FOR PATIENTS, SURVIVORS & THEIR CAREGIVERS

RARE CANCERS

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Navigating the UNKNOWN

Despite the challenges of diagnosing and treating liposarcoma and chondrosarcoma, experts are optimistic about future treatments for these two rare cancers.

VON HIPPEL-LINDAU DISEASE
Patients describe what it's like to live with this rare genetic condition.

CANCER OF UNKNOWN PRIMARY
Novel app allows patients and their providers to better predic survival rates.

CNS LYMPHOMA
A new memoir focuses on the importance of a positive mindset and a strong support team.

GENETIC MUTATION
It's important for those who have a genetic mutation to plan ahead.

SOFT TISSUE SARCOMA
Our whole world stood still for a moment, one survivor said.

HEAD AND NECK CANCER
A new possible treatment regimen gives patients hope for survival outcomes.

RARE CANCERS
SPECIAL ISSUE · 07.21

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Jamie Foxx for Stand Up To Cancer. Photo By G L Askew II

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STRATEGIC cure® ALLIANCE

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RARE CANCERS SPECIAL ISSUE · 07.21

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SPEAKING OUT: GASTRIC CANCER

chairman's letter

The Power of Human Connection

IF THERE'S ONE THING we learned throughout the COVID-19 pandemic, it is the importance of the human connection, whether from a distance or even online. Now that things are slowly getting back to normal as more people become vaccinated, we welcome back the idea with open arms of in-person connections. But there's still one population that needs more human connection: those with a rare cancer.

For patients in these smaller populations, it can be difficult to find and connect with fellow patients who have received a similar diagnosis and know the hardships that come with treatment. Many connect with others online, whether it be through social media or a blog, and some gravitate toward research, absorbing as much knowledge as possible to better understand the diagnosis.

Throughout this special issue of *CURE*®, the theme of connection is recurrent. Steve Kelley, who received a diagnosis of central nervous system lymphoma at 63 years old, had trouble finding anyone with the same diagnosis. His solution? He wrote a book, "Cancer R.I.P.: The Ultimate Fight," and through it, he's hoping to connect with others who might feel the same way. In our interview with Kelley, we take a deeper dive into his book as well as his positive outlook on life. We also spoke with Nicole Body, who was diagnosed with stage 3 undifferentiated pleomorphic sarcoma after doctors found a tumor during a surgery to remove her gallbladder. Today, she is living cancer free and spreading her story of faith and hope as a women's pastor in Florida. Both Kelley and Body offer inspiration and examples of finding connection after receiving a rare cancer diagnosis.

Because all the cancers you'll read about in this special issue of *CURE*® are rare, another theme within is information, or rather the lack thereof. We spoke with Arianne Missimer, who received a diagnosis of stage 3 liposarcoma at 34 years old and explained how difficult it was to find information about this type of cancer. Of the 1.9 million people who received a cancer diagnosis in 2020, less than 1% received a diagnosis of sarcoma. Although research is ongoing in this area, clinical trials for rare cancers occur more slowly than for other cancer types because there simply aren't as many patients to enroll. Another patient we spoke with, who received a lobular breast cancer diagnosis at age 32 and then also tested positive for a mutation in the CDH1 gene, enrolled herself in a clinical trial that focused on the best ways to screen for and treat the disease risks that come with this mutation. Through the trial, she was able to help increase the knowledge base around this rare subgroup of patients with the rare disease — proving how important participation is to advance treatments for rare cancers.

Also in this issue, we look into the development of treatments for patients with rare cancers. Among these developments is a new tool that can more accurately predict overall survival to guide health care specialists in planning the most appropriate treatment regimen for a patient with cancer of unknown primary (an umbrella term used to classify a diverse group of metastatic cancers based on the absence of an identifiable primary tumor). For patients, this tool provides a wealth of knowledge and helps them better prepare as they plan their course of treatment with their doctors. C

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Exploring Potential Treatment Options for Rare Cancers

AN ESTIMATED 1 IN 30,000 people receive a diagnosis of von Hippel-Lindau (VHL) disease, and 10% of them do not have a family history, according to the American Society of Clinical Oncology (ASCO).

The rare genetic disease is associated with tumors in multiple organs — including hemangioblastomas (blood vessel tumors of the brain), spinal cord tumors, endocrine (hormone gland) tumors and retinal angiomas (eye tumors) — and leads to an increased risk of developing clear cell renal cell carcinoma, a type of kidney cancer.

In this special issue of *CURE®*, you'll read more about VHL disease, seeing it through the eyes of two patients. One patient first started showing symptoms in sixth grade — when he had trouble making out the words. A trip to the doctor confirmed a diagnosis of pheochromocytoma on his adrenal gland.

Ten years later, he developed more tumors on his right retina. After genetic testing, he received a diagnosis of VHL. In 2019, another patient received a VHL diagnosis after experiencing debilitating migraines.

Both patients emphasize the importance of finding specialists who have experience treating VHL and putting together the right health care team to monitor the possibility of new tumors. Even though the disease is so uncommon, new drugs in clinical trials are targeting hypoxia, or oxygen deficiency in the tissues, and the HIF1A protein that is a master regulator of responses to hypoxia. This is important because VHL serves as an oxygen sensor, so VHL mutations cause tumors to believe they are not getting enough oxygen, prompting them to form more blood vessels that make them more resistant to cancer therapies. Therefore, a drug that targets hypoxia could work against VHL-related tumors or be effectively combined with other cancer therapies. Pioneers in this field were awarded a Nobel Prize in 2019 for this groundbreaking work.

Read more about the current research for the disease, as well as how these advances impact the patients diagnosed with it.

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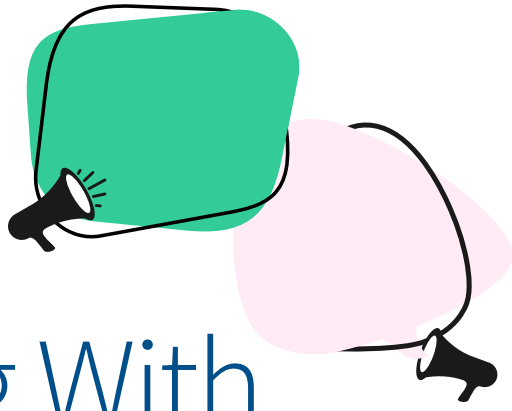

Tips for Coping With a Rare Cancer Diagnosis

We asked readers with rare cancers to share their advice on *CURE*®'s social media pages with patients who have received similar diagnoses. Here's what they told us.

> Find others who have the same type (of cancer) — we are here on social media. People who have been through it really understand it. Get more than one opinion, travel for the right specialist and follow your gut because you know you. If something seems off, it probably is. I had stage 4 choriocarcinoma caused by a molar pregnancy. I'm here if anyone has questions. — ***M.V.***

> Your journey will not look like someone else's, so be kind to yourself and don't judge what is and isn't happening to you by what is going on with them. — ***B.V.***

> Read, read, read. Learn everything you can and know that it will still be different for you. Know as much as you can about your cancer and make notes on how you feel day to day. Take these to every appointment and listen to your body. Above all, trust your instincts. — ***B.H.***

> If you have to Google, stay with reputable sites. Take each day as it comes — one step at a time — and don't compare your symptoms or treatments with others'. We are all different! Never ever give up hope. — ***A.P.***

> I have (myelodysplastic syndrome), which only (has) 10,000 cases diagnosed each year. My type is only 10% of that. It is rare, and I often feel lonely, but contacting national organizations like Aplastic Anemia and MDS International Foundation and the national MDS Foundation has been a huge help. I have also made contacts on social media with people across the country. — ***J.B.***

We want to know what you think about CURE®. *Address your comments to* **editor@curetoday.com**.
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Novel App Informs Patients With Cancer of Unknown Primary

An online tool developed by oncologists for this rare diagnosis individualizes survival estimates, resulting in candid discussions and better decision-making. *By* ANTONIA DEPACE

A DIAGNOSIS OF CANCER of unknown primary — an umbrella term used to classify a diverse group of metastatic cancers based on the absence of an identifiable primary tumor — can pose a challenge for both patients and oncologists. However, a novel prognostic model to predict overall survival may provide more insight and even spark a conversation between patients and their oncologists.

Although the exact number of cases of cancer of unknown primary diagnosed annually is unknown, the American Cancer Society estimates that 32,880 cases of cancer of unknown primary will be diagnosed this year in the United States, which represents about 2% of all cancers diagnosed.

According to Dr. Kanwal P.S. Raghav, an associate professor of gastrointestinal medical oncology at The University of Texas MD Anderson Cancer Center in Houston, it is extremely challenging to treat cancer of unknown primary because most cancer research is done based on primary location of tumors — even when it comes to predicting overall survival.

He and his colleagues sought to change that. They conducted a study that enrolled nearly 900 patients across MD Anderson, Tennessee Oncology and the University of British Columbia to test a web tool, or nomogram, that individualizes overall survival predictions based on baseline characteristics like biological sex, performance status and histology (tumor description). These characteristics are available to every patient at diagnosis and are important because they can reflect the severity of disease in cancer of unknown primary.

In an interview with *CURE®*, Raghav explained the trial results and how this app could positively affect the experiences of patients with cancer of unknown primary as well as increase communication with their health care providers.

Q: What led to the creation of this tool?

A: When somebody gets a diagnosis of metastatic cancer or cancer that has spread — such as cancer of unknown primary — one of the first questions in everyone's mind is: How long do I have to live? We don't really have a good answer to that.

The only way of estimating survival is with some older models that tell you whether you are in a good risk category or in a poor risk category, but they don't give you your prediction individually. All they can tell you is that if you are good risk, you would live a certain amount of time, and if you are poor risk, you would live a certain amount of time — but that's an average approximation. Therefore, we wanted to create a model that could provide an individualized survival estimate for patients with cancer of unknown primary.

The second problem with those models is that they're old and based on patients who probably didn't have access to some of the modern-day treatments that are out there now. So we designed the study to look at this individualized prediction using a more recent cancer of unknown primary group, and it is also one of the largest studies for patients with cancer of unknown primary, considering how rare this tumor is.

Q: How exactly can this tool help patients when making treatment decisions?

A: The estimate of one's survival probability is important in helping patients make an informed decision regarding their cancer care, advance directives and overall planning for the future as they go through treatment. It is also a helpful tool for physicians — since patients rely on them to make these estimates — and most often, they do not have well-developed tools like the nomogram.

Q: What can data from the tool tell patients or health care providers?

A: The average survival for our entire cohort was about 14 months. About a year is the average survival for most patients with cancers of unknown primary. … We then looked at patients who had lower scores and higher scores: the higher the score in the nomogram, the worse your survival. Our lowest-scoring people — the lower-third scores — had survival

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estimates as high as 40 months … and the other group, which had the highest scores, had a median survival of only about four months.

You can see that patients fall under a very large spectrum, and it is kind of important to recognize which patients will do well and which will do poorly with the disease. For patients who would otherwise do well, you can tend to be more aggressive, and you can plan for a longer duration of treatment. These are also patients who might be good candidates for clinical trials. Patients who are really doing poorly may not be patients who are good clinical trial candidates for now, but it might be important to develop more aggressive therapies for them in the future. These are not patients who can wait two or three months to start treatment. These are patients for whom you need to act quickly.

Q: Is there potential for the tool to cause panic in patients as they learn this information about overall survival?

A: Even though we think that estimate of survival in patients with cancer may cause panic, evidence has shown that not knowing one's prognosis results in overtreatment, heightened patient and caregiver distress, poor quality of life and, ultimately, poor outcomes. That is why a discussion of prognosis is endorsed in key cancer group guidelines. This tool allows a more objective and candid discussion of this aspect of care in cancer of unknown primary.

Q: How could the tool be further developed?

A: It would be important to keep working on this nomogram and add more and more factors that can adjust for newer treatments and newer prognostic factors that we figured out, especially genomic profiling. … I think integrating the tool into clinical care of patients is definitely a good way of looking at how this would perform in the real world and also integrating it in clinical trials.

What we actually need is more clinical trials for this orphan disease. Cancer is pretty overwhelming to begin with, irrespective of where it is. It is more overwhelming when you don't even know what the primary (cancer) is, and you cannot identify yourself with the 95% of other patients with cancer who know (where their disease originated). The uncertainty around prognosis, both from providers' as well as patients' perspectives, can make it very, very challenging. This nomogram is a tool to help our patients and our providers feel more comfortable with what their disease is and give them a resource that can help them make better decisions in clinical care.

GIVING HOPE

Study findings from China show that a new treatment option improves survival outcomes in nasopharyngeal carcinoma, but can U.S. populations expect similar results?

By ANTONIA DEPACE

FINDINGS FROM A PHASE 3 clinical trial demonstrated improved tumor shrinkage rates with the immune checkpoint inhibitor toripalimab and a first-line chemotherapy combination for nasopharyngeal carcinoma, a tumor that occurs in the nasopharynx (located behind the nose and above the back of the throat). The promising results may open the door to new clinical trials assessing triplet therapies with Food and Drug Administration (FDA)-approved drugs and provide hope for better treatment options for this patient population.

Results from the JUPITER-02 trial were presented at the 2021 American Society of Clinical Oncology (ASCO) Annual Meeting. In 2020, toripalimab received a breakthrough-therapy designation (approval to expedite drug development) for metastatic nasopharyngeal carcinoma. Of note, toripalimab is approved in China for several indications, but it is not FDA approved.

Currently, the worldwide standard of care for these patients is first-line chemotherapy with gemcitabine and cisplatin. "By adding immunotherapy to the combination, we hope to improve survival and increase the time from starting therapy to progression of the cancer," said Dr. Glenn Hanna, director of the Center for Salivary and Rare Head and Neck Cancers at Dana-Farber Cancer Institute in Boston, in response to the trial results. "If the triplet (therapy) has better rates of tumor shrinkage and prolongs survival with a reasonable side effect profile, that's a win."

The possible addition of a novel regimen is exciting. "Treatment advances for late-stage nasopharyngeal carcinoma have lagged behind those of other cancers," Dr. Julie R. Gralow, ASCO chief medical officer and executive vice president, said in a news release. "Findings from the JUPITER-02 study offer new hope for patients with advanced disease, changing how we care for them."

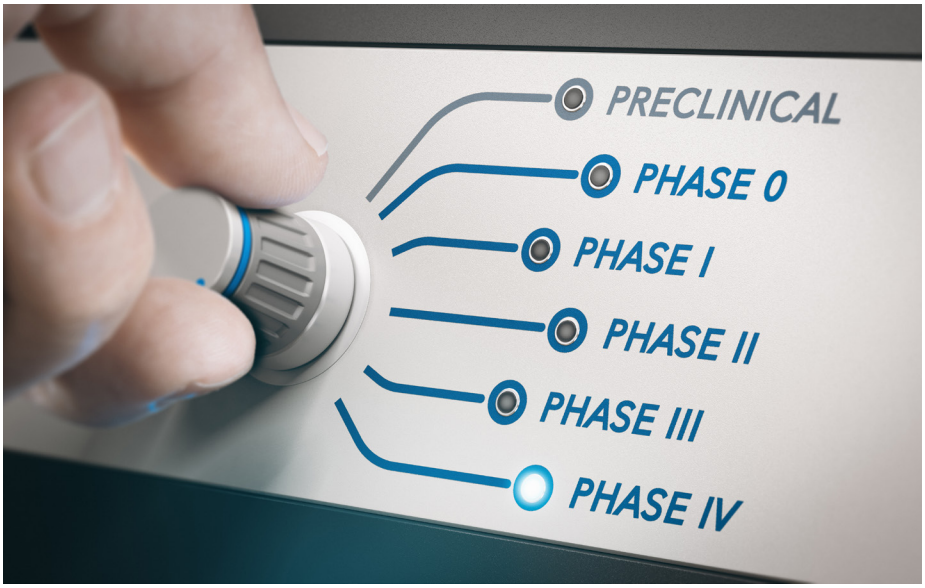
The trial was performed in China, and researchers observed an improved median progression-free survival (the length of time during and after treatment of a disease that a patient lives with the disease without it getting worse) of 11.7 months with the treatment regimen of toripalimab plus gemcitabine and cisplatin compared with eight months in patients treated with chemotherapy alone.

"It does get a little tricky when they're testing an agent that's primarily manufactured and approved in another country, but we did see practice-changing results," said Dr. Malini Patel, a medical oncologist in the lung cancer/thoracic oncology and head and neck oncology programs at Rutgers Cancer Institute of New Jersey. "I'm fairly confident that in the near future, we should be able to see this drug in the United States."

Patel noted that new clinical trials are underway replicating a similar treatment regimen with already-approved checkpoint inhibitors. "(JUPITER-02) is the first study to show a response like this in the first-line, recurrent and metastatic setting, and there are other trials using agents that we use in the United States that are piggybacking off this design," she explained.

Hanna noted a new trial by the nonprofit research organization NRG Oncology, which is examining the efficacy of gemcitabine and cisplatin in combination with Opdivo (nivolumab). The hope is to see similar, if not identical, results by using the FDA-approved immune checkpoint inhibitor Opdivo in place of the not-yet-approved toripalimab. "The concept is built on the success that's been observed in Asia," he said. "I think it will be an analogous study in our population. So, hopefully, we see similar results."

Both Hanna and Patel acknowledged, however, the possibility of seeing different results due to the difference in populations. Nasopharyngeal carcinoma is considered endemic in Southern China, Southeast Asia and Northern Africa, whereas it's rare in the United States, with less than 1 case per 100,000 people each year, according to the American Cancer Society.



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Although the exact reason for the uneven geographic distribution is unknown, it is partly due to the association with Epstein-Barr virus (EBV) — the infection of nasopharyngeal epithelial cells — that differs between the populations. EBV is known to increase the risk of developing various diseases, including nasopharyngeal carcinoma. "There are some EBV-associated endemic nasopharyngeal carcinomas that we see in the United States, primarily from those who migrate from areas of high risk to areas of low risk, but we encounter more smoking-related, non-EBV-related nasopharyngeal carcinomas (in the United States)," Patel explained.

Patel added that this doesn't change the importance of the trial results. "I don't think it should underscore the results of the study," she emphasized. "Our survival data (are) certainly immature, but we do see a trend for improvement in survival."

In addition to these studies, other trials have examined the use of drugs such as Keytruda (pembrolizumab) and Opdivo as single agents for the treatment of nasopharyngeal carcinoma. Hanna also noted that exciting new therapies targeting the EBV virus are on the horizon, as are studies combining immunotherapy with vascular targeting drugs, but that agreement on an official second-line treatment option remains an open question.

"Right now, outside of a clinical trial, it's a little bit heterogeneous in what doctors prescribe and use. We are in need of trials that focus on the population that (progressed after) chemotherapy and immunotherapy in the first-line setting," he explained. "It's a tough disease to treat."

Training for a MARATHON

Maintaining health before and after a diagnosis of myeloproliferative neoplasms could help patients as they undergo treatment. By ANTONIA DEPACE

BECAUSE DISEASE OF BLOOD vessels in the heart and elsewhere can affect the efficacy of treatment for patients with myeloproliferative neoplasms (MPNs), staying in close contact with a primary care team is extremely important.

"If you have … badly controlled diabetes and your cholesterol is bad, chances of something happening go up. That means the chances of getting ... to a (bone marrow) transplant successfully might go down," said Dr. Raajit Rampal, clinical director of the leukemia service at Memorial Sloan Kettering Cancer Center in New York City, in an interview with *CURE®*.

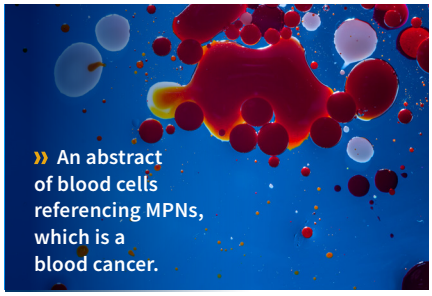
Routinely seeing a primary care team ensures that these controllable, treatable issues are managed.

"If a patient is diagnosed with an MPN, it's important that they recognize that their general health plays a contributing role (in) how they're going to do with (the) disease and how we may be able to treat (it) or not treat (it)," he said.

MPNs are types of blood cancer that begin with a mutation in a stem cell in the bone marrow, leading to an excessive and abnormal production of any combination of white cells, red cells and platelets, according to the Leukemia & Lymphoma Society.

Thrombotic and cardiovascular events occur in a minority of patients with MPNs, but the results can be devastating and even affect the efficacy of treatment, said Rampal. For example, those who develop thrombosis could see minor blood clots in the leg — but in more severe cases, a clot could also lead to stroke.

He also noted that preexisting risks, such as badly controlled diabetes or heart disease, could prompt health care teams to start treatment for MPNs earlier because the patient is already at a higher risk for developing complications.



» An abstract of blood cells referencing MPNs, which is a blood cancer.

When a patient receives a diagnosis of MPNs, "it's important to consider that diagnosis in the context of that patient's entire ongoing medical care," Rampal explained. "One of the things I always emphasize to (my) patients is that all the other parts of their health become magnified."

Smoking, obesity, diabetes, high blood pressure, high cholesterol, poor diet and lack of movement are all comorbidities that, if not managed, can increase the risk of developing both thrombotic and cardiovascular complications such as blood clots, stroke and heart disease — especially in patients with MPNs.

The cause of this increased risk is still unknown, although experts speculate that it may be due to genetic mutations associated with MPNs, such as a JAK2 gene mutation, which leads to uncontrolled blood cell production. Rampal noted that he considers this "one of the most important questions in MPN."

Rampal said his observations on overall health and patients with MPNs are drawn from the results of an epidemiological study of patients in the United Kingdom with an MPN that examined thrombotic and cardiovascular risks, as well as how the risks were managed in primary care. Findings demonstrated that patients with MPNs were often not prescribed the appropriate medications to manage cardiovascular and thrombotic risks, despite somewhat elevated rates of smoking and stroke. Results from this study were recently presented at the European Hematology Association 2021 Virtual Congress.

"I always tell (my patients with MPNs) it's sort of like training for (a) marathon" because of the long course of the disease, Rampal explained. "Dealing with a blood condition is absolutely important, but making sure that you're getting your blood pressure checked regularly, that you're getting your cholesterol checked, that you are maintaining your weight, that you're not smoking, that you're exercising — all of those fundamental things are part of the care of (patients with MPNs)." C

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Stomach Cancer 101 Series: Part II – Treatment

Monday, August 23, 2021 • 6 PM ET | 3 PM ET

Earlier this year, *CURE*®'s Educated Patient® Webinars partnered with Debbie's Dream Foundation to kick off its 3-part webinar series discussing news and updates related to stomach cancers. Join us on Monday, August 23 for "Part II – Treatment" where an expert panel will discuss topics highly relevant to patients, caregivers and advocates right now. Participants will have the opportunity to submit questions to be answered live by our expert panel.

Topics for discussion include:

- Treatment options, such as gastrectomy, chemotherapy, immunotherapy and targeted therapies
- Recent clinical data that shows the benefits of immunotherapies for patients
- Clinical trial options available to patients with stomach cancers

Later this year, Part III of the series will highlight a variety of tools to benefit mental health and overall quality of life for patients living with stomach cancer and their caregivers. Stay tuned for details.

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SPOTLIGHT

Keeping Faith

After receiving a diagnosis of stage 3 sarcoma, one survivor proves that anything is possible.

By ANTONIA DEPACE

IN 2014, NICOLE BODY was a pharmaceutical representative in Colorado and just married the love of her life, Wes. Shortly after, she began experiencing gastrointestinal issues and would get sick whenever she ate certain foods. Body remembers trying different diets, seeing several specialists and getting more ultrasounds than she could count. In the summer of 2017, she stopped being able to tolerate food at all. "That had never happened before, and so we immediately made a doctor's appointment to go in," she explained.

What started out as another ultrasound led to a CT scan and then surgery to remove her gallbladder. The surgeons found a racquetball-sized tumor, which they partially removed. They sent the tumor for analysis and reassured Body that there was a less than 1% chance of it being cancerous.

Twelve days later, it came back as stage 3 undifferentiated pleomorphic sarcoma, also known as malignant fibrous histiocytoma, a rare type of cancer that forms in the soft tissue throughout the body and usually occurs in older patients. Body was 27 years old at the time. According to the Liddy Shriver Sarcoma Initiative, there are only a few thousand cases diagnosed annually.

"You hear that there's a less than 1% chance that it's going to be cancer, and then you get diagnosed with the cancer that less than 1% of people get," Body said. "Our whole world stood still for a moment."

The tumor was described as angry, aggressive and high grade, so they had to act — and fast. "We just kind of got our game faces on and were ready to do whatever it took," she said.

Her surgeon recommended The University of Texas MD Anderson Cancer Center in Houston because it was a high-volume clinic. Coincidentally, Body's parents had just relocated to Houston, erasing the stress that can come from finding and paying for a place to stay during treatment.

At her first appointment at MD Anderson, Body went through a series of tests in order to create a treatment plan. The health care team decided on six rounds of chemotherapy followed by radiation and a Whipple procedure, a major surgery that removes the head of the pancreas, the first part of the small intestine, the gallbladder and the bile duct. From there, the remaining organs are reattached so patients can digest food after surgery. Throughout treatment, Body faced every day with immense faith. She took up journaling to process her thoughts and prayed.

Body refers to Wes as "Superman" during this time because he went with Body to every treatment and never left her side. "He just always did everything that he could

to try to make me laugh and smile so I didn't feel like I was missing out on anything," she said. "He created this new life for us to be living together, and they were some of the most beautiful moments I've ever experienced, even through the hardest season of my life."

In November 2017, Body's health care team stopped chemotherapy after four cycles, as the tumor was no longer responding to treatment, and admitted her to the hospital. They didn't think she was going to make it. Having just turned 28, Body was planning her own funeral. She asked her husband to share her story, as well as her journal entries, to the world if she didn't survive. "He said, 'I promise you, but I have a feeling that it's going to be you that gets to share it," Body remembered.

And she did. One month later, on December 13, Body went in for the Whipple procedure. A nine-inch incision was made in her abdomen, but when the surgeon went in, the cancer was gone. "I've been cancer-free ever since," she said.

Since then, Body has been able to publish her journal entries in her book, "When Love Broke Through," and even started a blog titled "Sparkly Survivor."

NAVIGATING FERTILITY AFTER CANCER

There was no time to preserve Body's eggs because the time between diagnosis and treatment had occurred within 10 days. Upon analysis, doctors found that Body had lost 75% of her ovarian follicles; the other 25% were described to her as "shriveled." Her levels of anti-Mullerian hormone, a substance that tells doctors about a woman's fertility and egg count, were also low, and it wasn't recommended for her to get pregnant for another two years after treatment.

Two years later, Wes and Body decided to go back for testing. "They said that 75% of my follicles had 'woken up,' and that if we got approval from the oncologist that we could try," she said. "I was just blown away. I didn't even know that follicles could wake up."

They were given the green light, and within a month, the couple naturally conceived their daughter, who was born in May. "Just being able to share this part of my story of having stage 3, rare, aggressive cancer and being cancer-free for three-and-a-half years, and we have a baby even with aggressive chemo treatment. … I just really hope that it brings encouragement in that anything is possible."

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Navigating the UNKNOWN

Despite the challenges of diagnosing and treating liposarcoma and chondrosarcoma, experts are optimistic about future treatments for these two rare cancers.

By STACY WILLINGHAM

When Arianne Missimer, a doctor of physical therapy, a dietitian and the founder of the Pennsylvania-based integrated health center The Movement Paradigm, discovered a mass behind her right knee after feeling nerve pain in her leg, she quickly scheduled an ultrasound.

"The pain wasn't anything that was really limiting me," Missimer says. "It was just an unusual symptom. If I didn't know my body so well, it was something I could have easily ignored."

After the ultrasound confirmed the mass was solid, she underwent an MRI. The results were startling. In March 2015, at age 34, Missimer received a diagnosis of stage 3 liposarcoma, a rare type of cancer that develops in the fatty tissue.

"I remember looking up 'sarcoma' and seeing that there are so many different types," she says. "Then I looked up 'liposarcoma,'… but there wasn't a ton of information out there."

This isn't that uncommon, according to Dr. Melissa Burgess, a medical oncologist at UPMC Hillman Cancer Center in Pittsburgh. "Unfortunately, for some of these diseases, there is no clear standard next step," she explains. "There's a lack of data because it's a difficult disease to treat. It's also rare, so it's hard to do large studies." »

ARIANNE MISSIMER received a diagnosis of stage 3 liposarcoma after discovering a mass behind her right knee.

CRISSY EVERHART

"Sarcoma" is the general term for a broad group of cancers in the bones and connective tissues. Out of the approximately 1.9 million people who received a cancer diagnosis in the United States in 2020, only 17,000 — less than 1% — had a sarcoma, according to Dr. Robert Maki, a medical oncologist and professor of medicine at the University of Pennsylvania Perelman School of Medicine in Philadelphia.

There are two general categories of sarcoma. Soft-tissue sarcomas affect tissues that connect, support or surround the organs and include sarcomas that are present in the muscles, tendons, fat, blood vessels, nerves, fibrous tissues and synovial tissues. Bone sarcomas grow in the bone or cartilage. Between these two categories, sarcomas span 70 subtypes, often making a precise diagnosis difficult.

Brenda Kennedy, a yoga instructor and personal trainer in El Paso, Texas, experienced this difficulty after visiting the doctor for a pain that she describes as a "dull toothache in the knee." After undergoing an X-ray, a bone scan, a PET scan and an MRI, she was found to have a grade 2 chondrosarcoma in 2009 at age 31.

"But the most frustrating thing was how long the imaging took. I couldn't get a referral to an orthopedic oncologist until they ruled out everything else," Kennedy says.

'BAD LUCK TUMORS'

"In terms of the frequency, about 3,000 people in the United States develop liposarcoma each year; for chondrosarcoma, it's around 1,000 people a year," Maki says. "But even the terms 'liposarcoma' (and) 'chondrosarcoma' represent a family of tumors with further subtypes."

Liposarcoma subtypes include well differentiated/dedifferentiated, myxoid/round cell and pleomorphic. For chondrosarcoma, approximately 90% are conventional chondrosarcomas, and the other 10% are subtypes, which can include dedifferentiated, clear cell, mesenchymal and myxoid.

In addition to being both rare and highly specific with their subtypes, liposarcoma and chondrosarcoma also have few risk factors and often-vague symptoms, increasing the difficulty and timeliness of diagnosis. Maki notes that certain genetic syndromes, exposure to radiation for treatment of another cancer, exposure to certain chemicals or a damaged lymph system could increase a person's risk for a sarcoma. For chondrosarcoma specifically, a family history of developing multiple benign cartilage tumors is one factor that could increase a person's risk.

"We consider them bad luck tumors," Maki explains. "There's nothing people did to get them. There's no association with eating, drinking, smoking … nothing like that."

"Over 80% of these cases are spontaneous," Burgess emphasizes. "That's what makes it so challenging. We don't know what causes them, we can't really screen for them and they are so rare."

Both Missimer and Kennedy led healthy lives as athletes prior to their diagnoses. Other than the leg pain that brought

them both to the doctor, neither of them exhibited any serious symptoms.

"I remember being so angry because I had done everything right," Kennedy says. "They say, 'You need to eat right. You need to exercise.' I taught fitness classes. … I did everything you are supposed to do, and I was (still) dealing with a cancer diagnosis."

THE SYMPTOMS OF SARCOMAS

Liposarcoma is most common in adults ages 40 to 60 and presents in the extremities (60%), abdomen (10%), and head and neck (10%). Chondrosarcoma, most common in adults who are 30 to 70 years old, can present in any part of the skeleton. When it comes to symptoms, the type and severity can largely depend on where the tumor is located as well as the stage and grade.

"Liposarcomas mostly show up as a painless lump, like most cancers," says Dr. Atrayee Basu-Mallick, director of Sidney Kimmel Cancer Center's Multidisciplinary Bone and Sarcoma Center. "That is why in certain locations — for example, within the abdomen — diagnosis can be delayed. Symptoms happen only when the tumor is pressing on another organ, nerves or blood vessels."

For Missimer, her pinpoint nerve pain likely occurred once the tumor grew large enough to press against her sciatic nerve. She noticed it most when sitting down and crossing her legs. A majority of patients may have a similar experience, but others could experience symptoms earlier.

Liposarcoma in the head and neck, for example, usually causes a noticeable fullness; in the abdomen, one may experience difficulty eating and going to the bathroom and swelling or distention due to growth of the tumor. As with most other cancers, it can also present with nonspecific symptoms, such as weight loss, chills, fever, fatigue and night sweats. For some, the tumor never exhibits symptoms at all and is found incidentally.

Chondrosarcoma symptoms, on the other hand, usually appear before a lump is noticed.

"(These) can include a sense of pain, stiffness and a change in the range of motion in the joints close to where the tumor (is) growing," Basu-Mallick explains. "If you have worsening symptoms, swelling or a lump you can feel, it is always good to get it evaluated."

MISSIMER underwent fertility preservation, six rounds of chemotherapy, radiation, proton therapy and limb-sparing surgery at Penn Medicine in Philadelphia.

A MULTIDISCIPLINARY APPROACH

According to Basu-Mallick, the best course of treatment for each patient typically depends on five factors: exact type of tumor or histology, grade, stage, location and the patient's overall clinical picture, which is determined by any other health issues.

"For sarcomas, 'grade' is the most important factor for long-term prognosis," she says. »

> Over **80%** of these cases are spontaneous. That's what makes it so challenging. We don't know what causes them, we can't really screen for them and they are so rare.
>
> — *DR. MELISSA BURGESS*

BRENDA KENNEDY, who is a yoga instructor and personal trainer, found it frustrating that she wasn't able to relieve stress the way she normally did: through fitness.

ANETTE GARCIA

Grade refers to how the tumor cells look under the microscope, whereas stage refers to the tumor size, and local and distant spread. To determine grade, factors such as how many cells are actively dividing, the number of cells that are dead and how the cells look in general compared to the primary tissue of origin are all taken into consideration.

In a grade 1 tumor, for example, a patient could have surgery for removal. However, for grades 2 and 3, treatment gets more complicated — sometimes including a combination of chemotherapy and radiation — and the surgery is often expanded to remove areas around the tumor itself.

"Sarcomas are like a mound of salt," Basu-Mallick says. "The mound is the tumor, but there are little grains all around it. We have to get that microscopic disease out … so to be safe, we have to take out a bigger section."

When putting together a treatment plan, Burgess, Maki and Basu-Mallick agree that taking a multidisciplinary approach is best.

"I always preach that it's helpful to have your case reviewed by multiple doctors in different disciplines who understand the disease and can help come up with the plan," Burgess says. "Getting to a center that has experience in sarcomas is also really important."

For Kennedy, treatment involved removing 15 centimeters of her femur and inserting a metal allograft. She then underwent three more surgeries — including a total knee

replacement, megaprosthesis and, due to her active lifestyle, repairing cracks in the polycarbonate structure — over the course of five years. Because she had relocated, Kennedy had surgery at different locations.

"Movement and being outside has always been my form of relieving stress," Kennedy says. "I was dealing with the most stressful thing in my entire life, and my one way of coping with it had been taken away from me."

Missimer, on the other hand, underwent fertility preservation, six rounds of chemotherapy, radiation, proton therapy and a limb-sparing surgery that removed the tumor and part of her hamstring.

"I felt really good during the proton therapy, mentally, emotionally and physically," says Missimer, who started training for American Ninja Warrior, a sports entertainment competition based on tough obstacle courses, while still in treatment. "Then I got the surgery, and that was emotionally tough."

KENNEDY attributes physical therapy and staying active for helping her regain her strength during and after treatment.

THE FUTURE OF TREATMENT

Despite the complications that rare cancers such as these can bring, medical professionals are optimistic about where the future is headed.

"Since these tumors represent multiple types of cancers, there's an interest in breaking each one down and finding specific treatments," Maki explains. "For example, half of regular chondrosarcomas have a mutation in a gene called IDH1 or IDH2, which lead to hyperactivation of the encoded enzyme isocitrate dehydrogenase, and there are now drugs that target those mutations. There are hints of benefit for people who receive those medications, though it's still very early in the development of those drugs."

Maki also notes a clinical trial that is looking at a different way to trigger the death of the chondrosarcoma cell without having to use chemotherapy.

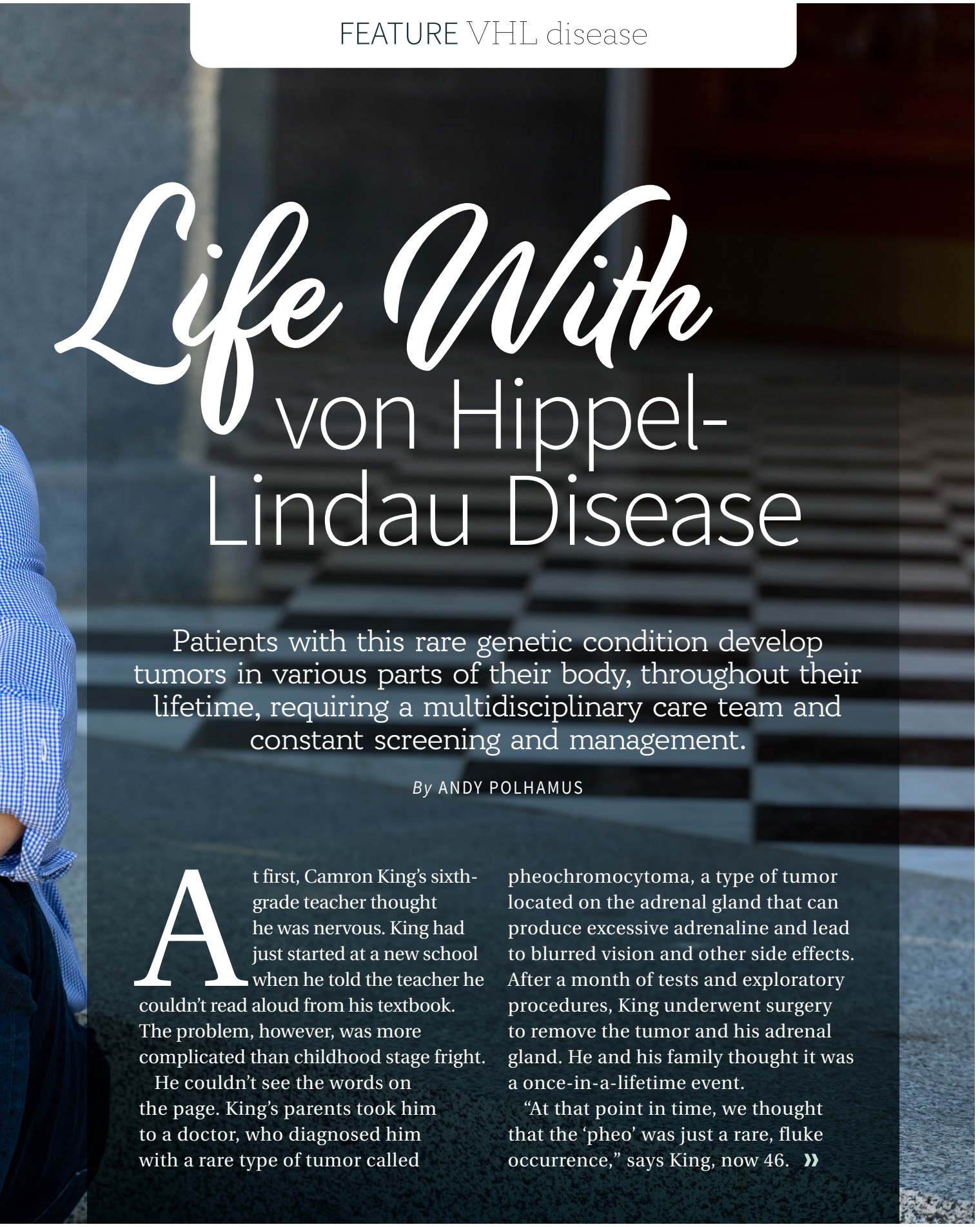
"The big problem with chemo for chondrosarcoma is that chondrosarcoma is in the cartilage, where there are no blood vessels. You can't just inject a drug into the veins and expect it to get to the tumor," he says. "But by using a monoclonal antibody that sticks around the body for weeks, you can achieve a level of medication in the body to kill off those tumor cells."

Finally, although sarcomas are broadly thought to be a cancer that haven't proved responsive to immunotherapy, oncologists including Burgess are dedicating their time to looking at certain genes that are expressed in the tumor and then identifying unique characteristics within subtypes that will be responsive to immune treatments.

Today, both Missimer and Kennedy are cancer-free. Kennedy's fourth and final surgery took place in March 2014, and she has maintained her active lifestyle by walking three half-marathons, teaching yoga, camping and keeping up with her four kids. As for Missimer, three months after her surgery, she went on to compete on "American Ninja Warrior" in May 2016.

"Physically, I have limitations, but I was able to manage my pain and do my physical therapy, and I attribute that to now being as functional as I am," Kennedy says. "I would tell patients to mentally prepare for pain; mentally prepare for keeping up with the physical therapy and be as active as you can, within reason, to keep your body going."

Although his first cancer diagnosis was earlier in life, **CAMRON KING** wasn't aware that he had a rare genetic condition until his early 20s.



Life With von Hippel-Lindau Disease

Patients with this rare genetic condition develop tumors in various parts of their body, throughout their lifetime, requiring a multidisciplinary care team and constant screening and management.

By ANDY POLHAMUS

At first, Camron King's sixth-grade teacher thought he was nervous. King had just started at a new school when he told the teacher he couldn't read aloud from his textbook. The problem, however, was more complicated than childhood stage fright.

He couldn't see the words on the page. King's parents took him to a doctor, who diagnosed him with a rare type of tumor called pheochromocytoma, a type of tumor located on the adrenal gland that can produce excessive adrenaline and lead to blurred vision and other side effects. After a month of tests and exploratory procedures, King underwent surgery to remove the tumor and his adrenal gland. He and his family thought it was a once-in-a-lifetime event.

"At that point in time, we thought that the 'pheo' was just a rare, fluke occurrence," says King, now 46. »

His endocrinologists, however, recommended ongoing tests to monitor adrenal tissue or growth over the course of King's life. As long as he got the tests, his care team said, he should be fine. "Well, I was, for about another 10 years," King explains.

In his early 20s, he started having migraines and began seeing floaters that interrupted his vision. He opened the phone book and made an appointment with a retinologist.

"It was divine intervention at that point," says King, who now owns a public relations consultancy and a management company that serves nonprofit organizations.

The retinologist determined that King had new blood vessel tumors called hemangiomas on his right retina. King was referred to genetic testing, and not long after, he received a diagnosis of von Hippel-Lindau (VHL) disease, a rare genetic disease that causes patients to develop tumors, some malignant and some benign, repeatedly over the course of their lifetime. According to the VHL Alliance, cases are diagnosed in every 36,000 people, and 97% of patients with the disease will experience manifestations in the form of cysts, tumors and/or abnormal blood vessels by age 60.

CAUSE, SYMPTOMS AND DIAGNOSIS

Everyone is born with two copies of the VHL gene, which plays a role in cellular functions like regulation of cellular metabolism and/or oxygenation. VHL, however, follows what is called an autosomal dominant inheritance pattern, which means that one mutated copy is inherited. A single acquired mutation in a cell will disrupt the usual cellular process.

"If you have VHL disease, one of the (VHL) genes you were born with was already mutated," says Dr. Nicholas Cost, director of the VHL Clinical Care Center Program at the University of Colorado Cancer Center, associate professor of surgery-urology at the University of Colorado School of Medicine and the co-director of the Surgical Oncology Program at Children's Hospital Colorado. However, about 20% of affected individuals will have a new (or "de novo") mutation, not from their parents, but one they can still pass on to their children.

The body's cells are constantly engaged in what Cost describes as "housekeeping," with the VHL protein helping to carefully balance cellular activities by responding to surrounding oxygen levels for the cells and determining how to use nutrients. If the gene is mutated, the VHL protein and its associated proteins cannot do their job, making the cell feel as though it is oxygen deprived. This leads to an unchecked accumulation of various "pro-growth" proteins, particularly hypoxia inducible factor 1-alpha (HIF-1-alpha).

"If you have (a functional VHL gene), this particular protein is kept at bay," says Dr. Othon Iliopoulos, an associate professor of medicine at Harvard Medical School and director of the VHL program at Massachusetts General Hospital in Boston. "If you don't, you start accumulating this protein in the cell, and then this protein ... turns on genes that make the cell cancerous."

The most common manifestations of VHL disease are clear cell renal cell carcinoma (kidney cancer), pancreatic neuroendocrine tumors — not to be confused with the more typical pancreatic cancer of the ductal cells — and hemangiomas of the retina, cerebellum, brainstem and spinal cord, as well as epididymal cystadenomas (benign para-testicular tumors) in men, broad ligament cystadenomas (benign para-uterine tumors) in women and pheochromocytomas (a type of adrenal tumor) or paragangliomas (similar to pheochromocytomas but not in the adrenal gland).

« **KING'S** son also received a diagnosis with VHL, and developed tumors.

MARITA MADELONI

VHL may be diagnosed with genetic testing after a patient presents with one or several of these tumors, but about 80% of VHL cases are inherited. Children of patients with VHL have a 50% chance of inheriting it. The VHL Alliance and the American Society of Clinical Oncology both recommend genetic counseling for patients with VHL who are considering having children.

Genetic testing has revealed that both of King's children have VHL, although only his son has developed tumors. His daughter has yet to experience any manifestations of

Intense migraines and a visit to the emergency room led **KWAME GARRETT-PRICE** to his diagnosis of von Hippel-Lindau disease

JARED REY HERNANDEZ

the disease. “As we had our children, it was like, ‘We already know what we’re dealing with,’” says King.

Dr. Samira Sadowski, an investigator at the National Cancer Institute in Bethesda, Maryland, says the more information patients can gather about VHL disease in their families, the better. “It’s an important question whether families or parents want to reproduce," she says. "These are very anxious and justified questions."

With advances in less invasive surgery, King says his son’s experience of VHL has been a little easier than his own. King describes his surgical scars as a “road map.” So far, he’s undergone surgery for the removal of kidney, spinal and adrenal tumors, as well as liver cysts. He’s also undergone gamma knife radiation therapy, during which beams of radiation are aimed at a target — in King’s case, a brain tumor — to precisely destroy a tumor without harming surrounding tissue. His son, on the other hand, has had a series of minimally invasive procedures that left behind much smaller scars.

LIFE WITH VHL

Kwame Garrett-Price, 34, of Dallas, says he got lucky by having a father and a brother who are both physicians. After Garrett-Price received a diagnosis of VHL disease in 2019, he found that many general physicians weren’t as familiar with the disease. With the help of his brother, he set out to assemble a care team.

“I’d been having migraines my whole life, and sometimes they were debilitating,” says Garrett-Price, a fashion designer who owns a company that sells luxury leather goods.

One morning, after a particularly brutal headache, he passed out. His mother took him to an emergency room, where he learned that his blood pressure was at stroke level. After some tests, a doctor gave him terrifying news: He had a tumor on his cerebellum. A visit to Baylor Scott & White Health in Dallas for more imaging revealed that Garret-Price had VHL.

He’d had surgeries before for injuries he sustained running track and playing soccer, “but this was quite »

GARRETT-PRICE describes his journey as "walking in the dark" because of the rarity of the condition.

JARED REY HERNANDEZ

different," Garrett-Price explains. "You instantly question your mortality and your impact on the world."

A neurosurgeon successfully removed the brain tumor that February, but shortly afterward, his care team found tumors on his pancreas, as well as kidney cancer. That October, his doctors found hemangioblastomas on his spine. Garrett-Price underwent a partial adrenalectomy for the pheochromocytomas in November 2019 and a surgery to remove two of the spinal tumors in February of this year. The kidney tumor remains under surveillance.

Care for VHL-associated cancers is different from other cancers because VHL care teams — knowing that a patient will likely develop many tumors and cysts over a lifetime — try to monitor tumors until they reach a size at which surgery is necessary, rather than operating immediately. Surgeons operating on patients with VHL will also usually try to conserve as much of the organ as possible, particularly in kidney cancers.

"What we've realized is that we could manage (patients with VHL) by waiting until they had a tumor that reached a size at which we would be worried about it spreading — that's at about 3 centimeters. And then at that point, (we) go into that kidney and take out all the possible tumors we can, (all while) leaving as much of that kidney as (we) can," Cost explains. "The reason … we do that is because we're balancing controlling the cancer with not putting them into renal failure and on dialysis."

> If you have VHL disease, one of the VHL genes you were born with was already mutated.
>
> —DR. NICHOLAS COST

Fortunately, says Cost, VHL-associated renal cell carcinomas tend to be low-grade tumors, so these surgeries can "reset the clock," and with any luck, the patient won't need another surgery for years. However, Cost notes, "it's so variable, and it speaks to why patients really need to be seen in a VHL center."

At the University of Colorado Cancer Center, Cost says that patients with VHL disease have urology and ophthalmology appointments every year and a visit with a neurosurgeon and an ear, nose and throat specialist every other year. Patients also meet with specialists as needed to conduct surveillance on tumors and form treatment plans if necessary. Cost says it's best to conduct MRIs rather than CT scans because they do not use ionizing radiation (a radiation consisting of particles, X-rays or gamma rays with sufficient energy to cause ionization), an important consideration for a screening that a patient will undergo many times.

"Essentially, (VHL) involves an annual follow-up with someone who is kind of a quarterback, who really understands the care of (the disease)," Cost notes.

Both Garrett-Price and King assembled their own care teams of neurosurgeons, oncologists, endocrinologists, ophthalmologists and audiologists. Garrett-Price obtained referrals from his primary care physicians once he figured out which specialists he needed to see, a process he describes as "like walking in the dark" because of how few doctors are familiar with VHL.

BREAKTHROUGH THERAPY

One of the most promising pieces of news for patients with VHL comes in the form of an experimental drug from Merck called belzutifan, which was granted priority review by the Food and Drug Administration in March.

Belzutifan is a HIF2A inhibitor, which means it blocks certain proteins that would otherwise promote blood vessel and tumor growth. This means that it can stop tumors from growing and even shrink them.

In a recent midstage clinical trial of patients with VHL disease, the drug demonstrated a response rate of 36.1% (22 of 61 patients enrolled in the study). Although this midstage trial was focused on patients with clear cell renal carcinoma, patients enrolled in the study also demonstrated shrinkage of pancreatic neuroendocrine tumors, hemangioblastomas of the central nervous system and retinal hemangioblastoma — showing promise for patients with VHL dealing with other types of cancer. In nonrenal cancers, researchers reported an 80% overall response rate to belzutifan.

"It has a widespread effect, and this is because the mechanism of these cancers is the same," explains Iliopoulos, who co-authored the study.

Sadowski, who hopes that belzutifan will offer patients a new treatment option, also is optimistic that research will lead to the development of better biomarkers to help care teams make treatment decisions.

As patients with VHL await these future therapies, Garrett-Price says he's faced VHL by taking charge of his physical and mental health by maintaining a healthy diet, exercising and managing anxiety. He and his brother are also working on starting a nonprofit to promote health care in underserved communities.

"These things are paying rent to me," he says of the malignancies, cysts and tumors. "I reversed it and said, 'I control you' because I control what I put in my body, I control my wellness and I control what I choose to feed these diseases. If I take care of myself mentally, to not be defeated by these diagnoses, it makes the landing a bit softer."

Looking FORWARD

Knowing they've inherited a genetic mutation for stomach or breast cancer gives patients the power to plan ahead.

By ALICE MCCARTHY

When Karissa Eifert's mother died in 2015 of hereditary diffuse gastric cancer (HDGC) caused by an inherited (also termed "germline") mutation in the CDH1 gene, Eifert's gynecologist proactively suggested she get genetic testing. Because of Eifert's family history of breast cancer and her mother's diagnosis, the doctor opted for a full panel of genetic screening.

A few weeks after, Eifert was told she had a mutation in the CDH1 gene. She was just 34 years old.

Each year, about 27,000 people in the United States receive a diagnosis of stomach cancer. A very small percentage — 1% to 3% — have HDGC. The most common cause of the disease is the presence of a germline hereditary mutation in the CDH1 gene, which leads to an increased risk of diffuse stomach cancer and lobular breast cancer.

"About 20% to 40% of people who appear to have HDGC have an inherited mutation in the CDH1 gene," says Dr. Jeremy Davis, a surgical oncologist at the National Cancer Institute (NCI) and lead investigator of the NCI's Research Study for Hereditary Stomach Cancer. »

KARISSA EIFERT received a diagnosis of a mutation in the CDH1 gene just weeks after her mother died from hereditary diffuse gastric cancer caused by the same mutation.

EIFERT BY KINSEY WHIDBY; MILASKI / STOCK.ADOBE.COM

KINSEY WHIDBY

The CDH1 gene directs development of a protein called epithelial cadherin, or E-cadherin. Found on cells that line the stomach and other organs, E-cadherin causes neighboring cells to stick to each other and form tissues. It can also function as a receptor involved in growth control. When the CDH1 gene is mutated, it causes abnormal, nonfunctional E-cadherin proteins that allow cells to grow and divide. It also increases the chances of cancer cells proliferating into the stomach wall and spreading throughout the organ.

More than 120 inherited types of CDH1 mutations are linked with HDGC.

Carriers of the CDH1 mutation have an elevated risk of developing either HDGC or, in women, lobular breast cancer, usually with onset before the age of 40. But not all patients with HDGC carry CDH1 gene mutations.

"The risk of getting gastric cancer (if you have a CDH1 mutation) is not 100%," adds Davis. "But statistically, we think that your risk is much, much higher than the average population." The latest evidence finds that these individuals have a 30% to 50% risk of developing HDGC by age 80. For women, the risk of lobular breast cancer is approximately 40% to 55% by age 80.

Genetic testing and counseling are two preliminary steps when a physician sees a patient with early-onset stomach

cancer, lobular breast cancer or a family history of stomach cancer. For these patients, testing for the CDH1 mutation is often the first genetic test.

"We might recommend the panel if we are not totally sure what we are looking for, but we suspect a hereditary gene syndrome is involved," Davis explains. "That is especially true if the CDH1 test comes back negative."

Eifert's family history of cancer concerned her, "but I had no clue I had (a mutation in) the CDH1 gene," she says. "I consider having that information to be a gift that my mother didn't have."

Kate King-Scribbins, who received a diagnosis of lobular breast cancer at age 32, also went through genetic testing before discovering that she was positive for a CDH1 mutation. While lobular breast cancer is the second most common type of breast cancer, it is 30 times less common to derive it from the CDH1 mutation compared with more common gene mutations like BRCA2.

"My mother had breast cancer, but she did not have CDH1," she says, explaining that the CDH1 mutation came from her father's side, with several family members having early breast cancer. "They were going to test only for BRCA1/2, but I wanted to push for all of the genes — given my family history — so I got the whole gene panel. That's when I learned I had the CDH1 mutation."

> About **20%** to **40%** of people who appear to have **HDGC** have an inherited mutation in the **CDH1 gene**.
>
> — DR. JEREMY DAVIS

TREATMENT OF HDGC

"For patients who have a family history of stomach cancer and the CDH1 (mutation), the recommendation is to have a total gastrectomy or removal of the stomach," Davis explains.

The decision to act on the discovery of a CDH1 mutation is influenced by many factors. If cancer is already present, the treatment choices are fairly straightforward: surgery usually followed by appropriate chemotherapy. When the CDH1 mutation is discovered but the patient has not developed any cancer, choices are more varied — especially if they have a family history of HDGC. They can either elect for gastrectomy (total removal of the stomach) or a period of intensive surveillance with endoscopy every 12 months.

Eleven months after Eifert's diagnosis, she opted for a total gastrectomy at the NCI at the age of 35. "My endoscopies were actually clear, but I wanted to move forward with the total gastrectomy," she explains. "I wanted to beat (HDGC) to the punch." The first year after surgery was hard; during that time, she experienced intense bile reflux and rapid weight loss. "I also lost the desire to eat since I was frequently nauseous," she says.

Eifert is now 18 months post-surgery and has been working regularly with a dietitian. "I feel like my old self again," she says, noting that she lives a fairly active lifestyle of hiking in Rapid City, South Dakota. "I have most of my energy back and eat most things. Eating is less of a chore, which makes a huge difference for me mentally. I now enjoy and crave food again."

After her surgery, however, Eifert received a diagnosis of stage 1A gastric cancer after a pathology on her stomach showed small areas of precancerous cells. Of note, she has not needed further treatment.

After undergoing a mastectomy, chemotherapy and radiation treatment for lobular breast cancer and learning she had the CDH1 mutation, King-Scribbins joined Davis' HDGC clinical study at the NCI, which is focused on learning the best ways to screen for and treat the disease. Like Eifert, she opted for a gastrectomy. "The whole process has definitely taken its toll. I lost both breasts, my stomach and ultimately my gall bladder," King-Scribbins says about her three years of surgeries and recovery. "I wasn't about to go through all that treatment for breast cancer and then let stomach cancer take me out."

Patients who do not wish to immediately move to surgery — either for a total gastrectomy to prevent diffuse stomach cancer or mastectomy to prevent lobular breast cancer — instead undergo intensive surveillance.

"The decision when to have a gastrectomy when you may be 25 years old is a heavy burden," says Dr. Fabian Johnston, division chief of gastrointestinal oncology at Johns Hopkins Medicine in Baltimore. He adds that he sees many patients who choose surveillance until they are in their early 30s or the risk of cancer increases.

Because HDGC is not symptomatic until it is relatively advanced, endoscopy can be useful for catching some cancers at an early stage. "Anyone with the CDH1 mutation should get the endoscopy when they are diagnosed and every year after that for monitoring," explains Dr. Daniel Sussman, professor of clinical medicine in the gastroenterology division at the University of Miami Health System. "The drawback of using endoscopy for surveillance is that we biopsy only certain areas of the stomach and can miss these early cancer cells." »

KATE KING-SCRIBBINS underwent three years of surgeries and recovery after discovering she had a mutation in the CDH1 gene.

LAURIE SCHNEIDER

During the procedure, a tube is inserted into the stomach through the mouth. Samples of stomach tissue are collected and analyzed in a lab for the presence of abnormal cancerous signet-ring-shaped cells. In HDGC, these cells grow and often cluster together in the diffuse pattern associated with the disease.

The decision between surgery and monitoring is further complicated because individuals with the CDH1 mutation may undergo prophylactic gastrectomy: the removal of the stomach prior to known evidence of cancer. "When we do random biopsies, we will find precancerous cells about 40% of the time if we just happen to hit the right spot," Davis adds, noting that he usually finds cancer cells in 95% of patients who have had prophylactic gastrectomy. "That tells me that endoscopy is not that great if we only find them 40% of the time as opposed to 95%."

For this reason, patients with HDGC or those with the CDH1 mutation are advised to seek care at a medical center experienced in monitoring, diagnosing and treating HDGC. This includes seeing an advanced endoscopist trained to monitor HDGC with specialized endoscopy scopes created to visualize hard-to-see cancerous cells.

For women with the CDH1 mutation or with stomach cancer diagnosed when they were young, breast cancer screening is recommended as early as age 30. "We recommend starting with breast MRI since lobular breast cancers are more insidious than diffuse breast cancer, and they are

Since her diagnosis, **KING-SCRIBBINS** has dedicated herself to helping others who also received a diagnosis of gene mutation at a young age.

harder to identify on mammography," Johnston explains.

Since her CDH1 diagnosis and gastrectomy, Eifert has been alternating between mammography and breast MRI screening tests every six months. "At this point, I'm not certain what steps I may take in the future," she says, referring to prophylactic mastectomy. "I'm in the early stages of learning and formulating a plan."

REMAINING QUESTIONS

As research into the genetics of the disease sheds more light on this rare cancer, some important questions remain. "We still don't know who should definitely choose a prophylactic gastrectomy," Davis explains. "Although the risk between CDH1 and HDGC is well established, beyond that, we cannot yet provide individual risk assessments."

Because some patients with the gene mutation never develop HDGC, it is also important to find out why. "Since we know we almost always find early signs of HDGC after gastrectomy, why do some of them appear to be relatively indolent and others are very aggressive?" asks Sussman. "We need to understand that so we can, hopefully, intervene and perhaps find ways to prevent advanced cancer."

Another relative unknown is what other genetic mutations may contribute to HDGC. Although CDH1 has the longest and strongest association with the cancer, other genetic mutations have been linked to it over the past several years.

ENJOYING LIFE, HELPING OTHERS

Today, Eifert is back to work as an interior designer and counsels others with similar diagnoses through her blog, Reverie Rising. Having battled insurance issues and the lack of resources in her area, she advises others to be informed, follow their instincts, advocate for themselves, push for what they need and look for answers in online Instagram and Facebook communities and from specialty medical centers. "Having the knowledge, it gives you the power to determine how you want to handle your options. So many people don't have the opportunity to proactively influence their outcomes, but you can with a CDH1 diagnosis," she says.

Similarly, King-Scribbins — who talks more about her journey on her blog, "My Pink Genes," where she also provides helpful resources for others with the disease — is committed to helping others. "I don't want (others) to feel as alone as I did going through this at such a young age," she says.

STEVE KELLEY used biking to keep his mind sharp throughout treatment.

NEVER Back Down

In his new memoir, a patient with central nervous system lymphoma emphasizes the importance of a positive mindset and a strong support system.

By ANTONIA DEPACE

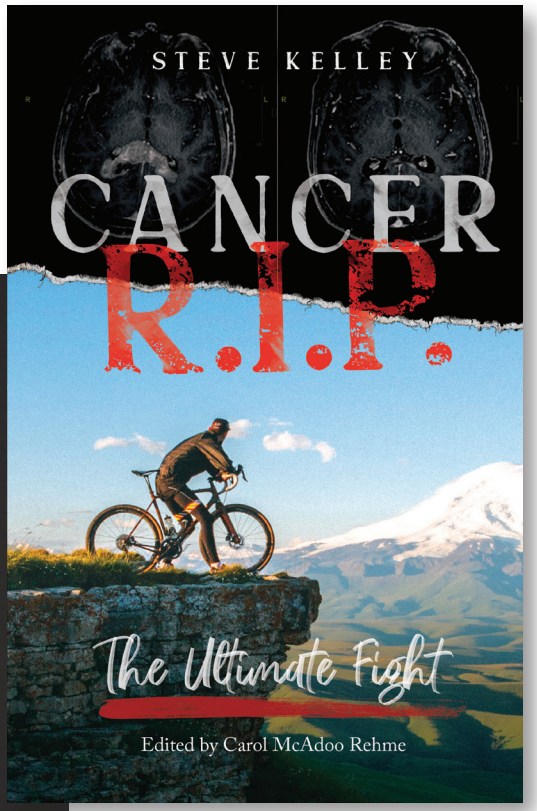
PHYSICAL ACTIVITY WAS ALWAYS an important part of Steve Kelley's life. Whether playing flag football or mountain biking, he strove to face the trials of life in the fast lane — even after receiving a diagnosis of central nervous system (CNS) lymphoma in 2018 at 63 years old.

Kelley stared cancer in the face with tenacity and a smile, all while hardly getting off his bike. Now he has published his experience in a memoir, "Cancer R.I.P.: The Ultimate Fight."

CNS lymphoma is a rare non-Hodgkin lymphoma (NHL) in which malignant cancer cells from lymph tissue form in the brain or spinal cord. This aggressive form of NHL constitutes 4% of all brain tumors and develops in approximately 5 individuals per million each year in the United States, for an estimated 1,500 cases annually, according to the National Organization for Rare Disorders. Symptoms vary depending on the location of the tumor and may include headaches, vomiting, facial weakness, and cognitive and behavioral changes.

Kelley's primary symptoms came in the form of cognitive changes that affected his memory. In 2018, he found himself driving home from

PHOTOS COURTESY OF KELLEY



SCAN THE QR CODE to listen to *CURE®*'s podcast with Steve Kelley.

work for three hours — even though his office was six miles away from his house.

"I kept taking turns and coming to places that I didn't recognize, and yet I knew the whole area," he remembered.

It wasn't until he couldn't find his way out of a local home goods store, where the aisles were organized in parallel grids, that he accepted that something was wrong. "It was a really scary moment to not be able to find my way back to the store entrance that I'd come in at," he said.

Within the pages of his book, which was released in May, Kelley describes his cancer journey from diagnosis to treatment and beyond in hopes of giving other patients with rare cancer the point of connection that he struggled to find. "I felt a little bit distanced from anybody who might have had my disease," he said. "I decided that I would write a book, and then people would be able to read about what it was like to have a serious brain disease."

The book also includes a chapter called Saints and Angels comprised of stories written by Kelley's family. "My sister, wife, grandchildren, sons … they got to write … what it was like to experience (my diagnosis) with me," Kelley explained. "It's a whole section devoted to the family's experience of cancer."

Readers can expect stories of countless ups and downs, from Kelley's struggle with MRIs (a fear that was first realized after he tore his rotator cuff playing slow pitch softball in 2003 and faced two more times before his diagnosis) to pranking his medical team, creating fake side effects by placing a miniature light-up traffic cone under his shirt and having two large carrots hanging out of his mouth.

Kelley's health care team also participated in the book; his oncologist, Dr. Lakshmi Nayak, director of the Center for CNS Lymphoma at Dana-Farber Cancer Institute and an assistant professor at Harvard Medical School in Boston, wrote the book's forward.

Nayak describes Kelley as an "eternal optimist" who never stops smiling. "As you journey with him, (Kelley) points out how each experience informed his life with lessons," she wrote. "He reveals his deepest secrets and eloquently exposes the fragile nature of the human mind and body."

According to Kelley, major takeaways from the book include the importance of developing your support team — whether it consists of medical personnel, family or friends — and challenging your mind and staying physically active. While undergoing treatment, he never slowed down. In fact, he insisted on having a stationary bike in his hospital room and riding it throughout treatment.

"I'd be on my bike, and there'd be multiple IV lines attached all around me, and I would just stay on the bike for as long as I could," he explained. "I got down to 10 (white blood cells), and even at that point, I was still getting on the bike."

When out of the hospital, he continued riding with his mountain bike group and credits that with keeping his mind active and sharp. "Just learning to look ahead and around the corner and (to) expect another route or stone … really forced me, at a fast pace, to make my brain work," he recalled.

Kelley said it's important to remember to stare cancer square in the face and to handle the situation with grace. "A positive attitude is really helpful for everyone around you and for you as well," he concluded, noting that the goal isn't just to survive but also to thrive.

Staying Aware

On behalf of Hope for Stomach Cancer, Dr. Yanghee Woo speaks with *CURE*® about risk factors for gastric cancer and the alarming rise in cases in young adults.

By ANTONIA DEPACE

DR. YANGHEE WOO

ALTHOUGH INCREASING CASES OF gastric cancer in adults 40 years old and younger remain unexplained, unmodifiable risk factors — the ones that someone is born with — are likely the cause, according to Dr. Yanghee Woo, director of the Gastroenterology Minimally Invasive Therapy Program and associate clinical professor in the division of surgical oncology at City of Hope in Duarte, California.

"Like other cancers, we can categorize gastric cancer risk factors into two groups: the modifiable risk factors, (which are) mostly environmental (and are) things that we can change, and the unmodifiable risk factors ... that we are mostly born with and either we cannot change them or they're not that easily changeable," said Woo. "Young gastric cancer patients are more likely to possess a lot of the unmodifiable features with the additional exposure to the modifiable risks."

In an interview with *CURE*®, on behalf of Hope for Stomach Cancer for its "Speaking Out" video series, Woo discussed the risk factors associated with gastric cancer in young adults, how age plays a role in prognosis and symptoms to watch for.

Q: Can you explain the rise in gastric cancer in young adults?

A: The reason for this rise in the incidence of gastric cancer in young adults actually remains unexplained because there are (only) a few studies that have investigated gastric cancer in people under the age of 40. (Very) little (is) known about why there is currently a rise in gastric cancer in this group, but efforts are being made to address this alarming observation. This trend is especially concerning because it goes against the decreasing overall numbers of gastric cancer cases in the United States and worldwide. For the past several decades, there had been a very steady decrease in the incidence of gastric cancer. ... As we investigate the reasons for this observation, though, the more urgent issue is to be aware of the risk factors that lead to the development of gastric cancer and what we can do about it in the young.

Q: What are the unmodifiable risk factors of gastric cancer in young adults?

A: Under the age of 40, you have not been exposed to the environmental risk factors as much as the older population,

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(so) it is most likely the unmodifiable risk factors that are dominant. For example, the average age of (patients with) gastric cancer in the United States is 68. They have had a lot of exposure to the environmental risk factors. So what are the nonmodifiable inherited risk factors that put somebody at an increased risk? Ethnicity; (specifically), ethnicity that is not Hispanic White. If you're Hispanic, if you're Asian or if you're a Black (person), you are at an increased risk of having gastric cancer at a younger age. If you have a family history of more than one family member, then you are at a higher risk than your friends who do not have family members who developed gastric cancer. If you are male, you are more likely — whether you're young or old — to have gastric cancer. Then there are (inherited/familial) genetic risks.

Q: What is the difference between gastric cancer in a young adult versus an older adult?

A: There are significant differences between patients who are older with gastric cancer and patients who are under the age of 40. We recently published a study that we performed in the California Cancer Registry, which is a (statewide) registry of (patients with cancer). We analyzed the difference, and we found that compared with older patients, young patients under 40 are more likely to be Hispanic (and) more likely to possess aggressive tumors that have poorly differentiated histology. They're higher grade, meaning they're more aggressive. These younger patients are more likely to present with metastatic stage 4 disease with the primary tumor in the stomach ... that has already spread to the peritoneum, which is much more difficult to treat.

> "This trend is especially concerning because it goes against the decreasing overall numbers of gastric cancer cases in the United States and worldwide. – DR. YANGHEE WOO

Q: What is the prognosis in young adults compared with that of older adults?

A: There's some good news and some bad news. The good news is that for each stage of diagnosis, meaning the extent of disease progression of gastric cancer at the time of diagnosis, there is no difference in outcome per stage whether you are young (or) old. It's just that more younger patients are receiving diagnoses in the more advanced stages, giving them the overall worst prognosis. (The) good news is that if you (receive a diagnosis) at a young age (of) a very early cancer, like stage 1 cancer, you actually do better. Your prognosis is better than that of the older patient population, probably because stage 1 cancer is usually curable and you are healthier as a younger person and can tolerate the treatments better. In general, age is not an independent predictor of gastric cancer survival, meaning other factors have a stronger impact on patient outcome — for example, the stage at the time of diagnosis; how you respond to the therapy; how good your surgery is (and) how responsive (the) tumor is to the chemotherapy and, possibly, other immunotherapeutic agents that are new to the treatment of gastric cancer. Your response to those will predict your overall outcome, not necessarily your age.

Q: Why is it important for young adults to understand this rise in cases?

A: Awareness is actually the first step to prevention and early diagnosis in these patients. We need to recognize that there are young adults at risk for gastric cancer and evaluate the (unknown) risk factors so we can address this cancer in the young and prevent cancer. It is very difficult to diagnose gastric cancer at an early stage without having suspected gastric cancer when the patients come with these symptoms. Early stages of gastric cancer are completely asymptomatic. Eighty percent of patients with gastric cancer don't have symptoms initially. (Once diagnosed, it is not unusual that) the alarming symptoms of weight loss, inability to eat, the belly getting big, pain and nausea ... have gone on for a fairly long time. And at that time, it's a more advanced stage of disease. So the data (are) clear that we either do not suspect this when patients who are young present with symptoms associated with gastric cancer or we dismiss it or treat it a different way. We need to be on high alert in recognizing these symptoms as well as risk factors in the young patient population.

This Speaking Out video series is supported by Bristol Myers Squibb.

LEARN MORE ONLINE SCAN the QR code to learn more about the social disparities and awareness associated with gastric cancer in young adults.

We are helping to move mountains for myeloma patients

Moving Mountains for Multiple Myeloma (MM4MM) is an award-winning collaboration between CURE Media Group and the Multiple Myeloma Research Foundation (MMRF), which raises funds and awareness for myeloma research.

Since its inception in 2016, Moving Mountains for Multiple Myeloma teams have climbed Mount Kilimanjaro, hiked the Grand Canyon, summited Mount Fuji, trekked the Inca Trail to Machu Picchu, reached Everest Base Camp and conquered Iceland's many landscapes. Our team members have raised over $3 million, 100% of which goes directly to the MMRF, which spearheads and funds critical myeloma research. These amazing journeys are captured via blogs, social media posts and video.

After pausing for the global pandemic, we are back with a new schedule of exciting climbs. Patients, caregivers, loved ones with myeloma, and others impacted directly by multiple myeloma will trek through the wilderness of Alaska's Kenai Peninsula, summit Mount Washington and discover the dynamic terrain of Colorado's Backcountry Continental Divide. They will raise funds for multiple myeloma research and demonstrate that the advancements being made in recent years, led by the MMRF, are helping patients live longer with a higher quality of life than ever before.

To learn more and join a MM4MM team visit:
MovingMountainsForMultipleMyeloma.com

To learn more about the MMRF, visit **TheMMRF.org**

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2021-2022 TREK SCHEDULE

Alaska Trek
August 16-21, 2021

Mount Washington
Late Summer / Early Fall 2021

Colorado Trek
September 9-14, 2021

Mount Kilimanjaro
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Greenland Trek
Summer 2022

Sweden Trek
Summer 2022

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