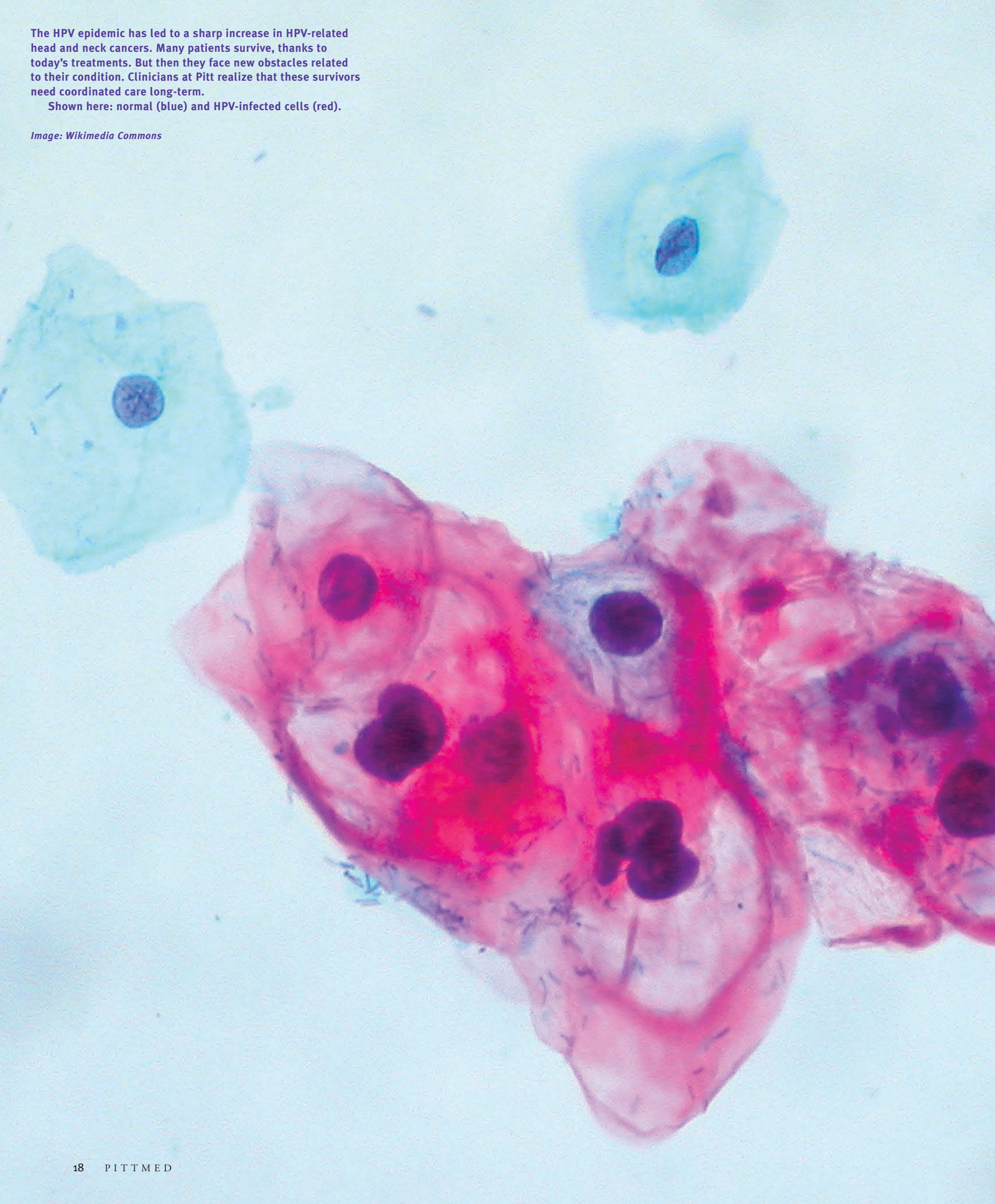
The HPV epidemic has led to a sharp increase in HPV-related head and neck cancers. Many patients survive, thanks to today's treatments. But then they face new obstacles related to their condition. Clinicians at Pitt realize that these survivors need coordinated care long-term.

Shown here: normal (blue) and HPV-infected cells (red).

Image: Wikimedia Commons





LIFE AFTER HEAD AND NECK CANCER CAN BE A STRUGGLE

BY GAVIN JENKINS

SURVIVING SURVIVAL

Jonas Johnson presses his hand on Edward Christopher's neck. The examination room at the UPMC Head and Neck Cancer Survivorship Clinic is chilly on this June morning as Johnson, chair of the University of Pittsburgh Department of Otolaryngology, glides his fingers along the left side of Christopher's throat.

"Your skin is stiff," Johnson says. "Scar tissue doesn't go away."

Five years ago, Christopher was diagnosed with human papillomavirus (HPV) positive cancer on the base of his tongue, left tonsil, and the lymph nodes on the left side of his neck. After undergoing surgery to remove the tumors, he received radiation treatment and chemotherapy, followed by another procedure to remove his lymph nodes.

When he completed the treatment, he posted a picture on Facebook holding a sign that read CANCER FREE! That night, he and his family celebrated with dinner at an Italian restaurant.

Christopher felt lucky to be alive and grateful to Pitt doctors. He had no idea how difficult the years to come would be.

Half a decade later, he struggles to swallow bread, and when he eats cookies—a daily, midday treat—the 68-year-old has to dunk them in coffee first.

Johnson turns to Kathy, Christopher's wife, and explains that the rigidity in Christopher's skin is a side effect from radiation and chemotherapy treatments; this is what's been compromising his swallowing and speech. "He's gotta keep stretching [his neck] forever, or else he'll pay the price," Johnson says.

That price could be choking to death, which nearly happened to Christopher a few years ago. He had taken a big bite out of his dinner and couldn't swallow it like he would have before he had cancer. Kathy slapped his back until he coughed up the food.

Johnson spent decades fixated on removing cancerous tumors from patients through surgery. After an operation, when he saw a patient, his main concern was whether cancer had returned. If it hadn't, Johnson asked, "How are you doing?" The patient, who also was focused on cancer returning, usually replied, "Fine."

Later Johnson would learn how some simple tasks of daily living can be arduous for head and neck cancer survivors. Now he understands that when patients are asked specific questions about their lives, including the economic cost of being a head and neck cancer survivor, they indicate that they're far from fine.

"The results are shocking," Johnson says. "They are still shocking to me."

He credits Marci Lee Nilsen, a nurse who is a PhD assistant professor in Pitt's School of Nursing, with opening his eyes.

In 2016, Johnson and Nilsen created the Survivorship Clinic to help patients like Christopher improve their quality of life after beating head and neck cancer. Most patients grapple with dysphagia—difficulty swallowing—and trismus, commonly known as lockjaw. They might experience a loss of taste, tooth decay, dry mouth, and mouth sores. The side effects from radiation and chemotherapy can often cause patients to struggle to talk, hear, and sleep, as well. The combination of these treatments with surgery can also lead to mobility issues; many patients end up on disability. Insomnia and sleep apnea can exacerbate anxiety and depression (which also are common issues).

Getting care for these conditions can place a financial strain on patients who have already spent tens of thousands of dollars to overcome cancer.

Survivorship clinics for head and neck cancer are sprouting up across the country. Some of those clinics have more than a few specialists. UPMC's clinic patients see an otolaryngologist, audiologist, dentist, speech pathologist, and physical therapist in one day. And unlike any other survivorship clinic in the United States, they are charged just one co-pay.

When patients are asked specific questions about their lives, including the economic cost of being a head and neck cancer survivor, they indicate that they're far from fine.

The Survivorship Clinic also sets itself apart by how it monitors patients from the start. Nilsen and Johnson meet with patients *before* they receive radiation and chemotherapy, and then again a month after treatment is completed. After that, patients visit the clinic at least once a year, and depending on their needs, Johnson and Nilsen will coordinate with the appropriate primary care physician, dentist, or physical therapist.

Historically, the struggles of head and neck cancer survivors have been approached as an afterthought by many hospitals and primary care physicians. That's changing as providers recognize the fallout from treatments, which can be lifesaving but also life hobbling. Johnson and Nilsen have seen more than a thousand patients in their three years at UPMC's Survivorship Clinic. Their work has highlighted the importance of long-term care.

For Johnson, a renowned head and neck cancer surgeon who has been with Pitt since 1977, the Survivorship Clinic represents a new chapter in his career.

"I've reinvented myself," he says. "I say to my residents: *Don't think I've repudiated the last 40 years of my career. I still believe in surgery. But I've embraced the notion that we must recognize the trouble we cause [treating cancer], and we have to help people with it.*"

Johnson and Nilsen started out as mentor and mentee in 2014. Nilsen was a postdoc, researching how taxing it can be to communicate after head and neck cancer treatment. She needed to work with patients before and after surgery, and Johnson accommodated her with patients and space at UPMC's Eye and Ear Institute. She hadn't expected him to be so helpful.

"Sometimes people don't understand when you're coming from a nursing perspective," Nilsen says.

"A physician once told me it was 'fluffy stuff.' But, from the beginning, Johnson was really open and interested."

Later that year, Nilsen won an Oncology Nursing Foundation career development award to research long-term effects of head and neck cancer. The award supported the second phase of her project: clinical observation and a systematic review. While embedded on Johnson's team, Nilsen gave him research papers on dysphagia and trismus as part of her systematic review. She also sent him a decade-old research paper from the National Academy of Medicine about the need for a coordinated approach to survivorship care.

"It was more like a book, not a paper," Johnson says, with a smile.

"I drilled it into his head," Nilsen says.

Johnson and Nilsen, who are almost 40 years apart in age, began meeting weekly to discuss her clinical observations, as well as the literature they were reading. "Everyone was looking at problems like dysphagia and trismus separately," Nilsen says. "But if you can't open your mouth, how can you chew and swallow properly? The problems can all compound each other. And Johnson said, 'We need to do this better.'"

Pitt hired Nilsen in August 2016, after



A team led by Marci Lee Nilsen and Jonas Johnson helps cancer survivors get their lives back.

Photo: Tom M. Johnson

she completed her postdoc, and UPMC gave them the green light to open the Survivorship Clinic. When Johnson told Nilsen the news, she opened her mouth and tapped her front teeth, as she recalls:

"He says: *You're happy about this?* And I was like, *No. Teeth. Dentist. We need a dentist for this. Do you know how many times your patients ask about their teeth?*"

There's no shortage of these patients.

HPV is the most common sexually transmitted disease, with approximately 80 percent of sexually active people contracting it at some point. Passed through intimate skin-to-skin exposure, HPV is harmless in most cases, as the body clears the infection. However, the virus can remain latent for decades and be transmitted to another partner later. It also can develop into cervical cancer or head and neck cancer.

As the virus has risen to epidemic-level proportions, with an estimated 79 million people currently infected, the number of HPV-positive head and neck cancer cases has grown tremendously.

Unlike HPV-positive cervical cancer, which can be detected early through a Pap smear, HPV-positive head and neck cancer isn't usually identified early. Robert Ferris is director of the UPMC Hillman Cancer Center and Pitt associate vice chancellor for cancer research. His team is attempting to detect HPV-positive head and neck cancer through saliva, so doctors can treat it early on.

Because there isn't an early detection method, the increase in HPV-positive head and neck cancer cases snuck up on experts, climbing at a rate of 5 percent a year for three decades. In the 1980s, HPV-positive head and neck cancer made up 20 percent of all instances of cancer related to the sexually transmitted disease. Now it's close to half of all diagnosed HPV-related cancer cases and, says Ferris, it may even exceed HPV-positive cervical cancer cases.

"We didn't even know we were treating HPV-related cancer," Ferris says. "We were treating head and neck cancer; and then, little by little, we started seeing more cases of HPV-positive patients in every clinical trial that got reported over 20 years."

Unaware that they were treating patients with the virus-associated cancer, doctors gave HPV-positive head and neck cancer patients the same doses of radiation and chemotherapy as they did people with other forms of oropharyngeal cancer. Yet, it turns out that HPV-positive patients don't need such high doses; those doses seem to harm them. But doctors didn't know that until earlier this decade, after a series of de-intensification clinical trials, including one led by Ferris at Hillman.

Compared to people with other forms of oropharyngeal cancer, HPV-positive head and neck cancer patients are, on average, about 10 years younger (in their 50s instead of 60s), and their survival rate is much higher (close to 90 percent over five years compared to 40 percent).

Researchers don't know why these patients are so much more likely to survive, and Ferris says unlocking this mystery, as well as discovering why and when HPV causes cancer, could lead to better treatment.

"There's probably a Nobel Prize in it for whoever can figure that out," he says.

Mark Beck smiles as he waits in a Survivorship Clinic examination room. The eighth-grade history teacher feels grateful that he was able to finish another school year. "I would like to teach forever," he says. But Beck, a 47-year-old

long-distance runner, doesn't know if he'll be able to reach retirement without going on disability.

In 2010, he was diagnosed with HPV-positive cancer on his tonsils. Before he started going to the Survivorship Clinic, his swallowing had worsened every year following his treatment. Beck has had two near-death choking incidents, and sometimes saliva drips into his airway while he's teaching, making him cough. He doesn't go anywhere without a bottle of water because he also suffers from cottonmouth, which has made teaching all day challenging.

This year, he has struggled with his voice. It's normal early in the morning, but by dinner he can barely talk. He's been wondering why. Just minutes ago, Nilsen and Johnson told Beck he has residual radiation damage to his thyroid, a common side effect for patients nearing 10 years after treatment.

"I thought the cancer had come back, but they were like: *No, typical*," Beck says. "It wasn't a shock to them at all. They really know how to track stuff here."

Johnson and Nilsen do this through a patient reported outcome (PRO), a 60-question survey taken on an iPad as patients arrive at the Survivorship Clinic. The clinic team sees about 30 people every Thursday who are asked pointed questions about mental and physical health, sleep quality, neck discomfort, swallowing ability, and other oral issues.

The PRO responses also determine which specialists a patient sees. Patients examined by speech pathologist Tamara Wasserman-Wincko might need a fiberoptic endoscopic evaluation of swallowing (FEES). During this procedure, a thin, flexible endoscope is inserted through the patient's nasal cavity. The patient is given liquid or food (usually water or pudding) to swallow that has been dyed blue. While watching a patient swallow, Wasserman-Wincko and Johnson can check for aspiration. This evaluation also tells them if it's likely cancer has returned.

Christopher didn't need a FEES on this June morning, but because he described issues related to dysphagia on his PRO intake, Wasserman-Wincko wants to review swallowing techniques, or "effortful swallowing." They discuss his diet, talk about the importance of drinking water while eating. Each swallowing evaluation is tailored to the patient. Because Christopher's tumors were on the left side of his neck, Wasserman-Wincko advises him to turn his head left when swallowing.

"This helps patients to block off the weaker and impaired side of their throat when swallowing," she says. "If a patient had a tongue cancer, then food placement is key. A head tilt to the stronger side may help with transfer of food. We can't prevent stiffening from radiation therapy, but we try to slow it down by doing range-of-motion exercises."

Dental hygiene is another concern. Radiation can disintegrate teeth, and it changes the pH of the saliva. A survivorship patient has a pH level of 4 or 5, says Elizabeth Pawlowicz, an assistant professor in the School of Dental Medicine on staff at the Survivorship Clinic.

"It's like walking around with Coca-Cola in your mouth all the time," she says.

After an evaluation, Pawlowicz gives clinic patients mouthwash and fluoride, and she advises them to visit their dentist four times a year. She also advises patients to tell their dentist that they are prone to gum disease, tooth decay, fungal infections, and ulcers because of cancer treatment.

Sometimes, if a patient suffers from a combination of side effects, going on disability can come as a relief. David Lacivita, 59, conquered HPV-positive tongue cancer seven years ago. Doctors removed the lymph nodes from his neck, and now he has progressive fibrosis—he can't turn his head. Lacivita feels a shooting pain in his neck and shoulders whenever he reclines in a chair or lies in bed. A former bus driver, he sleeps only two to four hours a day because of the pain. He has been working as a landscaper, doing what labor he can, but is applying for disability.

"I go to work in pain, and I come home, and I'm in pain," he says.

At his June visit to the Survivorship Clinic, Lacivita is examined by Susan George, a physical therapist who is an adjunct instructor in the School of Health and Rehabilitation Sciences. She asks him to stretch out his arms and lace his fingers together. Lacivita does this without any pain, but he can't raise his arms above his head. A shock runs down his arms and his hands tingle when they get halfway to his head. He explains to George that he only recently started seeing a physical therapist.

"That's okay," George says. "But I need to coordinate with him."

Lacivita suffers from anxiety, in part, because of his inability to sleep. Physical therapy should help his mobility, but Johnson said that it's going to be difficult to undo the stiffness that has set in through the past seven years.

"We try never to say, *Get used to the new normal*. It's so evil to call this normal," Johnson says.

There are two ways to prevent more patients from needing a survivorship clinic: HPV vaccinations and changing the way HPV-positive head and neck cancer patients are treated, also called a de-intensification of therapy.

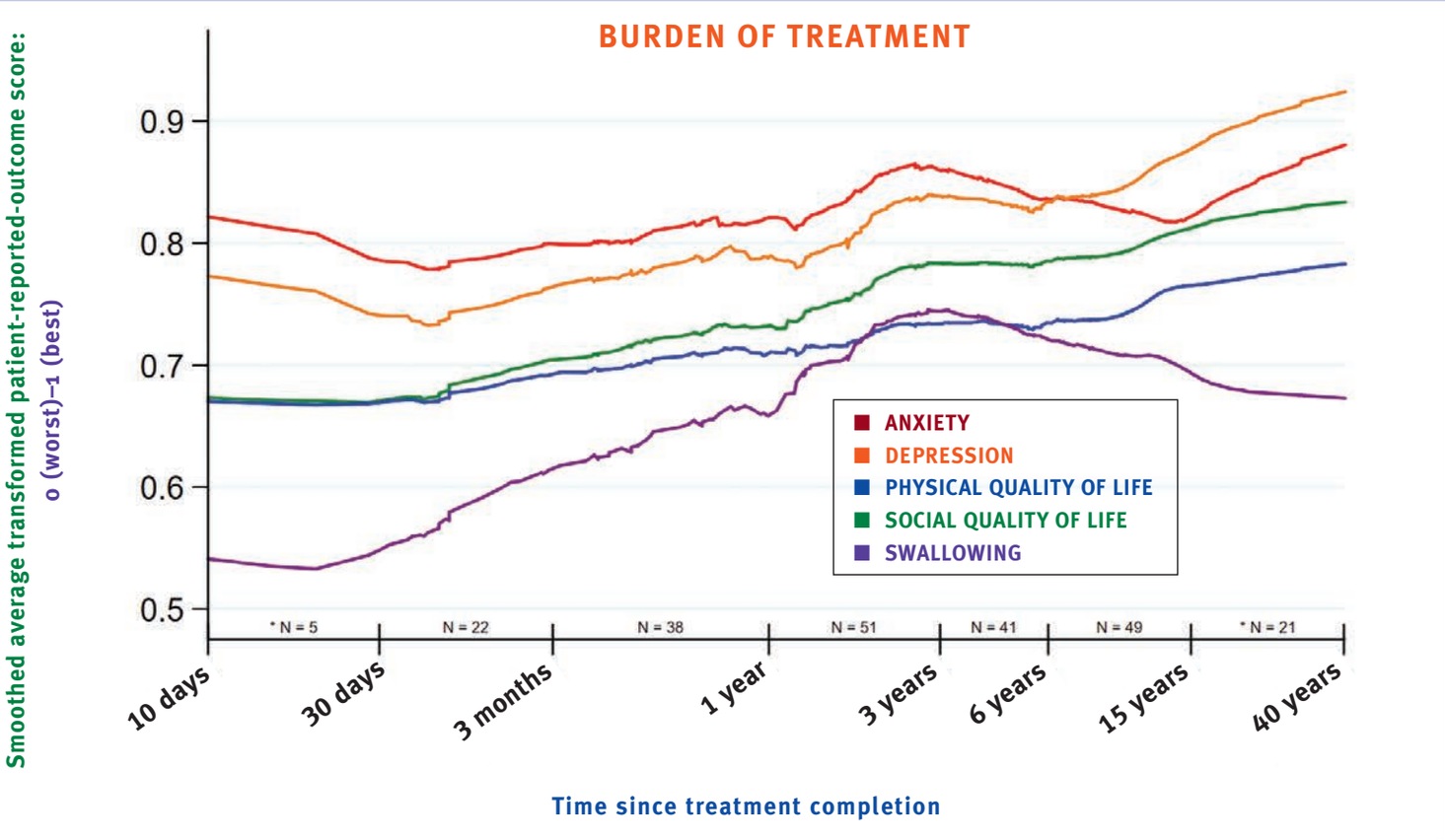
Normalizing HPV vaccinations in children is one possible solution. The Hillman Cancer Center has received funding for a grant from the National Cancer Institute to enhance awareness of the need for early inoculation. That effort is headed by Linda Robertson, assistant professor in Pitt's School of Nursing and associate director of health equity and community outreach and engagement; her team will work with pediatricians to increase HPV vaccination rates.

Hillman researchers are pursuing a number of ways to make treatment easier on patients. One team is developing a method that helps identify patients who will have trouble enduring radiation therapy.

Hillman is also the site of several clinical trials that aim to reduce dosages of radiation, eliminate chemotherapy, or attempt minimally invasive surgery. As part of a two-year trial that ended in July, surgeons used a transoral robotic device to perform surgery on 500 patients to reduce the dose of postoperative radiation. For example, if the dose would normally call for 70 gray (a radiation unit), the patients received a dose of 50 gray.

"We think if you can get 10 or 20 less gray of radiation that you'll have a better survivorship," Ferris says. "Fewer problems swallowing. Less scar tissue."

Ferris designed the trial, the first study of its kind using robotic surgery on HPV-positive head and neck cancer patients. Ferris won't know the trial's final results for months, but he says that 70 percent of participants were



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In a study of 228 patients at the UPMC Survivorship Clinic, symptoms linked to anxiety (red line), depression (orange), physical quality of life (blue), and social quality of life (green) improved over time. However, patients stopped getting better at swallowing (purple) six years after cancer treatment ended and began to decline in ability, which doctors fear could lead to choking incidents.

able to skip chemotherapy and about half were able to receive a reduced dose of postoperative radiation therapy.

Ferris and his team are also exploring ways immunotherapy could be used in treating HPV-positive head and neck cancer. He argues that if the immune system has failed to control a chronic viral infection leading to cancer, then it makes sense to integrate an immune system booster. The booster would, ideally, turn back the clock and provide virus recognition that the immune system provides for most people.

"Especially since everybody on the planet is exposed to HPV essentially throughout their body just by normal human contact," Ferris says. "But we don't understand why some [patients' bodies] allow this virus to propagate, [or] how [the virus] hides out in the cell and turns it into cancer."

In 2012, Ferris created the Tumor Microenvironment Center at Hillman to examine how viruses are propagated and how the immune system fails. Later, Ferris took the high-risk patients from his de-intensification trial—the 30 percent who were not able to skip chemotherapy—and started a new trial. That trial focuses on replacing chemotherapy with immunotherapy and combining it with radiation. Ferris says the results he's seen give him hope in the potential of immunotherapy in treating head and neck cancer, yet he doesn't want to eliminate the possibility of using radiation or chemotherapy in lower doses. Radiation and chemotherapy, Ferris says, are beneficial because they can cause a type of cell death that elicits an immune response.

In the future, as immunotherapy is likely to become more common, radiation and chemotherapy could be used "in a kind of homeopathic way," says Ferris. He imagines lower doses that partner with immunotherapy—and minimize side effects.

Ferris would like to start clinical trials to test interventions that could reverse certain side effects.

"And the prerequisite to doing that was having the Survivorship Clinic open," he says.

The rapport between Johnson and Nilsen is one of the reasons why the Survivorship Clinic has been successful. Every week, they meet and go through two stacks of files: last week's patients and this Thursday's. Their prep work makes each Thursday run smoothly. From 8 a.m. until the last patient leaves, they move nonstop. Almost. There's typically a lull around midday, when Johnson asks Nilsen what she wants for lunch. She always asks for soup from the lobby. Nilsen jokes that she only works with Johnson for the free lunch.

One June day, when Johnson sets a bowl of chicken noodle soup in front of Nilsen, she says, "Why are you holding out on me?"

Smiling, Johnson digs into his white coat pocket and retrieves crackers. He sets them down next to the soup.

"That's more like it," Nilsen says.

Ferris calls Johnson and Nilsen innovators for recognizing the importance of survivorship care before most cancer experts. Their advocacy has helped make long-term quality of life for cancer survivors a priority throughout the Hillman Cancer Center.

"We've now partnered with the School of Nursing across Hillman and given specific titles, roles, and resources to expand the survivorship model, symptom recognition, and symptom management from the toxicities of cancer treatment," Ferris says. ■