup time<br>• Stromal haze<br>• Increased mucous viscosity<br>• Rose bengal staining to the inferior palpebral conjunctiva |  |
| 2 | • Persistent epithelial defect with smooth rolled edges<br>  • Typically, in the central/inferior cornea<br>  • Surrounded by a rim of loose epithelium<br>• Stromal opacity<br>• Anterior chamber inflammatory reaction may be present |  |
| 3 | • Corneal ulcer<br>• Stromal thinning/ulceration<br>• Corneal perforation |  |

with stage 1 disease have punctuate epitheliopathy, staining, decreased tear film breakup time, and increased mucus viscosity. They may also have some stromal haze. Stage 1 may resemble dry eye. This is important because we've all had the recalcitrant dry eye patient who has been treated with every anti-inflammatory as well as meibomian gland treatment. We may try various other treatment options, and it's not getting better. That's when you need to think that there is something else going on. Once you do corneal staining or sensitivity testing, you're going to find a lot more patients with NK.

In the more advanced or moderate form of NK, patients will have persistent epithelial defect—that oval shape with smooth, rolled edges. Typically, it's found centrally or in the inferior part of the cornea and will be surrounded by loose epithelium. You may see some stromal swelling with folds in the Descemet membrane. Depending on the defect, an anterior chamber inflammatory reaction may be present. This is stage 2 disease.

In patients with advanced NK, or stage 3 disease, you'll see stromal thinning and ulceration, which could lead to corneal perforation. In these patients, you'll want to use lab testing and corneal cultures.

Although Mackie is three stages, there may be some overlap. They're clustered, with a number of distinct and often nonsequential phases of NK development into broad, nonspecific categories. The recent advent of more effective treatment options necessitates a more highly defined staging system that better reflects the evolution of the disease and alerts clinicians to the earlier stages of NK. Dr. Mah, tell us about this newly proposed way to identify and stage NK.

## The NK Study Group Classification System

**Dr. Mah:** The Mackie Classification Dr. Whitley so expertly described is the historic classification, which was updated by the NK Study Group (NKSG) a little more than 2 years ago. The issue we had with the Mackie Classification is that the stages are too broad. We started the NKSG to parse the different aspects and define the earlier stages so we can intervene as quickly as possible. NKSG members wrote a paper discussing this updated staging system including diagnosis, diagnostic techniques, and classifications. The paper has been submitted, and is currently under review. The NKSG proposed classification has 7 stages, which allows for earlier diagnosis as well as accurate monitoring of progression and evolution of recurrence. It really parses out the various different stages in much more distinct, finite sections (Table 4).

Stage 0 is altered sensation without keratopathy, which makes these patients difficult to identify. This is probably where things start. Patients typically don't complain, but they may say they have fluctuating vision. They won't have corneal findings. Previously, these patients would be classified as normal.

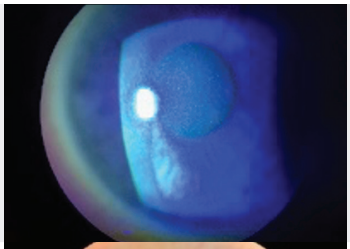
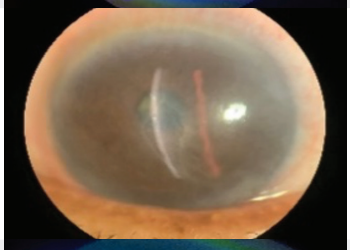
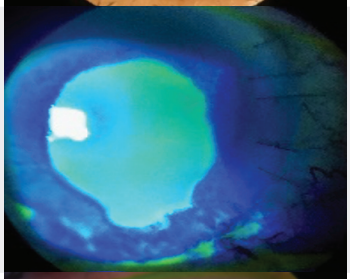
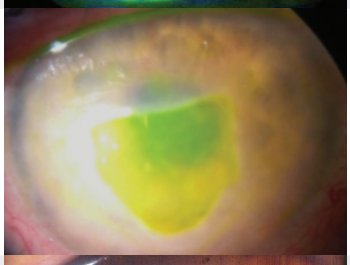
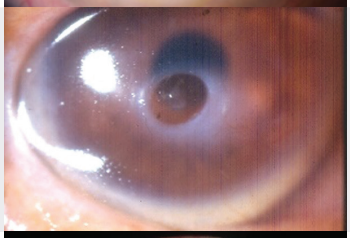
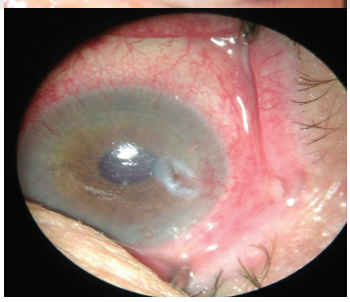
Stage 1 is mild. Patients will have some altered corneal sensation and epitheliopathy. There's no stromal haze. These are those difficult dry eye cases where you've prescribed every treatment possible and can't get the ocular surface to look normal. They look, for all intents and purposes, like dry eye patients. Stage 2, which is more moderate, is an epitheliopathy with a stromal haze. These patients have a damaged ocular surface, but they don't have an epithelial defect.

Stage 3 is severe NK. Patients have persistent or recurrent epithelial defects and a persistent breakdown of the epithelium. Persistent means different things to different people—some people say 1 week, some 10 days, some 14 days—as long as it's persistent, 10 days is what most clinicians accept. Stage 4 is when patients have stromal scarring without corneal ulceration. Stage 5 is corneal ulceration, and stage 6, the final stage, is perforation.

I think the NKSG staging, at least in the beginning, will be a bit academic and research-oriented. Importantly, stage 1 NK can look exactly like a recalcitrant dry eye or unresponsive dry eye. How do you differentiate early NK from dry eye?

**Dr. Whitley:** For me, it's important to follow OSD evaluation protocols.[12] At my practice, we start with various questionnaires. We use the SPEED questionnaire to assess dry eye symptoms.

**TABLE 4. NK STUDY GROUP PROPOSED STAGING SYSTEM**

| STAGE | CLINICAL FINDINGS | PRESENTATION |
|---|---|---|
| 0 (Mild) | Altered sensation without keratrophy | Appears to be a normal cornea |
| 1 (Mild) | Epitheliopathy without stromal haze |  |
| 2 (Moderate) | Epitheliopathy with stromal haze |  |
| 3 (Severe) | Persistent or recurrent epithelial defects |  |
| 4 (Severe) | Persistent or recurrent epithelial defect and stromal scarring without corneal ulceration |  |
| 5 (Severe) | Persistent or recurrent epithelial defect with corneal ulceration |  |
| 6 (Severe) | Corneal perforation |  |

Some of these patients may not have symptoms other than the fluctuating vision.[13] We'll do matrix metallopeptidase-9, tear osmolarity, meibography, or an imaging of the meibomian glands. Remember, you can't use anesthetic within the eye if you are going to evaluate corneal sensitivity. I follow that up with staining to evaluate tear film breakup time. As we mentioned with the Mackie Classification stage 1, NK patients will have decreased tear film breakup time.

**Dr. Mah:** In terms of telling patients apart, one of the big differences between dry eye and NK is corneal versus conjunctival staining. With dry eye, you'll have a lot more conjunctival staining to begin with that will extend into the cornea. You'll have both corneal and conjunctival staining.[13] With NK, you don't have much conjunctival staining. If you use lissamine green or rose bengal and see conjunctival staining, the patient probably has dry eye and not NK.

The second big differential is complaints of pain and discomfort and a scratchy or foreign body sensation in the eye.[13] Patients with NK don't typically have these complaints; they are shockingly comfortable. Their main complaint is fluctuating vision.

**Dr. Whitley:** It's also important to look at asymmetry patterns. When we think about one of the common causes of NK, viral infection like herpes simplex or zoster, typically that's unilateral. If you see significant staining in one eye versus another, that should be a clue. Second, if you have a patient being treated for dry eye and you've tried various medications and anti-inflammatories but still see staining, it's time to start testing corneal sensitivity and consider early-stage NK.

**Dr. Mah:** It's very easy to test that cornea as part of a dry eye workup. If you think the patient has dry eye and treatments aren't working, check the corneal sensitivity. The travesty would be ignoring it and pushing it off. Make the diagnosis. If you don't feel comfortable, refer the patient or attend more of these sessions and get comfortable with the algorithm to start the process. Grow and learn the different stages. At some point, you'll learn to incorporate some of these tips even if it's not all of them.

**Dr. Nichols:** There are many practices out there that focus on the ocular surface. Identify that practice, meet them, see what they are doing, and determine if you can use them to help comanage these patients until you feel comfortable.

## NK Treatment

**Dr. Mah:** Treatment for NK is focused on severity-based therapy (Table 5).[4,6] In early Mackie stage 1 disease, treat with preservative-free artificial tears. The preservative-free aspect is important because preservatives such as benzalkonium chloride could be a cause for NK.[7] Punctal occlusion is beneficial,

**TABLE 5. SEVERITY-BASED THERAPY FOR NK[4,6]**

| MACKIE STAGE | TREATMENT |
|---|---|
| 1 | • Preservative-free artificial tears formulations<br>• Punctal occlusion<br>• Hydrogel contact lens (consider large diameter)<br>• Recombinant human nerve growth factor (rhNGF, cenegermin)<br>• Serum/plasma/platelet-rich plasma |
| 2 | Supportive therapies plus:<br>• rhNGF<br>• Scleral lens (± serum/plasma)<br>• Amniotic membrane<br>• Botulinum induced ptosis, tarsorrhaphy |
| 3 | • rhNGF<br>• Keratoplasty + scleral lens, tarsorrhaphy, neurotization |

and large-diameter hydrogel contact lenses can be used for stages 1, 2, and 3. Recombinant human nerve growth factor (NGF), or cenegermin, is FDA approved for stages 1, 2, and 3.[14] If you have access, autologous serum tears (AST) or the platelet-rich plasma (PRP) is beneficial. There are also amniotic extract eye drops, which are beneficial. With the exception of cenegermin, we use all of these tools on severe dry eye patients.

For Mackie stage 2 disease, you can use a scleral lens if it's a chronic issue, AST/PRP, amniotic membranes, and cenegermin. You can also do some type of nonsurgical tarsorrhaphy, which is more chemical, like Botox or super glue. You can also do a suture tarsorrhaphy if the persistent epithelial defect won't heal.

For Mackie stage 3, which includes ulcerations and stromal melting, cenegermin is approved in this setting. Other options include keratoplasty, scleral lens, tarsorrhaphy, and neurotization. Dr. Whitley, is there anything you like to use for a specific stage of NK?

**Dr. Whitley:** In stage 1, punctal occlusion is definitely underused and it's very beneficial. Even though cenegermin is approved for Mackie stage 1 disease, I still go with the amniotic membrane first and step up to cenegermin if they haven't approved in a month or 2.

**Dr. Mah:** A preservative-free topical antibiotic should be used if there is an epithelial defect. Moxifloxacin is FDA approved, and I would use it, at minimum, 3 times a day. AST can be difficult to get, but they are effective. At a 20 to 50% concentration, AST have a success rate ranging from 71 to 100% in terms of healing epithelial defects in NK within 90 days.[15-17] There is some evidence that umbilical cord serum may be more effective and has a higher concentration of substance P and NGF than peripheral blood serum.[18] Studies have also shown that plasma-rich platelets and growth factors are also effective, with epithelial defects healed in 97.4% in stage 2 and stage 3 disease after 11 weeks.[19] Finally, silicon hydrogel contact lenses can be safely used in combination with AST; no inflammation or contact lens deposits were observed in a study by Choi et al.[20] However, there isn't any information on how successful that combination was in terms of healing epithelial defects in NK.

**Dr. Whitley:** Dr. Mah, what concentration of AST do you recommend? At 50%, you'll have too much transforming growth factor, which may limit epithelial healing. Do you have any comments on that?

**Dr. Mah:** AST is typically administered in a 20% concentration, but many clinicians are not using 20%; they are using 50 to 70%.[21] I personally recommend 50% for NK. You'll get a higher concentration of NGF, but you're not going to have transforming NGF.

Moving on to amniotic membrane transplant (AMT), this is a little easier to access because they are commercially available. One randomized clinical trial reported on the healing of refractory neurotrophic ulcers with conventional therapy (lubrication plus bandage contact lenses or tarsorrhaphy) compared with AMT and found that the healing rates were similar between the two groups (67% vs 73%, respectively).[22] A second study looked at AMT compared with AST in healing neurotrophic ulcers and found similar rates between them as well (73% vs 70%, respectively).[23] There are many studies looking at AMT, either in layers, glued on, or sutured on for NK, and they seem to work well.[24] There's a growing body of literature in the amniotic membranes that we use in the clinic, the freeze dried or the fresh frozen.[25,26] I prefer the fresh frozen, cryopreserved version. I haven't had as much success with the freeze dried amniotic membrane commercially available products. Dr. Whitley, Dr. Nichols, any comments?

**Dr. Whitley:** We've also had better clinical results anecdotally within our practice with the cryopreserved.

**Dr. Nichols:** There's a bit of comfort level associated with each technique as well. It may be easier for someone to start out with one versus the other, so it's worth trying to go to a session where you can see both in practice.

**Dr. Mah:** Moving on, the use of scleral lenses was reported several decades ago, and they are beneficial.[27] Nonhealing corneal epithelial defects healed in all nine patients treated with the PROSE scleral lens.[28] Overnight wear with close monitoring may accelerate healing.[29] Scleral lenses are a great technique, but time consuming because they have to be ordered and fitted. You can't use it emergently or urgently. If the person is relatively stable, it's a good method.

Corneal neurotization restores corneal sensitivity using a multidisciplinary surgical technique involving an orbital surgeon and a corneal specialist. It is relatively exciting. You take the free sural nerve and attach it end to side with the supratrochlear nerve, which is why you need an orbital surgeon. The distal portion

of the nerve is separated into different fascicles and distributed around the limbus, which is why you need a cornea specialist.[30]

Several groups have reported on the efficacy of corneal neurotization.[31-33] In general, patients have some corneal sensitivity resulting in resolution of the NK and epithelial defects. This is a valid, exciting approach, but reimbursements are poor and it's a very long procedure.

## CENEGERMIN: A FIRST-IN-CLASS TREATMENT FOR NK

**Dr. Whitley:** Cenegermin is a human NGF that is structurally identical to the NGF protein within the body.[14,34] It was approved by the FDA in 2017 for the treatment of NK. Corneal integrity is maintained by three mechanisms. Endogenous NGF acts through specific high affinity and low affinity NGF receptors in the anterior segment of the eye.[1] If those nerves aren't functioning properly, then that epithelium is not going to maintain its regularity, which creates a feedback loop. That's why it's important for us to address the nerves, to get them to grow, and to improve their function.

When it comes to corneal innervation, NGF plays a role in the function and stimulates the regeneration and survival of the sensory nerves.[6,35] It also stimulates cell proliferation and differentiation and helps with the survival of the corneal epithelial cells.[1] NGF, combined with the receptors on the lacrimal glands, promotes the sensory mediated reflex tearing secretion.[36] To make sure we address the feedback loop, we need to address the underlying issue of denervation, which is where cenegermin comes in. Dr. Nichols, please take us through some of the clinical trial data that led to the approval of cenegermin.

**Dr. Nichols:** The safety and efficacy of cenegermin dosed six times a day was assessed in two trials: NGF0214 (n = 48), which was conducted in the United States, and REPARO (n = 104), which was conducted in Europe.[37,38] Patients were assigned 1:1 to treatment or placebo. At week 8 in NGF0214, 65% of patients were healed with cenegermin versus 16% with placebo ($P$ = .001). This is a 6 times a day treatment, but you're also applying placebo 6 times a day a well. You will see some beneficial effect of the repeated lubrication over a period of weeks.

REPARO had similar results but in a bit larger of a study, with 72% of patients at 8 weeks treated with cenegermin showing statistically significant clearance with no staining present versus 33% with placebo ($P$ = .001).[37,38] One of the key questions is how long does a single series of treatment last? Do we have enough data to show over time what the trend is? Do you need to do it again? Of that 72% in REPARO who had clearance at 8 weeks, 80% were still clear after a year.

Pooled together, 50 sites across the world were involved. The most common adverse event was eye pain, which is interesting because these patients don't experience pain; they have decreased sensation.[37,38] Therefore, how does this pain occur? Does it mean they are improving and are starting to feel again? That could be part of it. The other part could be in the vague way questions are asked in clinical trials. A lot of things are lumped into eye pain.

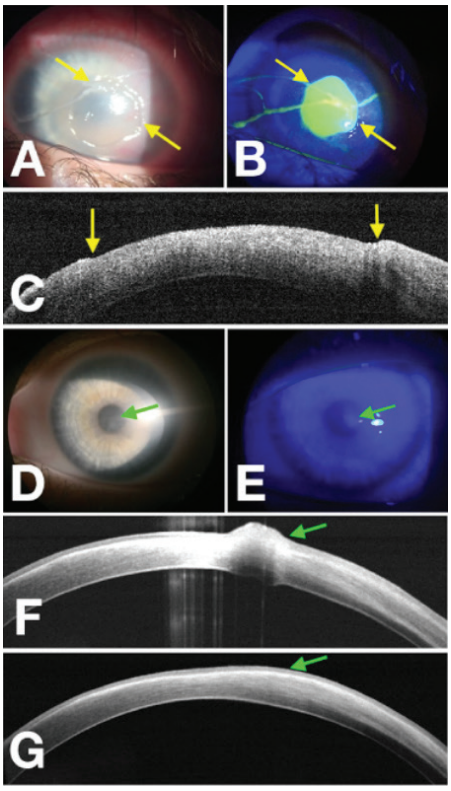



Figure 3. Corneal wound healing of pediatric NK using cenegermin imagined with a multimodal approach.[41] Yellow arrows point at the edges of the epithelial fronts in the photograph obtained at baseline with diffuse white light (A), with fluorescein staining (green) photograph obtained under cobalt-blue light illumination (B), and points to the epithelial edges in the OCT scan over the thinnest area at baseline (C). Images acquired at the end of the treatment at Week 8, and the green arrows show a residual paracentral corneal epithelial hyperplasia. About 1 month later, OCT scan (G) reveals complete regression of the corneal epithelial hyperplasia (D-F).

If they had irritation in and around the eye, they could call that eye pain. In most instances, the pain was mild and transient. Dr. Mah, in your experience, what do your patients say about the sensations they experience while using this drop?

**Dr. Mah:** I tell patients they might get pain, which typically begins 2 to 3 weeks after they start treatment. I explain that it's a good thing because it means that the nerves, which have deadened, are waking up and they are starting to feel again. Invariably at the end of the treatment, it goes away. As long as they know this is normal, most patients will power through it. They don't discontinue because of pain.

**Dr. Nichols:** Now that cenegermin is approved, people want to know the long-term effect. What do we know about the continued beneficial effect over 1, 2, or 3 years out? Are we still seeing improvements in sensitivity and best-corrected visual acuity (BCVA)?

Four studies were published in the last year that help answer some of these questions. Bruscolini et al performed a retrospective chart review of 18 patients with Mackie stage 2 or 3 NK with a least 2 years of follow-up.[39] Some patients were followed up to 48 months. There were 4 instances of recurrence over the entire period. At 1 year, three patients recurred. The fourth recurrence occurred at month 36. Visual acuity, corneal sensitivity, and tear production had statistically significant differences at 1, 2, and 3 years. The authors concluded that cenegermin does produce lasting results, even with just one treatment.

In a second study, Pedrotti et al performed a prospective case series of 18 patients with 8 months of follow-up.[40] The majority,

| | |
|---|---|
| Rx | • Currently using ciprofloxacin 3-4 x a day |
| VA | • OD: 20/40 ph no improvement<br>• OS: 20/40 ph 20/20 |

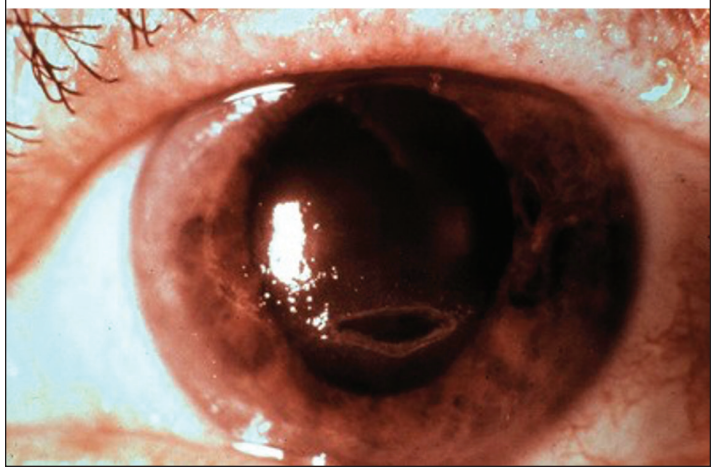


Figure 4. Case 1: Baseline imaging after referral.

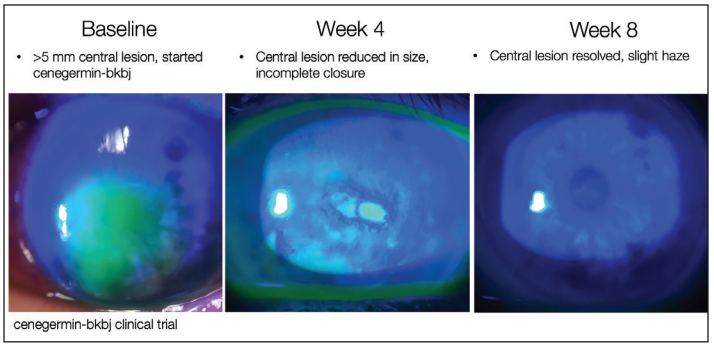



Figure 5. Case 2: Baseline imaging through week 8 of cenegermin treatment.

14 of 18 patients, stayed clear at 4 and 8 months. In vivo corneal microscopy was used to evaluate corneal nerve regeneration. Significant peripheral corneal nerve growth and branching was seen at 2 months and central advancement across the 8 months. Corneal sensitivity improved. The nerve regeneration was partially visible at 8 weeks. It continued after treatment with the hypothesis that the initial growth sustained further regeneration because the reestablishing of the connections allows the nerves to continue to regenerate.

Bonzano et al evaluated anterior segment OCT in 16 patients with NK, half of whom were treated with 50% AST and half of whom were treated with cenegermin.[41] The researchers wanted to see what was happening with corneal thickness as healing progressed. Figure 3 shows that there's a lumpiness that smooths out, which is especially apparent in Figure 3, images F and G.

Researchers compared the differences between AST and cenegermin and found that both were effective but at different time points. Cenegermin was faster than AST, at 3.9 versus 5.9 weeks, respectively. They were particularly interested in looking at the cornea and how quickly it healed the epithelial layer, if they could see the scar tissue, if the scar tissue improved, and what the overall profile of the cornea looked like. Both improved, perhaps a bit quicker than they suspected, which they hypothesized was due to the peripheral nerve regeneration.

Finally, Sacchetti et al evaluated two groups: amniotic membrane transplant (n = 15) and cenegermin (n = 24) with 12 months of follow up.[42] A total of 13 patients in the AMT group and 23 patients in the cenegermin group cleared. Similar to other studies, there was a 13% recurrence rate, which favored cenegermin. BCVA was statistically significantly improved. Patient satisfaction with treatment and outcomes was higher in the cenegermin group. Now, of course, you're comparing a surgical technique versus a drop, and so that probably influenced satisfaction.

I will say, too, that if you look at patients in some of these studies, they did treat the patients who recurred. In general, patients who recurred remained clear at least a year, assuming they were followed. A second treatment could be useful if there's recurrence.

**Dr. Mah:** This is fantastic. There's growing evidence of efficacy and a greater understanding of the effect of the drug on the human cornea.

**Dr. Nichols:** Being able to see the nerve regeneration is fascinating.

**Dr. Whitley:** The data you showed are impressive, but there is a 13% recurrence rate, meaning some patients may need retreatment. We don't have enough evidence there. Hopefully some of you can share your experience with another round of cenegermin in your patients. I've done it on a couple of patients so far.

**Dr. Nichols:** One thing we don't know is if patients who recur are more likely to have more severe disease at enrollment. These sample sizes are too small to say. I think the mounting body of evidence will help guide future decisions. If patients have a certain severity or a cluster of systemic diseases, they may be more likely to need a second treatment. That information helps with setting patient expectations.

## CASE 1: LASIK-INDUCED NK

**Dr. Mah:** Our first case is a 53-year-old woman who works at a computer all day. She had a history of LASIK in April 2017, but she also had a history of right-sided trigeminal neuralgia, at least it was diagnosed as such. It was pain on the right side of her face. In June 2017, she had a rhizotomy as a potential treatment for the trigeminal neuralgia and the pain. It did not resolve the facial pain and resulted in right-sided facial and eye numbness. Although this is not a common complication of rhizotomy, it can happen.

Her current complaint is decreased vision. She doesn't have pain. As the day progresses, her central more than her peripheral vision becomes hazy in that right eye. She uses artificial tears and was referred by a neuro-ophthalmologist for an epithelial defect.

The neuro-ophthalmologist started her on ciprofloxacin three or four times a day. Figure 4 shows her right eye when she came to me. She was 20/40 in her right eye with no improvement. She was 20/40 with 20/20 pinhole in the left eye.

I healed her up using ointment four times a day. Remember, this case is from 2017 and 2018 before we had cenegermin. The problem was, over the next 12 months, every time she stopped the ointment another abrasion or epithelial defect formed. She didn't like the ointment because it blurred her vision, and she works in front of a computer. She developed an abrasion four times within a year. We tried self-retaining AMT. We used ointment, but she kept breaking down when she decreased the ointment use. She was fitted for a scleral lens, but she just couldn't tolerate it. She finally had a tarsorrhaphy and hated it, but it kept her intact. Cenegermin was launched in early 2019, and I prescribed it immediately. After an 8-week course, 6 times a day, she was healed. She has remained healed just using preservative-free artificial tears. Her vision is 20/25.

## CASE 2: NK WITH HISTORY OF HERPES ZOSTER AND LASIK

**Dr. Mah:** Case 2 is a 75-year-old man with a 3- to 4-month nonhealing epithelial defect. He has a history of bilateral LASIK, herpes zoster, and a previous corneal abrasion about a year prior that healed after 2 weeks of aggressive lubrication antibiotic eye drops. Previous treatments include bandage contact lens, two rounds of self-retained AMT, and AST. At the time of referral, he was on antibiotic eye drops, artificial tears, and valacyclovir. Corneal sensitivity was tested and it was complexly absent. He had > 5 mm central abrasion. The diagnosis was nonhealing neurotrophic corneal epithelial defect. He was started on cenegermin, and 4 weeks later half way through treatment, the > 5 mm central abrasion was a small epithelial defect (Figure 5). It completely resolved at week 8, with the patient only reporting a slight bit of haze.

## CASE 3: OSD OR NK?

**Dr. Whitley:** Our last case is an 84-year-old woman referred for an ocular surface evaluation. She has a 10-year history of dry eye syndrome, a history of herpes stromal keratitis, anterior scleritis, and previous glaucoma medication (eg, chronic preservatives). She has diabetes and seasonal allergies, which she has treated with topical allergy drops. Those have preservatives as well. Previous treatments include punctal cautery and two rounds of cryopreserved, self-retaining AMT. She's currently on preservative-free artificial tears and cyclosporine twice a day in both eyes. I checked her corneal sensitivity and it was centrally absent. I diagnosed her with a nonhealing punctate keratopathy, which is stage 1 NK. I treated her with 8 weeks of cenegermin. Her ocular surface improved, the nerves regenerated, and the epithelial cells healed.

**Dr. Nichols:** Any final words on setting expectations with patients treated with cenegermin?

**Dr. Mah:** I am very happy with cenegermin in terms of effectiveness and durability. The side effect profile is tolerable as well, but I do tell patients to expect some pain. I've also been pretty happy with the ability of my patients to access cenegermin. It's relatively expensive, but the pharmaceutical company has been good about getting patients access.

**Dr. Nichols:** Thank you all for an excellent discussion on diagnosing and managing patients with NK. ■


1. Mastropasqua L, Massaro-Giordano G, Nubile M, Sacchetti M. Understanding the pathogenesis of neurotrophic keratitis: the role of corneal nerves. *J Cell Physiol.* 2017;232(4):717-724.
2. Dua HS, Said DG, Messmer EM, et al. Neurotrophic keratopathy. *Prog Retin Eye Res.* 2018;66:107-131.
3. Saad S, Abdelmassih Y, Saad R, et al. Neurotrophic keratitis: Frequency, etiologies, clinical management and outcomes. *Ocul Surf.* 2020;18(2):231-236.
4. Sheha H, Tighe S, Hashem O, Hayashida Y. Update on cenegermin eye drops in the treatment of neurotrophic keratitis. *Clin Ophthalmol.* 2019;13:1973-1980.
5. Versura P, Giannaccare G, Pellegrini M, Sebastiani S, Campos EC. Neurotrophic keratitis: current challenges and future prospects. *Eye Brain.* 2018;10:37-45.
6. Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Ophthalmol.* 2014;8:571-579.
7. Goldstein MH, Silva FQ, Blender N, Tran T, Vantipalli S. Ocular benzalkonium chloride exposure: problems and solutions. *Eye (Lond).* 2022;36(2):361-368.
8. Bron AJ, de Paiva CS, Chauhan SK, et al. TFOS DEWS II pathophysiology report [published correction appears in *Ocul Surf.* 2019;17(4):842]. *Ocul Surf.* 2017;15(3):438-510.
9. Banerjee PJ, Chandra A, Sullivan PM, Charteris DG. Neurotrophic corneal ulceration after retinal detachment surgery with retinectomy and endolaser: a case series. *JAMA Ophthalmol.* 2014;132(6):750-752.
10. Tinley CG, Gray RH. Routine, single session, indirect laser for proliferative diabetic retinopathy. *Eye (Lond).* 2009;23(9):1819-1823.
11. Mackie I, Fraunfelder F, Roy F. Current ocular therapy. Current Ocular Therapy 4th ed Philadelphia, PA: WB Saunders 1995:506-508.
12. Starr CE, Gupta PK, Farid M, et al. An algorithm for the preoperative diagnosis and treatment of ocular surface disorders. *J Cataract Refract Surg.* 2019;45(5):669-684.
13. Akpek EK, Amescua G, Farid M, et al. Dry eye syndrome Preferred Practice Pattern. *Ophthalmology.* 2019;126(1):P286-P334.
14. Deeks ED, Lamb YN. Cenegermin: A review in neurotrophic keratitis. *Drugs.* 2020;80(5):489-494.
15. Guadilla AM, Baladó P, Baeza A, Merino M. [Effectiveness of topical autologous serum treatment in neurotrophic keratopathy]. *Arch Soc Esp Oftalmol.* 2013;88(8):302-306.
16. Jeng BH, Dupps WJ Jr. Autologous serum 50% eyedrops in the treatment of persistent corneal epithelial defects. *Cornea.* 2009;28(10):1104-1108.
17. Pflugfelder SC. Is autologous serum a tonic for the ailing corneal epithelium? *Am J Ophthalmol.* 2006;142(2):316-317.
18. Yoon KC, You IC, Im SK, Jeong TS, Park YG, Choi J. Application of umbilical cord serum eyedrops for the treatment of neurotrophic keratitis. *Ophthalmology.* 2007;114(9):1637-1642.
19. Sanchez-Avila RM, Merayo-Lloves J, Riestra AC, et al. Treatment of patients with neurotrophic keratitis stages 2 and 3 with plasma rich in growth factors (PRGF-Endoret) eye-drops. *Int Ophthalmol.* 2018;38(3):1193-1204.
20. Choi JA, Chung SH. Combined application of autologous serum eye drops and silicone hydrogel lenses for the treatment of persistent epithelial defects. *Eye Contact Lens.* 2011;37(6):370-373.
21. Pan Q, Angelina A, Marrone M, Stark WJ, Akpek EK. Autologous serum eye drops for dry eye. *Cochrane Database Syst Rev.* 2017;2(2):CD009327.
22. Khokhar S, Natung T, Sony P, Sharma N, Agarwal N, Vajpayee RB. Amniotic membrane transplantation in refractory neurotrophic corneal ulcers: a randomized, controlled clinical trial. *Cornea.* 2005;24(6):654-660.
23. Turkoglu E, Celik E, Alagoz G. A comparison of the efficacy of autologous serum eye drops with amniotic membrane transplantation in neurotrophic keratitis. *Semin Ophthalmol.* 2014;29(3):119-126.
24. Mead OG, Tighe S, Tseng SCG. Amniotic membrane transplantation for managing dry eye and neurotrophic keratitis. *Taiwan J Ophthalmol.* 2020;10(1):13-21.
25. Lamon M, Bertolin M, Trojan D, et al. Cryopreservation of human amniotic membrane for ocular surface reconstruction: a comparison between protocols [published online ahead of print, 2022 Mar 25]. *Cell Tissue Bank.* 2022;10.1007/s10561-022-10002-y.
26. Memmi B, Leveziel L, Knoeri J, et al. Freeze-dried versus cryopreserved amniotic membranes in corneal ulcers treated by overlay transplantation: a case-control study. *Cornea.* 2022;41(3):280-285.
27. Romero-Rangel T, Stavrou P, Cotter J, Rosenthal P, Baltatzis S, Foster CS. Gas-permeable scleral contact lens therapy in ocular surface disease. *Am J Ophthalmol.* 2000;130(1):25-32.
28. Ling JD, Gire A, Pflugfelder SC. PROSE therapy used to minimize corneal trauma in patients with corneal epithelial defects. *Am J Ophthalmol.* 2013;155(4):615-619.e6192.
29. Lim P, Ridges R, Jacobs DS, Rosenthal P. Treatment of persistent corneal epithelial defect with overnight wear of a prosthetic device for the ocular surface. *Am J Ophthalmol.* 2013;156(6):1095-1101.
30. Elbaz U, Bains R, Zuker RM, Borschel GH, Ali A. Restoration of corneal sensation with regional nerve transfers and nerve grafts: a new approach to a difficult problem. *JAMA Ophthalmol.* 2014;132(11):1289-1295.
31. Giannaccare G, Bolognesi F, Pellegrini M, et al. Corneal neurotization: a novel surgical procedure for neurotrophic keratopathy. *Cornea.* 2022;41(4):403-407.
32. Liu CY, Arteaga AC, Fung SE, Cortina MS, Leyngold IM, Aakalu VK. Corneal neurotization for neurotrophic keratopathy: Review of surgical techniques and outcomes. *Ocul Surf.* 2021;20:163-172.
33. Fogagnolo P, Giannaccare G, Bolognesi F, et al. Direct versus indirect corneal neurotization for the treatment of neurotrophic keratopathy: a multicenter prospective comparative study. *Am J Ophthalmol.* 2020;220:203-214.
34. Dohlman TH, Singh RB, Dana R. Advances in the medical management of neurotrophic keratitis. *Semin Ophthalmol.* 2021;36(4):335-340.
35. Müller LJ, Marfurt CF, Kruse F, Tervo TM. Corneal nerves: structure, contents and function [published correction appears in *Exp Eye Res.* 2003 Aug;77(2):253]. *Exp Eye Res.* 2003;76(5):521-542.
36. Muzi S, Colafrancesco V, Sornelli F, Mantelli F, Lambiase A, Aloe L. Nerve growth factor in the developing and adult lacrimal glands of rat with and without inherited retinitis pigmentosa. *Cornea.* 2010;29(10):1163-1168.
37. Bonini S, Lambiase A, Rama P, et al. Phase II randomized, double-masked, vehicle-controlled trial of recombinant human nerve growth factor for neurotrophic keratitis. *Ophthalmology.* 2018;125(9):1332-1343.
38. Chao W. Healing of persistent epithelial defects or corneal ulcers by recombinant human nerve growth factor eye drops in patients with stage 2 or 3 neurotrophic keratitis. Congress of the European Society of Ophthalmology. Barcelona, Spain; 2017.
39. Bruscolini A, Marenco M, Albanese GM, Lambiase A, Sacchetti M. Long-term clinical efficacy of topical treatment with recombinant human nerve growth factor in neurotrophic keratopathy: a novel cure for a rare degenerative corneal disease?. *Orphanet J Rare Dis.* 2022;17(1):57.
40. Pedrotti E, Bonacci E, Chierego C, et al. Eight months follow-up of corneal nerves and sensitivity after treatment with cenegermin for neurotrophic keratopathy. *Orphanet J Rare Dis.* 2022;17(1):63.
41. Bonzano C, Olivari S, Cutolo CA, et al. Recombinant human nerve growth factor (cenegermin)-driven corneal wound healing process: an evidence-based analysis. *Front Pharmacol.* 2022;12:760507.
42. Sacchetti M, Komaiha C, Bruscolini A, et al. Long-term clinical outcome and satisfaction survey in patients with neurotrophic keratopathy after treatment with cenegermin eye drops or amniotic membrane transplantation. *Graefes Arch Clin Exp Ophthalmol.* 2022;260(3):917-925.

# A STEP FORWARD: THE LATEST DEVELOPMENTS IN NEUROTROPHIC KERATITIS

COPE Release Date: September 1, 2022
COPE Expiration Date: September 30, 2023

## INSTRUCTIONS FOR CREDIT

To receive credit, you must complete the attached **Pretest/Posttest/Activity Evaluation/Satisfaction Measures Form** and mail or fax to Evolve Medical Education LLC; 353 West Lancaster Avenue, Second Floor, Wayne, PA 19087; Fax: (215) 933-3950. To answer these questions online and receive real-time results, go to https://evolvemeded.com/course/2221-supp. If you experience problems with the online test, email us at info@evolvemeded.com. *NOTE: Certificates are issued electronically.*

Please type or print clearly, or we will be unable to issue your certificate.

Full Name_____ DOB (MM/DD): _____

Phone (required) _____ Email (required*) _____

Address/P.O. Box_____

City _____ State/Country _____ Zip _____

License Number:_____OE Tracker Number:_____National Provider ID:_____

*Evolve does not share email addresses with third parties.

## DEMOGRAPHIC INFORMATION

Profession
___ MD/DO
___ OD
___ NP
___ Nurse/APN
___ PA
___ Other

Years in Practice
___ >20
___ 11-20
___ 6-10
___ 1-5
___ <1

Patients Seen Per Week (with the disease targeted in this educational activity)
___ 0
___ 1-15
___ 16-30
___ 31-50
____ >50

Region
___ Midwest
___ Northeast
___ Northwest
___ Southeast
___ Southwest

## LEARNING OBJECTIVES

| Did the program meet the following educational objectives? | Agree | Neutral | Disagree |
|---|---|---|---|
| **Summarize** the etiologies of neurotrophic keratitis (NK) and how to differentiate it from similar diseases | _____ | _____ | _____ |
| **Recognize** the newly proposed stages of NK | _____ | _____ | _____ |
| **Describe** the stepwise approach to therapy and determine when to refer patients | _____ | _____ | _____ |
| **Review** clinical data on new and emerging treatments for NK | _____ | _____ | _____ |

# POSTTEST QUESTIONS

Please complete at the conclusion of the program.

**1. Based on this activity, please rate your confidence in your ability to describe the stepwise approach to neurotrophic keratitis (NK) therapy and determine when to refer patients (based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).**

a. 1
b. 2
c. 3
d. 4
e. 5

**2. Endogenous nerve growth factor helps preserve and restore the ocular surface by which of the following mechanisms?**

a. Strengthening tight junctions between epithelial cells to enhance corneal epithelial barrier functions
b. Providing nutrition to conjunctival goblet cells and eyelid tear glands in order to increase tear production and improve tear quality
c. Stimulating limbal stem cells to generate new epithelial cells
d. increasing tear production at the lacrimal gland, stimulating nerve regeneration, and supporting epithelial cell proliferation and differentiation

**3. A 54-year-old patient presents to your office for routine evaluation. He is a contact lens wearer with a history of visually significant cataracts, severe primary open-angle glaucoma on maximal medical drop therapy, and dry eye disease (DED). On exam, you note loss of corneal sensation bilaterally and diagnose him with NK. All of the following conditions may have led to his condition, EXCEPT:**

a. DED
b. Contact lens-related disorders
c. Cataracts
d. Topical drug toxicity

**4. All of the following statements about NK are true, EXCEPT:**

a. NK is a degenerative corneal disease
b. NK results from damage to cranial nerve VII
c. NK results in loss of corneal sensation
d. NK causes impaired corneal healing

**5. Corneal innervation is essential for good epithelial health. How do corneal nerves maintain a healthy corneal surface?**

a. Provide stromal, epithelial, and Bowman's structural support
b. Maintain sensory functions that are essential to tear film maintenance
c. Facilitate protective functions of blinking and tear production as well as trophic support
d. Provide key nutrients to the epithelium while also serving as a physical barrier to microbes

**6. A 69-year-old man presents to your office for routine eye examination. He has a history of LASIK OU. On slit lamp examination, you note an inferior, oval-shaped corneal epithelial defect with smooth and rolled edges. However, the patient does not report any pain. What is the next best diagnostic step to aid in this patient's diagnosis?**

a. Dilated fundus examination
b. Corneal sensitivity testing
c. Corneal pachymetry
d. Corneal hysteresis measurement

**7. A 56-year-old patient presents to your office with evidence of NK. On exam, you note a persistent oval-shaped epithelial defect with smooth, rolled edges and stromal haze. According to the Mackie Severity Classification, what stage of NK does this patient have?**

a. Stage 1
b. Stage 2
c. Stage 3
d. Stage 4

**8. All of the following are examples of QUALITATIVE corneal sensitivity testing, EXCEPT:**

a. Cotton swab testing
b. Cotton wisp testing
c. Cochet-Bonnet esthesiometer
d. Dental floss testing

**9. What is a benefit of the proposed new 7-step clinical staging system for NK?**

a. To allow for earlier diagnosis of NK
b. To differentiate between NK and infectious keratitis
c. To determine which patients with NK need surgical therapy
d. To determine systemic risk factors for NK

**10. A 79-year-old patient presents to your office for routine evaluation. Slit lamp examination reveals a normal anterior segment examination. Corneal sensation testing reveals absent corneal sensation. According to the staging system proposed by the NK Study Group, what stage of NK does this patient have?**

a. Stage 0
b. Stage 1
c. Stage 2
d. Stage 3

**11. A 46-year-old contact lens wearer presents to your office for routine examination. On exam, you note diffuse punctate epitheliopathy with no other significant findings on slit lamp exam and dilated fundus exam. What test might determine whether this patient has NK or DED?**

a. Tear film breakup time
b. Meibography
c. Corneal sensitivity testing
d. Schirmer testing

**12. The Mackie Neurotrophic Keratitis Classification System breaks NK into three stages. Recently, the Neurotrophic Keratitis Study Group has developed a new 7-step staging system. The purpose for this new system is:**

a. To replace an outdated system
b. To allow for more accurate monitoring of progression of the disease as well as delineate which patients may respond well to particular therapies and evaluate response to treatment
c. To better educate patients about their disease and help them understand the prognosis and possible consequences of the condition
d. To determine which patients need amniotic membrane grafting

**13. You are evaluating a patient in your office with stage 2 NK. All of the following treatments are reasonable therapies for this patient, EXCEPT:**

a. Amniotic membrane
b. Scleral lens
c. rhNGF
d. Keratoplasty

**14. NK is a rare disease with fewer than _____ affected in the United States.**

a. 25,000
b. 65,000
c. 105,000
d. 250,000

# ACTIVITY EVALUATION

Your responses to the questions below will help us evaluate this activity. They will provide us with evidence that improvements were made in patient care as a result of this activity.

---

Rate your knowledge/skill level prior to participating in this course: 5 = High, 1 = Low_____

Rate your knowledge/skill level after participating in this course: 5 = High, 1 = Low_____

This activity improved my competence in managing patients with this disease/condition/symptom. _____ Yes _____No

Probability of changing practice behavior based on this activity: _____High _____ Low _____No change needed

If you plan to change your practice behavior, what type of changes do you plan to implement? (check all that apply)

Change in pharmaceutical therapy _____ Change in nonpharmaceutical therapy _____

Change in diagnostic testing _____ Choice of treatment/management approach _____

Change in current practice for referral _____ Change in differential diagnosis _____

My practice has been reinforced _____ I do not plan to implement any new changes in practice _____

Please identify any barriers to change (check all that apply):

_____ Cost _____ Lack of consensus or professional guidelines

_____ Lack of administrative support _____ Lack of experience

_____ Lack of time to assess/counsel patients _____ Lack of opportunity (patients)

_____ Reimbursement/insurance issues _____ Lack of resources (equipment)

_____ Patient compliance issues _____ No barriers

_____ Other. Please specify: _____

| | | |
|---|---|---|
| The design of the program was effective for the content conveyed | ___ Yes | ___ No |
| The content supported the identified learning objectives | ___ Yes | ___ No |
| The content was free of commercial bias | ___ Yes | ___ No |
| The content was relative to your practice | ___ Yes | ___ No |
| The faculty was effective | ___ Yes | ___ No |
| You were satisfied overall with the activity | ___ Yes | ___ No |
| You would recommend this program to your colleagues | ___ Yes | ___ No |

Please check the Core Competencies (as defined by the Accreditation Council for Graduate Medical Education) that were enhanced through your participation in this activity:

_____ Patient Care

_____ Practice-Based Learning and Improvement

_____ Professionalism

_____ Medical Knowledge

_____ Interpersonal and Communication Skills

_____ System-Based Practice

Additional comments:

_____

_____ I certify that I have participated in this entire activity.

This information will help evaluate this activity; may we contact you by email in 3 months to inquire if you have made changes to your practice based on this activity? If so, please provide your email address below.

_____

_____