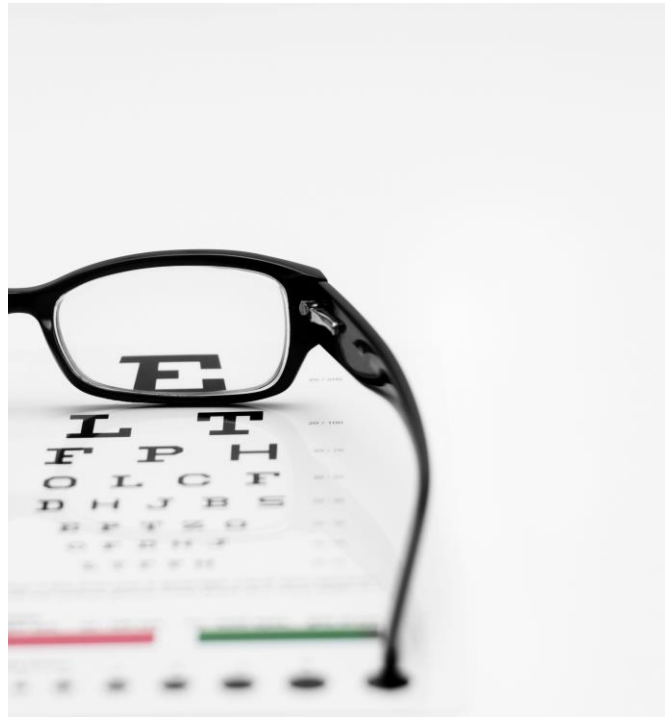


# The Eyes Have It: Why and how you see



**Thursday, March 6, 2014  
6:00 – 7:30 p.m.**

The Joseph B. Martin Conference Center  
The New Research Building  
Harvard Medical School  
77 Avenue Louis Pasteur  
Boston, MA 02115



**HARVARD**  
MEDICAL SCHOOL

# The Eyes Have It: Why and how you see

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## Moderator



### **Carolyn E. Kloek, MD**

Assistant Professor of Ophthalmology, Harvard Medical School  
Associate Chief for Practice Management, Massachusetts Eye and Ear  
Infirmery  
Clinical Director of Massachusetts Eye and Ear Infirmery, Longwood

## Speakers



### **Louis R. Pasquale, MD, FARVO**

Director, Glaucoma Service, Mass Eye and Ear Infirmery  
Director, Telemedicine, Mass Eye and Ear Infirmery  
Director, Glaucoma Fellowship, Mass Eye and Ear Infirmery  
Co-Director, Glaucoma Center of Excellence, Harvard Medical School  
Associate Professor of Ophthalmology



### **Constance L. Cepko, PhD**

Bullard Professor of Genetics and Neuroscience, Departments of  
Genetics and Ophthalmology  
Harvard Medical School  
Investigator, Howard Hughes Medical Institute

## About the Speakers

### **Carolyn E. Kloek, MD**

Dr. Carolyn E. Kloek is an assistant professor of ophthalmology at Harvard Medical School (HMS) and a comprehensive ophthalmologist at the Massachusetts Eye and Ear Infirmary (MEEI). Dr. Kloek received a BA in biochemistry and molecular biology from Dartmouth College followed by a MD from Harvard Medical School. Dr. Kloek served as a medical intern at Brigham and Women's Hospital and subsequently completed ophthalmology residency at the Harvard Medical School Department of Ophthalmology Residency Training Program. Upon completion of residency, Dr. Kloek was selected for the prestigious Chief Resident position at MEEI and served as Director of the Eye Trauma Service, the busiest eye trauma service in New England. Dr. Kloek is currently a member of the Comprehensive Ophthalmology and Cataract Surgery Service at Mass. Eye and Ear. Her busy clinical practice is focused on providing high quality, personalized eye care and ophthalmic surgery to the Boston population and beyond.

Dr. Kloek serves as clinical director of Mass. Eye and Ear, Longwood, a state-of-the-art eye care facility providing ambulatory and operative services to patients. Dr. Kloek spearheaded the development of this practice and continues to play a key role in managing the physicians and operations within this practice. Under Dr. Kloek's leadership this practice has thrived and continues to expand.

Since 2008, Dr. Kloek has served as the HMS Department of Ophthalmology Associate Residency Program Director where she provides oversight and leadership to one of the largest and most prestigious residency training programs in the country. She is dedicated to medical education and was selected as the first ophthalmologist in the department to serve as an HMS Rabkin Fellow in Medical Education. She has developed numerous curricular initiatives, and speaks and publishes on the topic of ophthalmic medical education.

As associate chief for practice management at Mass. Eye and Ear, Dr. Kloek oversees physician practice assignments to balance the needs of physicians, patients, services, and locations.

### **Louis R. Pasquale, MD, FARVO**

Born and raised in the East Harlem section of New York City, Dr. Louis Pasquale graduated from Manhattan College and received an MD with Distinction in Research degree from SUNY Stony Brook. After internship at Bronx Municipal Hospital affiliated with Albert Einstein School of Medicine, he completed his ophthalmological training at Temple University School of Medicine in Philadelphia.

Immediately after a 2-year fellowship in Glaucoma at the Wilmer Eye Institute in Baltimore in 1992, he built a large glaucoma practice at Brigham and Women's Hospital, where he also forged important research collaborations that drive much of his research efforts today. In 1996, he joined the Glaucoma Service at Mass Eye and Ear Infirmary and rose through the ranks to become Service Director in 2010.

Dr. Pasquale is associate professor of ophthalmology at Harvard Medical School. In addition to directing the Glaucoma Service at Mass Eye and Ear Infirmary, he directs the Glaucoma Fellowship Program, the MEEI Teleretinal Program, and co-directs Harvard's Glaucoma Center of Excellence. He is a Heed ophthalmic fellow and ARVO silver fellow as well as recipient of the AAO's Achievement Award and Secretariat Award. In 2009 he was the recipient of Research to Prevent Blindness' Physician Scientist Award. He is also an NIH Principal Investigator with continuous support since 2006. His research focuses on the discovery of primary prevention strategies in the open-angle glaucomas.

Dr. Pasquale has dedicated himself to become a physician scientist who seeks opportunities to translate basic science discoveries into better treatments for glaucoma patients. He has published 112 peer-reviewed articles in scientific journals, 56 reviews/book chapters/editorials, and has given numerous talks/courses around the world.

### **Constance L. Cepko, PhD**

Dr. Constance L. Cepko is the Bullard Professor of Genetics and Neuroscience in the Department of Genetics at Harvard Medical School.

Dr. Cepko received a Bachelor of Science degree from the University of Maryland, College Park, followed by her PhD from the Massachusetts Institute of Technology. Upon completion of her postdoctoral studies at the Whitehead Institute in Cambridge, Dr. Cepko joined Harvard Medical School as an assistant professor. She has been at HMS since 1985.

Dr. Cepko has received numerous awards for outstanding mentorship, most recently the A. Clifford Barger Excellence in Mentoring Award from HMS in 2010. She also serves on several academic committees, advisory boards and editorial boards for academic journals. Since 2005, she has been the Co-Director of the Leder Program in Human Biology and Translational Medicine at HMS.

Dr. Cepko's lab primarily investigates the mechanisms that cells use when they are choosing their fate during the development of the central nervous system. Her lab has focused studies on the retina, a tractable model for the rest of the central nervous system. In addition, researchers in her lab are interested in why photoreceptor cells die in many forms of retinal degeneration.

Dr. Cepko is also a Howard Hughes Medical Institute Investigator.

## The Eyes Have It

Why and how you see

Longwood Seminars, March 6, 2014

# How the eye works

The eye is often compared to a camera, but in truth, the organ of sight is far more complex and efficient. Not only does the eye focus and snap pictures, but it also works continuously with the brain and nervous system to process ever-changing images, providing you with the visual information you need for doing everything from hitting a golf ball to preparing your taxes.

## Eyeball engineering

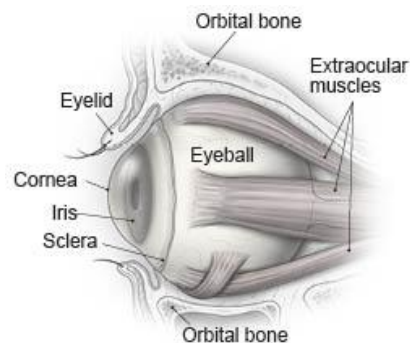
Despite its reputation as a delicate organ, the eye is remarkably resilient and hardy, engineered by nature to last from infancy through old age. Shaped like a sphere, the eyeball is about an inch in diameter, with a slight protrusion in front. It sits in a bony, protective socket of the skull, called the orbit, and is surrounded by a cushiony layer of fibrous tissue, fat, and muscles.

Eyelids and eyelashes act like windshield wipers, constantly brushing and blinking away dust and other debris that might otherwise blow into the eye. The lacrimal gland, located behind the upper lid, produces tears that course over the eye surface and keep it lubricated, nourished, and clear of foreign matter. Tears drain off into the nose through ducts at the eye's innermost corner.

The conjunctiva is a thin, colorless membrane that lines the inner surfaces of the eyelids and the front portion of the sclera, the eye's white outer surface. The conjunctiva is so sensitive that when it becomes aware of a foreign body, it automatically triggers a protective reaction, such as tearing or blinking.

Six extraocular muscles regulate each eye's up-and-down, side-to-side, diagonal, and rotational motions. The muscles come in pairs and run from the back of the orbit to the sides of the eyeball, beneath the conjunctival membrane (see Figure 1).

*Figure 1: Eye anatomy*



The eyeball is surrounded by ligaments, fat, and muscles and rests in a protective, bony socket called the orbit. Six extraocular muscles control the eyeball's movement. The cornea, a tough, transparent dome that helps focus light, and the sclera, the white portion of the eye, protect the interior of the eye.

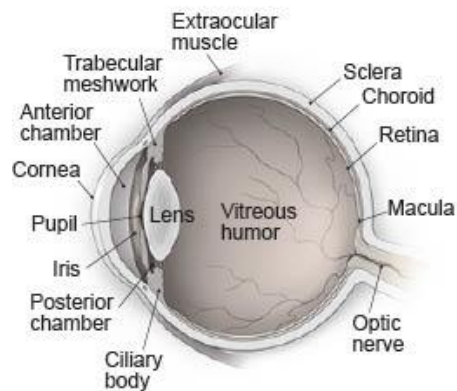
## The Eyes Have It

Why and how you see

Longwood Seminars, March 6, 2014

Three distinct layers of tissue surround the eye and form its wall (see Figure 2). The surface layer (approximately 1 millimeter thick) is made of tough collagen. You see it in the visible part of the eyeball as both the sclera (the white part) and the cornea, a clear, dome-like window at the front of the eye.

*Figure 2: The inside story*



Rays of light pass through the cornea, the anterior chamber, and then through the lens, which focuses images. The lens is nourished by the aqueous humor, a clear, watery solution that circulates from the posterior chamber into the anterior chamber and helps maintain normal pressure. Light reaches the retina after it passes from the lens through the vitreous humor, a clear gel that fills most of the eyeball. The retina has light-sensitive cells that capture images, which are then sent to the brain via the optic nerve. At the retina's center is the macula, a small region that provides sharp, central vision.

The middle layer, called the uveal tract, comprises the iris, ciliary body, and choroid. The iris—the pigmented segment, which might be blue, green, brown, or another color—forms a ring around the pupil, a black hole in the center of the iris. Basically a circular curtain of muscle fibers, the iris controls how much light enters the eye. As with an automatic camera, which adjusts the size of its aperture (opening) to the available light, the involuntary muscles of the iris open to allow more light to enter the pupil in dim light, and close to make the pupil smaller in bright light. A good example of the eye's adaptation is the mildly painful change that occurs when you walk into sunlight after sitting in a dark movie theater. Even subtle alterations in light prompt a response from the eye, and the iris muscles are continually adjusting to the environment.

Just behind the pupil and iris lies the crystalline lens, which is connected at its outer rim to the ciliary body by ligaments called zonules. The lens focuses light rays on the retina, the thin, light-sensitive inner layer at the rear of the eye. Muscles in the ciliary body enable the flexible lens to alter its shape and allow the eye to focus on objects at varying distances. When you look at a tree far away, for instance,

## **The Eyes Have It**

Why and how you see

Longwood Seminars, March 6, 2014

the muscles relax and stretch the zonule ligaments, which in turn pull on the lens, causing it to flatten and assume a thin contour. But shift your gaze to something close, such as a computer screen, and the muscles contract and loosen the zonules, which makes the lens thicker and curved more in the middle. The ability of the lens to focus from far to near is called accommodation.

The ciliary body also produces aqueous humor, a watery fluid that provides nutrients to the lens. The aqueous humor is found principally in the space between the iris and the cornea, known as the anterior chamber. The fluid flows to this region from the posterior chamber—the area between the iris and the lens—and then carries waste products from the eye through the trabecular meshwork and Schlemm's canal, a circular drainage system located where the clear cornea, white sclera, and colored iris meet. In a healthy eye, this circulation constantly drains and resupplies the aqueous humor, maintaining a balance of fluid in the two chambers.

Behind the lens is the vitreous humor. This clear, stable gel, which looks like raw egg white, supports and fills the rear two-thirds of the eyeball. This gel provides a pathway for light coming through the lens.

The choroid is sandwiched between the sclera and retina in the rear of the eye. This membrane is packed with blood vessels that carry oxygen and other nourishment to the adjacent outer portion of the retina.

The retina, the innermost layer, is where images are captured and recorded. This mass of unique nerve cells and fibers sends the brain visual messages about the size, shape, color, and distance of the objects you see. The images travel along the optic nerve, which carries the signals to the brain.

Within the retina are about 150 million rods and seven million cones—specialized cells made up of chemicals that react to different wavelengths in light. Located mainly in the periphery of the retina, the rods do not perceive color. The cones, which do perceive color, are responsible for fine detail in the center of vision. They enable us to read words on a page and recognize a familiar face from across the room. Cones are most active in bright light, while rods are most sensitive in the dark; this is why it is hard to detect colors and fine details in the dark. The cones are located primarily in the macula, a remarkably small part of the retina that gives us sharp central vision. The best vision—for reading or detailed work—comes from the fovea, at the center of the macula. The rest of the retina delivers peripheral vision (side vision), which is less sharply focused.

## **The art of seeing**

Sight is not fully developed at birth; the brain and eyes have to learn to work together in the first months of life. Once sight is well developed, the eyes and the brain team up to provide virtually instantaneous visual information.

Consider what happens when you walk through a parking lot and spot your car. First, you are actually seeing the light reflected off the car that enters your eye; some light must be present in order to see.

## **The Eyes Have It**

Why and how you see

Longwood Seminars, March 6, 2014

If the image is clear, it means that light thrown off the surfaces of the automobile hits your cornea, where it is refracted, or bent, inward and is then sent through the aqueous fluid until it reaches the lens. The light rays are then bent further, passed through the vitreous fluid, and projected onto the retina as a flat, upside-down image.

The light is absorbed by the retina and turns into electrical energy, which the optic nerve then conveys to the visual area of the brain. Data about your car—its size, shape, color, and position—are sent along the optic nerve as impulses, a sort of neurologic code that the brain deciphers. Although the image is upside down on the retina, the brain automatically turns it right side up.

Although it is possible to see with only one eye, you generally rely on binocular vision—vision with both eyes—for depth perception. You get a three-dimensional view of your vehicle because the brain interprets what is seen from your two eyes (each with a slightly different perspective) as a single image.

If a flashy car nearby catches your attention, you instantly shift your gaze without a thought. The external muscles of the eyes are synchronized to keep the eyes aligned and to coordinate their movement.

### **Why aging may cause problems**

Just as hair turns gray and skin sags with age, the eyes, too, undergo a metamorphosis as you grow older. Although many of these changes are part of normal aging, some set the stage for more serious eye problems.

As eyes age, eyelid muscles weaken and skin becomes thinner and more flaccid. This can cause the upper lid to droop or the lower lid to sag. Eyelashes and eyebrows may lose their lushness and thin out considerably.

Tear production also drops off, and the oily film that tears provide decreases as lubricating glands in the conjunctiva and lids fail. These changes can lead to a buildup of mucus, resulting in stickiness, or make the cornea dry, causing irritation or an uncomfortable, gritty sensation in the eye.

The conjunctiva turns thinner and more fragile with age and takes on a yellowish tinge from an increase in elastic fibers. The white of your eye (sclera) also assumes a yellow hue from a collection of lipid, or fat, deposits. Calcium may deposit in the sclera, leading to patches of grayish translucency. The exposed conjunctiva between the lids begins to degenerate, and the cornea can develop an opaque white ring around its edge.

With time, the crystalline lens hardens and loses its elasticity. This makes it more difficult to focus on near objects, a common condition called presbyopia. You might also find that your night vision grows poorer. These changes usually occur simultaneously in both eyes.



## The Eyes Have It

Why and how you see

Longwood Seminars, March 6, 2014

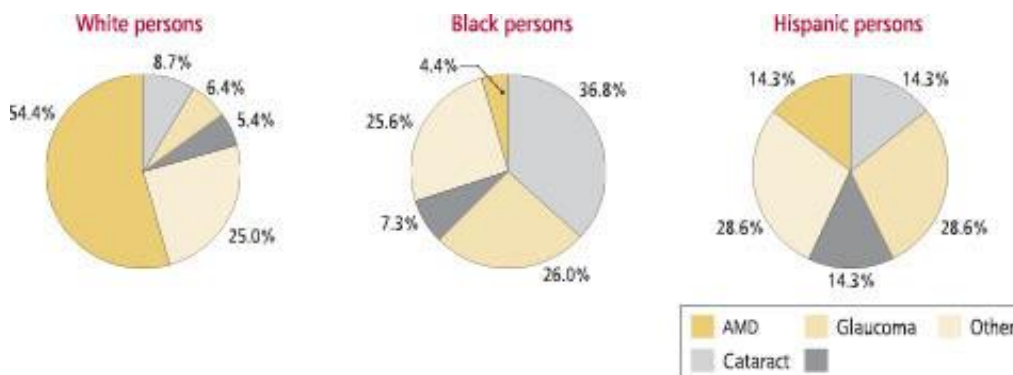
Aging can also cause the lens to darken, grow opaque, and in some cases thicken, causing nearsightedness. Clouding of the lens, which is called cataract, usually develops slowly over many years. It may go unnoticed until the cloudiness blocks the central line of sight and impairs vision.

Over time, the anterior chamber in each eye may become shallower in some susceptible people—those who have small eyes and are farsighted, for example. This raises the risk for blockage of the aqueous humor drainage system near the iris. The resulting fluid backup may lead to higher pressure inside the eye that damages the optic nerve, a condition known as closed-angle glaucoma. Left untreated, it can cause blindness. Another form of glaucoma, called open-angle glaucoma, occurs when pressure builds up in the eye because of a different problem: the aqueous humor is less able to flow out through the trabecular meshwork and Schlemm's canal. Because glaucoma can silently steal sight before symptoms develop, it is important to have routine eye exams.

The aging retina thins and may grow less sensitive because of cell loss, a reduced blood supply, or degeneration. Especially prone to deterioration is the macula; age-related macular degeneration is a serious disease that can steal a person's central vision.

Although age-related changes affect everyone, your race affects your risk for specific types of eye disease. In Americans older than 40, the leading cause of blindness in white people is age-related macular degeneration, while in black people it is cataract, and in Hispanic people it is glaucoma (see Figure 3). This probably results from a combination of factors such as genetics, dietary patterns, and access to medical care.

*Figure 3: Causes of blindness by race*



The leading causes of blindness vary by race and ethnicity.

*Adapted with permission from Archives of Ophthalmology.*

## **The Eyes Have It**

Why and how you see

Longwood Seminars, March 6, 2014

### **To learn more...**

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## The Eyes Have It

Why and how you see

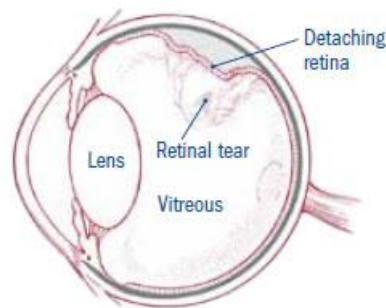
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# Specks in your vision can signal serious eye conditions

*These “floaters” are not just bothersome. They can be signs of potential retinal disease.*

Floaters, those tiny specks that drift across your field of vision, are usually harmless and often disappear or become less noticeable on their own. But sometimes they indicate a condition that can lead to vision loss. “A new onset of floaters may herald retinal disease,” says Dr. Jeffrey Heier, director of the retina service at Ophthalmic Consultants of Boston and clinical instructor in ophthalmology at Harvard Medical School.

### **Retinal detachment**



If the vitreous detaches, it may pull on the retina and cause a tear. This may cause blood to ooze into the vitreous gel, and a person will see black spots or floaters. Without treatment, progression from a tear to a retinal detachment could cause permanent vision loss.

### **Those pesky specks**

Floaters are pieces of debris that block the light shining into the retina—the part of your eye that captures light and sends it to the brain via the optic nerve. The debris is usually made of pieces of the vitreous—a thick, jelly-like substance that fills the center of your eye and attaches to the retina. Aging causes the vitreous to liquefy and break apart; parts of the vitreous that don't liquefy can be perceived as spots or lines in the eye. “A lot of people complain that floaters affect their vision and disrupt their ability to read,” says Dr. Heier. But he says floaters often settle over time and become less noticeable.

Sometimes the vitreous detaches from the retina. While noticeable as a large floater, it doesn't hurt, doesn't require treatment, and often becomes less bothersome in weeks or months. But the tugging of the vitreous on the retina can cause traction on blood vessels, leading to bleeding, which appears as many floaters, and it can also cause tears in the retina, sending many small spots across the field of vision.

## **The Eyes Have It**

Why and how you see

Longwood Seminars, March 6, 2014

A retinal tear isn't painful, but it does have symptoms: the sudden onset of brief, flashing lights or a shower of floaters. Untreated, retinal tears can lead to a vision-threatening retinal detachment.

### **Diagnosis and treatment**

If you've lived with an abundance of floaters for a long time, there's little you can do. Dr. Heier warns against treatments that promise to use lasers to dissolve floaters: "Some people say it's safe, but the reality is we've never studied it in an appropriate clinical trial." Surgery to remove the floaters is possible, but only rarely offered, and only in severe, disabling cases.

If you notice a sudden increase in floaters, you may have a retinal tear and should be examined urgently, notes Dr. Heier. Without treatment, progression from a tear to a retinal detachment could cause permanent vision loss.

### **Prevention**

There's no way to prevent floaters, and no nutrition component or supplement regimen that will stop the vitreous from shedding debris as you age. The secret to coping with floaters is patience.

But the good news is that you can help prevent retinal detachment by being proactive if you experience a sudden increase in floaters. And the sooner you get to your ophthalmologist, the better.

#### **To learn more...**

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## The Eyes Have It

Why and how you see

Longwood Seminars, March 6, 2014

# The glaucoma you may be missing

*Sometimes normal eye pressures mask the condition.*

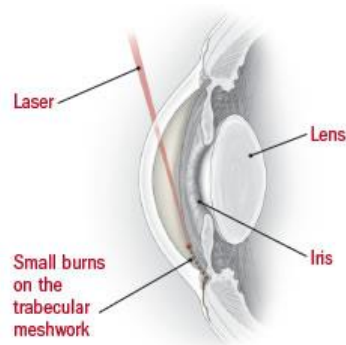
Ever get an eye pressure measurement at the eye doctor's office? The doctor directs a probe or a puff of air at your cornea to find out if the pressure inside the eye is elevated, often a major sign of glaucoma. But increased eye pressure isn't always an accurate way to detect the condition. You can sometimes have normal eye pressure and still have glaucoma.

## Types of glaucoma

The vision loss of glaucoma is caused by damage to the optic nerve. That's the nerve that sends electrical signals to the brain, which then interprets the signals as images. Nerve damage often results when pressure gets too high because of fluid buildup inside the eye. With the most common type of glaucoma, open-angle glaucoma, damage to the nerve is usually painless and occurs gradually. (With the less common closed-angle glaucoma, people can experience sudden pain and nausea.)

But sometimes nerve damage occurs without high pressure or fluid buildup. That's called normal-tension glaucoma (NTG). "In some patients, pressure in the normal range may cause damage. It may have something to do with intracranial pressure in the brain or compromised blood flow, depriving the nerve of oxygen and causing damage. But the consensus is that the optic nerve is just more fragile in some patients," says ophthalmologist Dr. Lucy Shen, a glaucoma specialist at Harvard-affiliated Massachusetts Eye and Ear Infirmary.

## Laser trabeculoplasty for glaucoma



In this procedure, the surgeon uses a high-energy beam of light to improve the flow of fluid in and out of the eye.

## Diagnosis and treatment

Glaucoma is usually painless, with no symptoms until you begin losing peripheral vision. That's why comprehensive eye exams are important. But sometimes NTG is missed despite an exam. "We see that happen in cases where the optic nerve was not carefully evaluated," says Dr. Shen.

## **The Eyes Have It**

Why and how you see

Longwood Seminars, March 6, 2014

Diagnosing NTG involves measuring the pressure in your eye and the thickness of the cornea, inspecting the optic nerve for damage, testing the visual field to determine the function of the nerve, and taking pictures of the optic nerve and the back of the eye. NTG is treated the same way as regular glaucoma: by trying to lower eye pressure—even if the pressure is “normal.” This is done using either eye drops or laser therapy (trabeculoplasty) to improve fluid drainage in the eye. If the glaucoma continues to worsen with these treatments, surgery to enlarge the eye’s drain may be necessary.

### **What you can do**

In order to prevent NTG and any other glaucoma, avoid smoking and excessive caffeine consumption, which may raise eye pressure. Dr. Shen says no particular nutrients are known to help prevent glaucoma. The best way to catch and stop glaucoma may be with comprehensive eye exams. People at risk for glaucoma should get an annual dilated eye exam. People over 65, African Americans, people with a family history of glaucoma, and people with heart disease, high blood pressure, diabetes, or underactive thyroid are at increased risk.

#### **To learn more...**

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## The Eyes Have It

Why and how you see

Longwood Seminars, March 6, 2014

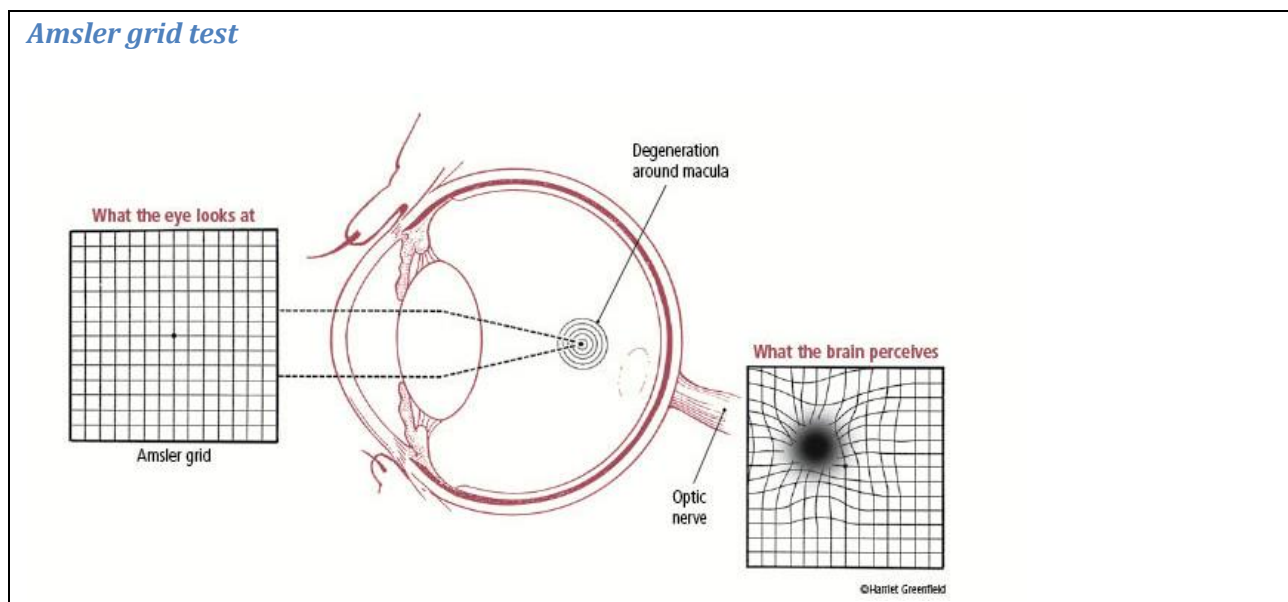
# Keep an eye out for age-related macular degeneration

Age-related macular degeneration (AMD) strikes at the macula, the heart of the eye's vision center. This small part of the retina is responsible for sharp, central vision. People with AMD often develop blurred or distorted vision and cannot clearly see objects directly in front of them. Eventually they may develop a blind spot in the middle of their field of vision that increases in size as the disease progresses. There are two types of AMD: dry and wet.

Most people with AMD have the dry version. It is caused by a breakdown or thinning of the retina. Although symptoms vary, people with dry AMD usually first experience blurred vision and difficulty reading or distinguishing faces. In some people, dry AMD progresses to the more serious wet form, which is the most common cause of severe vision loss. It occurs when abnormal blood vessels develop in the layer of cells beneath the retina. When they leak blood or fluid into the retina (hence "wet"), they can cause scarring in the macula, leading to a blind spot at the center of the visual field. Over time, this area may enlarge.

Your doctor can often detect signs of age-related macular degeneration before sight is affected and before permanent visual loss occurs. She or he may suspect this condition if the view through an ophthalmoscope reveals clumps of pigment or clusters of drusen (small yellow deposits that build up under the macula). A complete eye exam can detect coexisting eye diseases, such as cataract or glaucoma.

An Amsler grid test can help to identify the distorted vision typical of AMD. For this test, you focus your eyes on a central dot on a grid that resembles graph paper. If the lines near the dot appear wavy or are missing, AMD may be to blame. Distortion that appears on the grid may be a sign of the wet form of AMD.



## **The Eyes Have It**

Why and how you see

Longwood Seminars, March 6, 2014

### *A tiny telescope inside the eye*

A telescopic lens the size of a pea that is surgically placed within the eye may help older people with severe AMD see more clearly. The implantable miniature telescope (IMT) functions like a telephoto lens on a camera, magnifying images by two to three times. The telephoto effect allows images in the central visual field (so-called straight-ahead vision) to focus not on the damaged macula but instead on other, healthier areas of the retina. By reducing the “blind spot” that results from severe AMD, the implant enables people to recognize images that had been either difficult or impossible to see.

In a study of 206 people who received the IMT, 67% of the treated eyes had an improvement of three lines or greater on the eye chart, compared with 13% of the non-implanted control eyes. The IMT is designed to go in one eye only, for jobs like reading and recognizing faces, while the other eye is used for peripheral vision during other activities such as walking. People who receive the IMT must participate in a structured vision rehabilitation program to learn to use and maximize the different abilities of their eyes.

The device, which was approved by the FDA in 2010, isn't appropriate for most people with AMD. To be considered for the implant, you must be at least 75 years old, have end-stage AMD, and be legally blind (that is, your best corrected distance vision is between 20/160 and 20/800). People with better vision would not benefit from the enlarged image the device provides. As of early 2012, the surgery to implant the device is done only by cornea surgeons at selected centers in the United States.

Routine eye exams and early detection are important. The earlier AMD is detected, the more likely it can be treated successfully.

### **To learn more...**

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Why and how you see

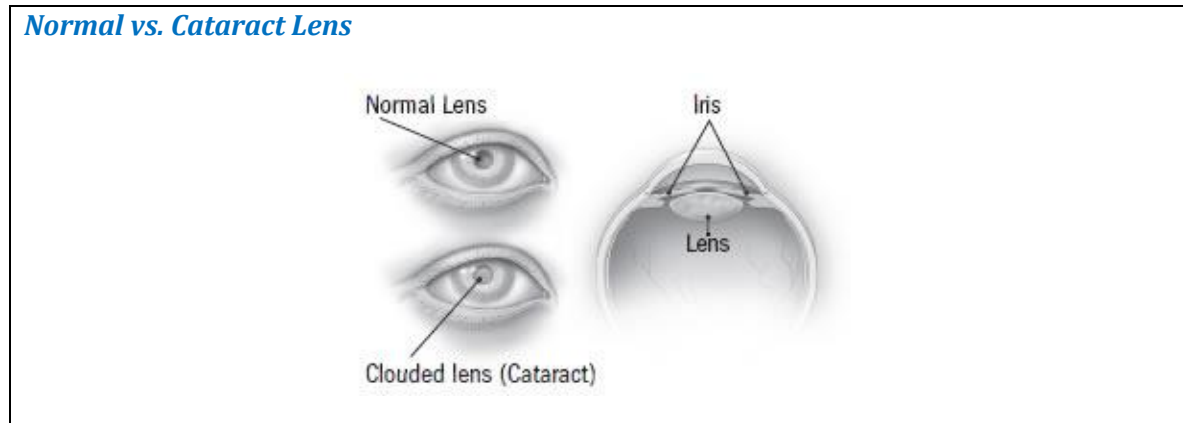
Longwood Seminars, March 6, 2014

# Advances in eye surgery

*Finally, lasers for cataracts, thanks to 3D imaging.*

We often think of three-dimensional (3D) images and lasers in terms of science fiction movies. But these two technologies are now being used in the very real realm of cataract surgery. “They both already exist, and we are just now bringing them together for novel use,” says Dr. Roberto Pineda, director of refractive surgery at the Harvard-affiliated Massachusetts Eye and Ear Infirmary.

### Normal vs. Cataract Lens



### Cataract surgery

When the natural lens of your eye becomes cloudy—often with age—it’s called a cataract. It can be removed and replaced with an artificial lens implant. This is a common outpatient procedure. An ophthalmologist uses surgical instruments and ultrasound power to break up, remove, and replace the eye’s cloudy lens.

Because surgeons are dealing with such tiny spaces in the eye, they’ve looked to lasers, not blades, for improved precision. But lasers have been used only for other eye surgeries, such as vision correction (LASIK) surgery. Cataract surgery requires surgeons to look much deeper into the eye. That’s where 3D imaging comes in.

### Marriage of 3D and lasers

The 3D imaging is called optical coherence tomography (OCT), and it allows the tiniest inner structures of the eye to be seen and measured very precisely. OCT was developed a decade ago and has been used to create images of the retina and the optic nerve. But the marriage of OCT and lasers is brand-new.

Here’s how it works: Ophthalmologists place a special device on the eye, which sends a 3D image to a screen. The surgeon looks at the image and tells a computer where the laser is to make incisions. The laser then executes the cuts and also breaks up the cataract. When the laser procedure is finished, a matter of minutes, the surgeon uses surgical instruments to remove the fractured cataract and position the new lens implant.

## **The Eyes Have It**

Why and how you see

Longwood Seminars, March 6, 2014

### **Risks and benefits**

The main benefit of 3D imaging and lasers is the increased precision in making incisions and carrying out the difficult steps of cataract surgery, especially placement of the new lens. “It takes away part of the human factor, where there can be complications,” similar to the use of robotic surgery to reduce human error, says Dr. Pineda. But he says it’s too early to tell if the technique is better than traditional surgery.

Risks are the same for laser cataract surgery as they are for traditional cataract surgery, including a slight chance of detachment of the retina, infection, and bleeding. However, laser surgery proponents suggest the procedure reduces those risks by providing a higher level of precision. The procedure is so new, it’s not yet widely available and it’s not covered by all insurance—so you’ll likely have to pay out of pocket (about \$1,000) beyond what insurance pays for traditional cataract surgery.

#### **To learn more...**

This information was prepared by the editors of the Harvard Health Publications division of Harvard Medical School. It originally appeared in the February 2013 issue of the *Harvard Health Letter*, available at <http://hvrld.me/tWeix>.

## The Eyes Have It

Why and how you see

Longwood Seminars, March 6, 2014

# Safeguarding sight

Although aging puts people at greater risk for serious eye disease and other eye problems, loss of sight need not go hand in hand with growing older. Practical, preventive measures can help protect against devastating impairment. An estimated 40% to 50% of all blindness can be avoided or treated, mainly through regular visits to a vision specialist.

Regular eye exams are the cornerstone of visual health as people age. Individuals who have a family history of eye disease or other risk factors should have more frequent exams. Don't wait until your vision deteriorates to have an eye exam. One eye can often compensate for the other while an eye condition progresses. Frequently, only an exam can detect eye disease in its earliest stages.

You can take other steps on your own. First, if you smoke, stop. Smoking increases the risk of several eye disorders, including age-related macular degeneration. Next, take a look at your diet. Maintaining a nutritious diet, with lots of fruits and vegetables and minimal saturated fats and hydrogenated oils, promotes sound health and may boost your resistance to eye disease. Wearing sunglasses and hats is important for people of any age. Taking the time to learn about the aging eye and recognizing risks and symptoms can alert you to the warning signs of vision problems.

Although eyestrain, spending many hours in front of a television or computer screen, or working in poor light does not cause harmful medical conditions (see "Common eye myths dispelled"), they can tire the eyes and, ultimately, their owner. The eyes are priceless and deserve to be treated with care and respect—and that is as true for the adult of 80 as it is for the teenager of 18.

### *Common eye myths dispelled*

**Myth:** Doing eye exercises will delay the need for glasses.

**Fact:** Eye exercises will not improve or preserve vision or reduce the need for glasses. Your vision depends on many factors, including the shape of your eye and the health of the eye tissues, none of which can be significantly altered with eye exercises.

**Myth:** Reading in dim light will worsen your vision.

**Fact:** Although dim lighting will not adversely affect your eyesight, it will tire your eyes out more quickly. The best way to position a reading light is to have it shine directly onto the page, not over your shoulder. A desk lamp with an opaque shade pointing directly at the reading material is the best possible arrangement. A light that shines over your shoulder will cause a glare, making it more difficult to see the reading material.

**Myth:** Eating carrots is good for the eyes.

**Fact:** There is some truth in this one. Carrots, which contain vitamin A, are one of several vegetables that are good for the eyes. But fresh fruits and dark green leafy vegetables, which

## **The Eyes Have It**

Why and how you see

Longwood Seminars, March 6, 2014

contain more antioxidant vitamins such as C and E, are even better. Antioxidant vitamins may help protect the eyes against cataract and age-related macular degeneration. But eating any vegetables or supplements containing these vitamins or substances will not prevent or correct basic vision problems such as nearsightedness or farsightedness.

**Myth:** It's best not to wear glasses all the time. Taking a break from glasses or contact lenses allows your eyes to rest.

**Fact:** If you need glasses for distance or reading, use them. Attempting to read without reading glasses will simply strain your eyes and tire them out. Using your glasses won't worsen your vision or lead to any eye disease.

**Myth:** Staring at a computer screen all day is bad for the eyes.

**Fact:** Although using a computer will not harm your eyes, staring at a computer screen all day will contribute to eyestrain or tired eyes. Adjust lighting so that it does not create a glare or harsh reflection on the screen. Also, when you're working on a computer or doing other close work such as reading or sewing, it's a good idea to rest your eyes briefly every hour or so to lessen eye fatigue. Finally, people who stare at a computer screen for long periods tend not to blink as often as usual, which can cause the eyes to feel dry and uncomfortable. Make a conscious effort to blink regularly so that the eyes stay well lubricated and do not dry out.

### **To learn more...**

This information was prepared by the editors of the Harvard Health Publications division of Harvard Medical School. It is excerpted from the 2012 edition of the Special Health Report *The Aging Eye*, available at [hvr.d.me/tWdqU](http://hvr.d.me/tWdqU).

## The Eyes Have It

Why and how you see

Longwood Seminars, March 6, 2014

# Top foods to help protect your vision

*You'll want to concentrate on yellow and orange fruits and vegetables, plus egg yolks and fatty, cold-water fish.*

When it comes to protecting your vision, what you eat may affect what you see. Certain vitamins and minerals found in food may play a role in preventing two common causes of vision problems: cataracts—cloudy areas in the lens of the eye—and age-related macular degeneration (AMD)—a condition that causes vision loss in the macula, the part of the eye that controls central vision. “While there is no definite proof, some studies suggest that eating a diet rich in certain nutrients may help,” says Dr. Ivana Kim, associate professor of ophthalmology at Harvard Medical School.

## Nutrients to consider

Some evidence shows that dietary antioxidant vitamins and minerals (A, C, and E, and the mineral zinc) may help prevent the progression of macular degeneration. “The retina, especially the macula, is thought to be an environment of high oxidative stress, meaning that there is an abundance of free radicals—molecules that damage proteins and DNA within cells. Antioxidants fight free radicals and are thought to help protect the retina from this damage,” explains Dr. Kim.

Lutein and zeaxanthin are carotenoids found in the retina, and dietary intake of these compounds has been shown to have antioxidant properties and to improve pigment density in the macula. This pigment protects the cells in the macular area by absorbing excess blue and ultraviolet light and neutralizing free radicals. Lutein and zeaxanthin are usually found together in food.

Dietary intake of the omega-3 fatty acid DHA (docosahexaenoic acid) may be important to retinal health. “DHA is present in high concentrations in the outer segments of retinal photoreceptors,” says Dr. Kim. “Omega-3 fatty acids have been shown to have anti-inflammatory properties, and there is evidence to suggest that inflammation plays a role in AMD.”

## Finding the nutrients

You'll find lutein and zeaxanthin in most fruits and vegetables, especially yellow and orange varieties and leafy greens. Egg yolks are an even richer source of these nutrients. Omega-3 fatty acids are found in coldwater fish, flaxseed, and walnuts. Good sources of zinc include red meat and shellfish. You'll find vitamins A, C, and E in many vegetables, fruits, nuts, and seeds.

Research hasn't proved how much of these nutrients we need in order to help prevent eye problems, but Dr. Kim suggests following a heart-healthy diet with fish at least twice a week and at least five servings of fruits and vegetables daily.

## The Eyes Have It

Why and how you see

Longwood Seminars, March 6, 2014

<b>Best food sources of eye-healthy nutrients</b>	
<b>Nutrients</b>	<b>Foods</b>
Lutein, zeaxanthin	Broccoli, Brussels sprouts, collard greens, corn, eggs, kale, nectarines, oranges, papayas, romaine lettuce, spinach, squash
Omega-3 fatty acids	Flaxseed, flaxseed oil, halibut, salmon, sardines, tuna, walnuts
Vitamin A	Apricots, cantaloupe (raw), carrots, mangos, red peppers (raw), ricotta cheese (part-skim), spinach, sweet potatoes
Vitamin C	Broccoli, Brussels sprouts, grapefruit, kiwi, oranges, red peppers (raw), strawberries
Vitamin E	Almonds, broccoli, peanut butter, spinach, sunflower seeds, wheat germ
Zinc	Chickpeas, oysters, pork chops, red meat, yogurt

### To learn more...

This information was prepared by the editors of the Harvard Health Publications division of Harvard Medical School. It originally appeared in the August 2013 issue of the *Harvard Health Letter*, available at <http://hvr.d.me/tWeix>.

# Harvard Medicine

The following articles are selections from *Harvard Medicine* magazine's spring 2010 edition. Additional content can be found online, please visit: <http://harvardmedicine.hms.harvard.edu/>

## What Meets the Eye

Our ability to take in visuals may reveal only a small portion of what is really there.

by Jessica Cerretani

Vision, wrote Jonathan Swift, is the art of seeing the invisible. In truth, however, we may not even notice the obvious, says Jeremy Wolfe, HMS professor of ophthalmology and head of Brigham and Women's Hospital's Visual Attention Lab. Together with Todd Horowitz and other colleagues, Wolfe is identifying the ways in which we search for objects and detect changes in what we see—research that has real-world implications for fields as diverse as baggage screening and radiology. The researchers' conclusion: We often miss what's right in front of our eyes. "We believe we're viewing the whole world," explains Wolfe. "But we're only processing a small part of it at any one time."

We perform visual searches every day, whether rifling through a drawer for car keys or assembling a jigsaw puzzle. But some searches—for a gun in carry-on baggage or a tumor on an MRI scan—are more crucial than others. Studies by Wolfe, Horowitz, and others suggest that the less common an object is, the harder it is to spot it when it appears. "Targets like guns and tumors are relatively rare," says Horowitz, an HMS assistant professor of ophthalmology. "So we're less likely to notice them when they do show up."

Inspired by findings from their laboratory research, in which volunteers were asked to locate unique letters or symbols on a computer screen—a single letter *T* in a field of *L*s, for example—Wolfe and his colleagues have expanded their experiments. In one recent study, they asked participants to search for weapons in computer-simulated baggage. The participants were told the rough likelihood that a weapon would be present and were rated on both the time it took them to identify the object and their accuracy. When told that weapons were rare, participants dismissed luggage more quickly and failed to locate more of the weapons that were present. When told that the weapons were common, they dismissed luggage more slowly and reported seeing weapons that were not present.

“This phenomenon is likely ancient and widespread rather than a product of modern civilization,” Wolfe says. “If a prehistoric ancestor was examining a bush that almost always yielded food, for example, she probably kept searching for a long time.”

The vision laboratory’s findings have practical applications for training airport security personnel, Wolfe adds. He is planning to conduct similar investigations working with radiologists, who worry about misses as well as the consequences of false-positive reports of tumors. The research may also translate to other types of visual searchers, from Coast Guard officers looking for overturned boats to government employees interpreting spy satellite images.

## **Vision Quest**

HMS discoveries have helped shape our vision of the future.

by Jessica Cerretani

**1950** More than half a century ago, famed retinal surgeon Charles Schepens saw the need for a research organization dedicated to exploring new treatments for incurable eye disorders. Originally called the Retina Foundation, the HMS affiliate has since been renamed the Schepens Eye Research Institute for its founder. Its researchers have published nearly 5,000 scientific papers and books about health and eye disease.

**1959** Glimpses into a cat’s eye shed light on the way nerve cells respond to light, motion, depth, color, and other visual stimuli. With their studies of the feline visual system, David Hubel and Torsten Wiesel, both researchers in the then-new HMS Department of Neurobiology, laid the foundation for the field of visual neurophysiology and greatly expanded knowledge of sensory processing. Their work was recognized with the 1981 Nobel Prize in Physiology or Medicine.

**1965** When Lloyd M. Aiello, now an HMS clinical professor of ophthalmology, began treating patients blinded by diabetic retinopathy, his waiting room was filled with seeing-eye dogs—many of which outlived their owners. Now, the vast majority of people with the disease retain their vision, thanks to Aiello’s pioneering work. With his late father-in-law, he pioneered pan-retinal coagulation, a treatment that uses a laser to halt the sight-stealing proliferation of blood vessels in people with diabetes.

**1992** Thousands of patients have avoided blindness thanks to FDA approval of the Boston Keratoprosthesis, an artificial cornea developed by Claes Dohlman, former chief of ophthalmology at the Massachusetts Eye and Ear Infirmary. His invention is used in people with severely diseased corneas when transplants from human donors fail.

**1994** Like father, like son: A third-generation ophthalmologist at Joslin Diabetes Center and HMS, Lloyd P. Aiello has spearheaded his own research into the roots of vision loss. His studies have shown that vascular endothelial growth factor, or VEGF, plays a major role in the



proliferation of blood vessels in eye diseases including diabetic retinopathy and age related macular degeneration.

**2000** Age-related macular degeneration is still the leading cause of blindness in older adults, but its treatment has improved over the years, thanks in part to the efforts of Joan Miller '84, chief of ophthalmology at the Massachusetts Eye and Ear Infirmary. Along with her colleague Evangelos Gragoudas, she pioneered the use of photodynamic therapy to damage abnormal blood vessels in the eye without harming the retina. This approach, which was approved in 2000 as the first treatment for age-related macular degeneration, has reduced vision loss in many patients.

**2006** The rich legacy of angiogenesis pioneer Judah Folkman '57 has not been limited to cancer treatment. Research by the late investigator and others at Children's Hospital Boston led to the creation of the anti- VEGF drug ranibizumab for the treatment of age-related macular degeneration. The FDA approved the medication after data showed that it might not only slow vision loss but also restore sight in some patients.

**2010** Once the stuff of science fiction, a bionic eye is closer than ever to becoming reality, courtesy of researchers at the Boston Retinal Implant Project—a joint effort of the Massachusetts Eye and Ear Infirmary, the Veterans Affairs Boston Healthcare System, and the Massachusetts Institute of Technology and co-founded by HMS Associate Professor of Ophthalmology Joseph Rizzo III. The device would require users to wear a small camera mounted to eyeglasses. The camera would transmit signals to a surgically implanted chip behind the retina, helping people with macular degeneration or retinitis pigmentosa regain some vision.

## Probing the Genetics of Blindness

Genes causing a rare but devastating type of inherited blindness form a puzzle, but researchers are assembling the pieces

By MASSACHUSETTS EYE AND EAR

*July 30, 2012*

Researchers have isolated an elusive human gene that causes a common form of Leber congenital amaurosis (LCA), a relatively rare but devastating type of early-onset blindness. The newly found LCA gene is called NMNAT1. Finding the specific gene mutated in patients with LCA is the first step toward developing sight-saving gene therapy.

LCA is an inherited retinal degenerative disease characterized by reduced vision in infancy. Within the first few months of life, parents usually notice a lack of visual responsiveness and unusual roving eye movements known as nystagmus. LCA, which typically involves only vision problems, can be accompanied by disease in other organ systems in a minority of patients, and is a common reason that children are enrolled in schools for the blind.

“The immediate benefit of this discovery is that affected patients with mutations in this new LCA gene now know the cause of their condition,” said [Eric Pierce](#), co-senior author and HMS associate professor of ophthalmology at [Massachusetts Eye and Ear](#). “Scientists now have another piece to the puzzle as to why some children are born with LCA and decreased vision. The long-term goal of our research is to develop therapies to limit or prevent vision loss from these disorders.”

Collaborators also included researchers from the [Children's Hospital of Philadelphia](#) and [Loyola University Chicago Health Sciences Division](#). The findings were published July 29 online in [Nature Genetics](#).

NMNAT1 is the 18th identified LCA gene. The gene resides in a region that has been known to harbor an LCA gene since 2003, but the specific disease gene was undiscovered until now.

To identify NMNAT1, scientists sequenced the protein-coding regions of the genome (a technique called exome sequencing) of the family of two siblings who initially presented for evaluation of LCA but who had no mutations in any of the known LCA genes. Evaluation by a multidisciplinary team that took the case from careful clinical characterization to genetic testing to the research laboratory was an essential ingredient for success.

By using this particular sequencing technique, “we found a mutation in a gene that no one could have predicted would be associated with LCA,” said Pierce.

“Whereas most of the known LCA genes involve dysfunction of retinal ciliary proteins necessary for light detection in the eye, NMNAT1 is uniquely distinguished by being the first metabolic enzyme linked to LCA,” said Marni J. Falk, co-first author and clinical geneticist at the Children’s Hospital of Philadelphia and the Perelman School of Medicine at the University of Pennsylvania.

Having found a mutation in NMNAT1 in this one family, the investigators next asked if mutations in NMNAT1 also cause disease in other patients with LCA. Screening of 284 unrelated patients with LCA from the U.S., England, France and India allowed them to identify 13 other patients with mutations in NMNAT1 as the cause of their disease.

Falk, Pierce and colleagues also studied how the identified mutations in the NMNAT1 gene affects the protein it produces, possibly causing dysfunction and death of the light-sensitive photoreceptor cells in the retina. Working together with Eiko Nakamaru-Ogiso in the department of biochemistry and biophysics at the University of Pennsylvania, they found that mutations appear to decrease the ability of the NMNAT1 protein to produce NAD<sup>+</sup>, a key mediator of cellular signaling and energetics.

Early treatment for patients with NMNAT1-related LCA could be especially beneficial.

Researchers found that all but the youngest patient with NMNAT1 mutations had damage to the macula, the center of the retina that is needed for central vision. “This 4-year-old girl who doesn’t have central vision loss yet can possibly benefit substantially if we can devise a therapy for her NMNAT1-mediated LCA that prevents her from developing severe central vision loss,” Pierce said.

This study is an example of the multidisciplinary collaboration among the three institutions, using exome sequencing to discover genes involved in inherited diseases caused by mutations in a single gene.

“With the robust database and pipeline that we have developed, we have analyzed more than 300 whole exomes of patients and families with single-gene diseases,” said Xiaowu Gai, co-senior author and director of the Center for Biomedical Informatics at Loyola University Chicago Stritch School of Medicine. “We are following up on a number of strong candidate genes. We are sequencing many new samples and expect similar exciting discoveries for other diseases.”

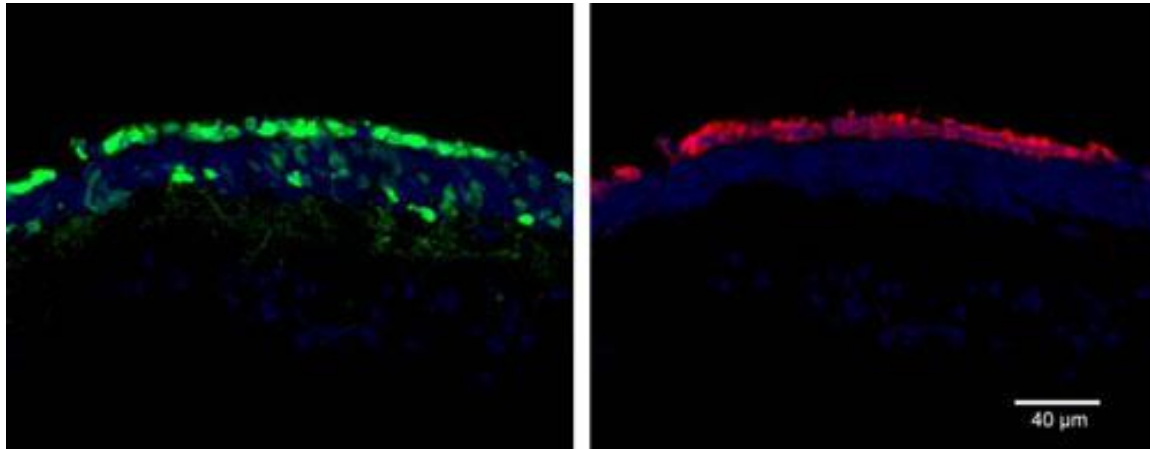
Adapted from a Massachusetts Eye and Ear press release.

## **Cone Death in Retina Traced to Lack of Nutrition**

**Alyssa Kneller**

*January 23, 2009*

Rods and cones coexist peacefully in healthy retinas. Both types of cell occupy the same layer of tissue and send signals when they detect light, which is the first step in vision. The incurable eye disease retinitis pigmentosa, however, reveals a codependent relationship between the two that can be destructive. When flawed rods begin to die, otherwise normal cones follow them to the grave, leading to blindness.



Sight saver. Researchers inserted extra copies of the HDAC4 gene (left) into the retinas of newborn rd1 mice. Despite their damaging rod-specific mutations, these mice still possessed rods when they were 50 days old (right). Courtesy Constance Cepko and Science.

Researchers have proposed a variety of hypotheses to explain the loss of cones in patients with mutations in rod-specific genes, but it was not clear that these could explain all of the observations in patients and animal models of the disease. Howard Hughes investigator [Constance Cepko](#), an HMS professor of genetics, took a fresh approach to the problem along with colleagues and published a new hypothesis in the January *Nature Neuroscience*.

Postdoctoral researcher Claudio Punzo gathered four strains of mice, each with a different rod-specific mutation and a different rate of disease progression. He discovered an interesting pattern—cone death always began after the major phase of rod death.

Punzo and collaborator Karl Kornacker, a professor at Ohio State University, analyzed gene expression before and after this point in each strain. During the cone death phase, 230 genes were always expressed at higher levels. Sleuthing revealed that 34.9 percent of these play a role in cellular metabolism, including 12 genes in the insulin/mTOR pathway.

mTOR serves as a signaling hub, gathering information about the environment and helping the cell decide whether it has enough nutrients to make new proteins. Punzo now had a lead.

Further experiments suggested that the cones lacked nutrition. The cells revealed their problems when they were examined for evidence of self-digestion, or autophagy, a last ditch effort by the cell to survive a nutritional crisis by digesting its nonessential components. The cones appeared to be undergoing autophagy when the cone population was dying. To see if the self-digestion could be interrupted, Punzo tricked the cells into thinking they had enough nutrition by injecting the mice with insulin. Indeed, the death of cones was temporarily slowed.

Cepko said this nutrition hypothesis makes structural sense. Rods outnumber cones by more than 20 to 1, and retinal pigment epithelial (RPE) cells, which touch the photoreceptors and supply them with nutrients, probably sag when too many rods disappear. The structural change likely disturbs the contacts between RPE cells and cones, possibly impeding the flow of nutrients.

“This points us in a new direction,” said Cepko. “We’re currently exploring ways to boost nutrient levels in the cones.”

Cepko’s team is searching for other ways, as well, to boost photoreceptor survival. In a study published in the Jan. 9 issue of *Science*, postdoctoral researcher Bo Chen applied electroporation to show that he could keep rods and cones alive in mice with retinal disease by overexpressing the gene HDAC4. Chen injected DNA coding for HDAC4 into the retinas of newborn mice and administered an electric current to force the DNA into the cells. The mice with extra copies of the gene retained their rods and cones longer than mice without the extra copies. HDAC4 may protect the cells by stabilizing HIF1alpha, which regulates oxygen homeostasis.

*Conflict Disclosure: The authors report no conflicts of interest.*

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## The Gene Therapy Renaissance

**How one experimental technique overcame a troubled legacy and today is helping the blind to see**

**By R. ALAN LEO**

*April 18, 2013*

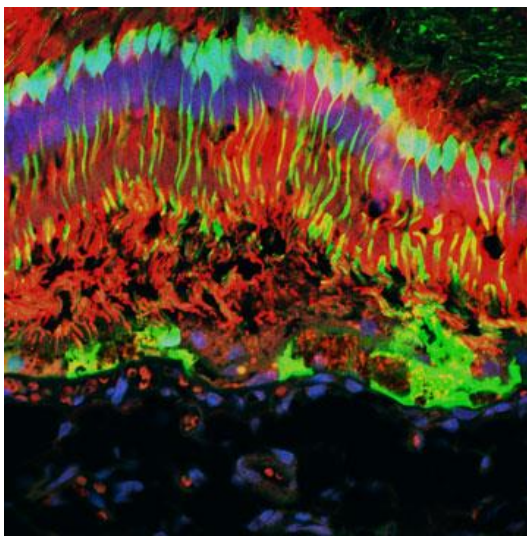
In 1999, researchers at the University of Pennsylvania injected 18 people with a virus carrying a gene designed to correct a rare metabolic disease. Early results appeared promising: Among the first 17 adult subjects, the worst symptom was a fever, an expected response to the modified virus that carried the therapeutic gene.

The 18<sup>th</sup> subject was Jesse Gelsinger, who died.

Investigators still debate exactly what went wrong, but most agree that the delivery virus triggered a massive and fatal overreaction from the 18-year-old's immune system. For the field of gene therapy, the Gelsinger case became shorthand for a sea of troubles.

Some saw a story of tragic hubris: a teenager paying with his life when researchers pushed too far, too fast. Others pointed to flaws in design and conduct specific to that trial, but the damage to the field was done. The Penn trial was halted immediately. So were other planned trials. Congressional hearings followed. Federal regulators and institutional review boards increased scrutiny that continues to this day. Investors shied away from new ventures and shelved ones already begun.

Gene therapy's golden dawn had ended. But through the twilight years that followed, researchers learned from each setback and forged ahead. Today, many researchers investigating gene therapies and their biological underpinnings share an optimism long absent or long unseen. When it comes to conditions of the eye, gene therapists have achieved some of their most exciting successes to date. Researchers at HMS are building on that progress to help the blind to see.



Section of retina targeted with adeno-associated viral (AAV) gene transfer. Photoreceptors and pigment epithelium express a fluorescent protein following gene delivery. Image by Luk H. Vandenberghe

## Refocusing

One such researcher is [Eric Pierce](#), the Solman and Libe Friedman Associate Professor of Ophthalmology at Harvard Medical School and director of the [Ocular Genomics Institute](#) at the [Massachusetts Eye and Ear Infirmary](#).

But in 1999, the pediatric ophthalmologist and HST alum was just setting up his new academic lab at Penn's Scheie Eye Institute, to investigate the genetics of retinal diseases. This was also the year Jesse Gelsinger died.

Though he wasn't yet involved in gene therapy, Pierce was soon drawn to its potential after colleagues reported in 2001 that they had restored vision to a population of dogs with a condition nearly identical to a human retinal disease, [Leber congenital amaurosis](#), or LCA. That team, led by husband-and-wife researchers Jean Bennett and Albert Maguire, injected the dogs' retinas with a virus carrying a functional copy of a defective gene, [RPE65](#).

Encouraged by those results, Pierce set up a retinal degeneration and genetics program in the Division of Ophthalmology at Children's Hospital of Philadelphia, to prepare for the day if and when ocular gene therapy reached human trials. "I thought I was getting ahead," Pierce recalls. "But within a year, Jean and Albert came to me and said, 'We want to do a clinical trial. Would you help?' So I just got started in time."

That collaboration led to the most celebrated success in gene therapy. In 2008, the team reported that the first three patients, young adults, all saw modest improvement in retinal function with almost no adverse effects. Dozens have been treated since, with the greatest benefits accruing to the youngest patients.

"Between tests, kids would say, 'I can ride my bicycle around the neighborhood' or 'I can play soccer on my own'—in other words, without an aide to help find the ball," Pierce said. "Adults would say, 'I can find my way to my seat in the restaurant for dinner, even if the lights are down' or 'I can see my kid play sports that I could never see before.'"

These were the sort of results researchers wait careers for. And it was just the beginning.



Schematic illustration of subretinal injection of adeno-associated viral vector (AAV) with different types of AAV, each of which have distinct specificity for the various retinal cell types. Image by Peter Mallen

## Setting sights

The LCA trial delivered a single gene—*RPE65*—to correct a single genetic defect. But the disease, which affects about 1 person in 80,000, is part of a much larger family of degenerative eye diseases known collectively as inherited retinal degenerations. The most common cause of inherited retinal degeneration, retinitis pigmentosa (RP) affects about 1 person in 3,000, and about half of those cases have been linked to mutations in any of 200 different disease genes. Researchers are working today to replicate the success of *RPE65* therapy with some of these other genes—but they are also looking for ways to move beyond that scattershot approach.

“LCA is very specific. You’re replacing a diseased gene, but you can’t do that for every gene. That one trial may have cost \$10 million, and you can’t do that for every disease,” said [Joan Miller](#), Henry Willard Williams Professor of Ophthalmology and chair of the Department of Ophthalmology at HMS. “So you need to look for pathways that are common to classes of disease.”

That’s how Miller, who is chief of ophthalmology at Mass Eye and Ear, recruited Pierce. Her pitch: Build a center for collaboration among the world’s leading experts on retinal degenerations and other eye diseases to find common pathways and strategies to treat them.

Pierce joined the Berman-Gund Laboratory for the Study of Retinal Degenerations, whose director, Eliot Berson, had built a large databank of 9,000 blood samples and 14,000 examination results from inherited retinal degeneration patients. Pierce directs the Ocular Genomics Institute, a group that includes glaucoma geneticist Janey Wiggs, Paul Austin Chandler Associate Professor of Ophthalmology, and HMS Professor of Neurology Elizabeth Engle, an expert on the genetics of eye movement disorders. “I don’t think there’s any other group around the world that’s got such a great combination of people focused on the genomics of eye disease,” Miller said. “The Ocular Genomics Institute is primed to do something big with genetics and gene-based therapies.”

Miller plucked another rising star from Penn, virologist [Luk Vandenberghe](#). Vandenberghe’s specialty is adeno-associated viruses (AAVs), a promising class of “stealth” viruses that naturally infect humans without causing any known disease.



## Revamping Vectors

Researchers point to the development of AAV vectors as a driving force in gene therapy's comeback. Unlike the adenovirus given to Jesse Gelsinger, they don't provoke the immune system while they deliver the desired gene. And unlike retroviruses used in other forms of gene therapy, they operate alongside, rather than within, the host's DNA, avoiding potential cancer-causing mutations. (Their stealth comes with a price, however: a relatively small cap on the size of the genes they can carry.)

"AAV has chosen a path, it seems, to basically fly under the radar as a virus," said Vandenberghe, now a member of the Ocular Genomics Institute and a HMS lecturer in ophthalmology at [Schepens Eye Research Institute](#) and Mass Eye and Ear. "And as a vector, that's actually an ideal property because we do not want to alert the immune system to our presence, because that could lead to dire clinical consequences and the elimination of the genetic graft."

This year, Vandenberghe opens the doors of a core facility to engineer new viral vectors and provide them to researchers across the HMS community. Among those researchers is [Connie Cepko](#), Bullard Professor of Genetics and Neuroscience in the [HMS Department of Genetics](#).

In the 1980s, Cepko had developed some of the first retroviral vectors as a postdoc at MIT and the Whitehead Institute. When she opened her own lab, she used some of these same tools to explore fundamental questions about how the eye develops. She kept an interest in gene therapy from the sidelines. Then came the first success of *RPE65* therapy, in dogs.

"From that moment I knew that AAV would work, and I thought it would work in humans," said Cepko, who is also a [Howard Hughes Medical Institute](#) Investigator. "So we started a new project to ask, 'What could we do that would be a fairly generic gene therapy for the various genetic forms of blindness?'"

## Common Vision

Cepko's team began by asking: Why do photoreceptors die? The answer hinges on the two kinds of photoreceptors: rod photoreceptor cells, responsible for vision in dim light, and cone photoreceptor cells, responsible for color and detail. In most types of RP, the rods express a disease gene, while cones do not. This means that individuals with RP are born night-blind, but they can see quite well during the day—at first, anyway. Depending on the individual, color vision starts to fade during childhood, while in others it can fade as late as age 50.

“We thought if we could understand why the cones lose function and then die, there might be a generic way to combat that,” Cepko said. “Because no matter what the rod disease gene is, the cones always die.” They looked at four mouse models of RP, each with a different genetic defect in their rods, and asked what is common at the time cones start to die.

They found an answer in a metabolic regulator, mTOR, which plays a key role in cell growth, survival and proliferation. “We knew something was wrong with the cones very early on the disease, because mTOR was not phosphorylated,” Cepko said. The researchers used insulin, which can trigger phosphorylation of mTOR, and found that this treatment prolonged the survival of the cones.

“So we said, okay, can we think of other ways to metabolically intervene and help these sick cones? We started thinking along these lines as daily injections with insulin over many years will not be a good therapy” Cepko said. “We have been asking, if there is a way we can augment the metabolism, sort of give the cells a booster, like a generic tonic for their metabolism?”

Now, Cepko is screening a handful of genes in mice that may provide that metabolic boost. Her lab develops some of its own viral vectors, and sources others from outside providers. Animal tests and vector development are time-consuming and profoundly expensive, she says—endeavors that would benefit from shared resources and facilities.

“Right now, every time we come up with an idea for a new gene to try, we run up against the expense of this type of work. The expenses limit what we do in a very serious way,” Cepko said. “A core here for basic science and preclinical work would be a fantastic resource and would help move things along.”

It’s a common vision among gene therapy researchers, and one Pierce and Vandenberghe would like to take a step further—a core facility certified to produce viral vectors for use not only in labs, but also in patients.

“Developing a clinical virus production facility in the Harvard community could facilitate many things,” Pierce said. “It could help us get to clinical trials faster. The intellectual property of Harvard-derived vectors could be a revenue source. And the scale is such that having the larger Medical School community be part of that process could make it work better.”

The researchers are profoundly optimistic about the potential to treat not just one defect, but entire classes of eye disease, and other diseases as well.

It’s an optimism that Cepko contrasts with the blue-sky enthusiasm of the 1980s and ’90s, when

the public—and some scientists—discussed gene therapy as a panacea for inherited disease.

“I think the original optimism was just not well founded in science,” Cepko said, “and I hold some of the scientists responsible for that. Richard Mulligan, one of the people who created this field, was right when he cautioned that the time course being touted was just too ambitious, considering where we were in our understanding of the vectors, their delivery, and the diseases.”

According to Cepko, this second wave of optimism is based on two things. First, researchers have learned a lot more about the technical aspects of the field, such as vector design, production, delivery, types of diseases to target, which vector for which disease, to name a few. And second, they have learned from the experiences in the clinic—including the disasters.

“The therapy in the eye didn’t have any disasters. It was just: AAV worked; we’re all very happy about that. It was an insightful choice for Bennett and her colleagues to use AAV, and their choice was based upon good science. But it’s also good fortune. Many things might not have worked. Future attempts might fail due to some technical issues, but it is important that this first case did not have safety issues. It will spur the development of gene therapy for many other diseases. We have come to appreciate how idiosyncratic each case will be, and thus not all will work. But having such a wonderfully successful trial in the eye gives us great encouragement, and it is very likely that at least some other attempts also will be successful.”

## For More Information

\*If clicking on a link below does not take you to the website, please copy and paste the URL into your browser\*

### **Science Matters video with Connie Cepko: Uncovering Mother Nature's secrets**

HMS video

<http://hms.harvard.edu/videos/science-matters-connie-cepko>

### **Massachusetts Eye and Ear Infirmary**

<http://www.masseyeandear.org/>

### **Really? On a Cloudy Day, Your Eyes Can Be Sunburned?**

The New York Times

<http://well.blogs.nytimes.com/2012/12/10/really-on-a-cloudy-day-your-eyes-can-be-sunburned/>

### **How do your eyes work?**

<http://www.nei.nih.gov/health/healthyeyes/index.asp>

### **Eye Healthy Tips**

<http://www.nei.nih.gov/healthyeyes/eyehealthtips.asp>

### **Good Foods for Eye Health**

<http://www.webmd.com/healthy-aging/nutrition-world-3/foods-eye-health>

### **Safer Cataract Surgery at Hand**

Massachusetts Ear and Ear story

<http://news.harvard.edu/gazette/story/2012/06/safer-cataract-surgery-at-hand/>

### **Research & Discovery**

[http://www.masseyeandear.org/gedownload!/4 Frontiers in Ophthalmology Research+Discovery.pdf?item\\_id=70290048&version\\_id=70290049](http://www.masseyeandear.org/gedownload!/4%20Frontiers%20in%20Ophthalmology%20Research+Discovery.pdf?item_id=70290048&version_id=70290049)

### **Postmenopausal Estrogen Therapy Tied to Lower Glaucoma Risk**

HealthDay News

<http://consumer.healthday.com/eye-care-information-13/eye-and-vision-problem-news-295/postmenopausal-estrogen-may-reduce-glaucoma-risk-684350.html>

### **Common Glaucoma Drug May Cause Droopy Eyelids, Study Finds**

HealthDay News

<http://consumer.healthday.com/general-health-information-16/misc-drugs-news-218/common-glaucoma-drug-may-cause-droopy-eyelids-study-finds-676631.html>

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