FOR PATIENTS, SURVIVORS & THEIR CAREGIVERS

GASTROINTESTINAL CANCERS

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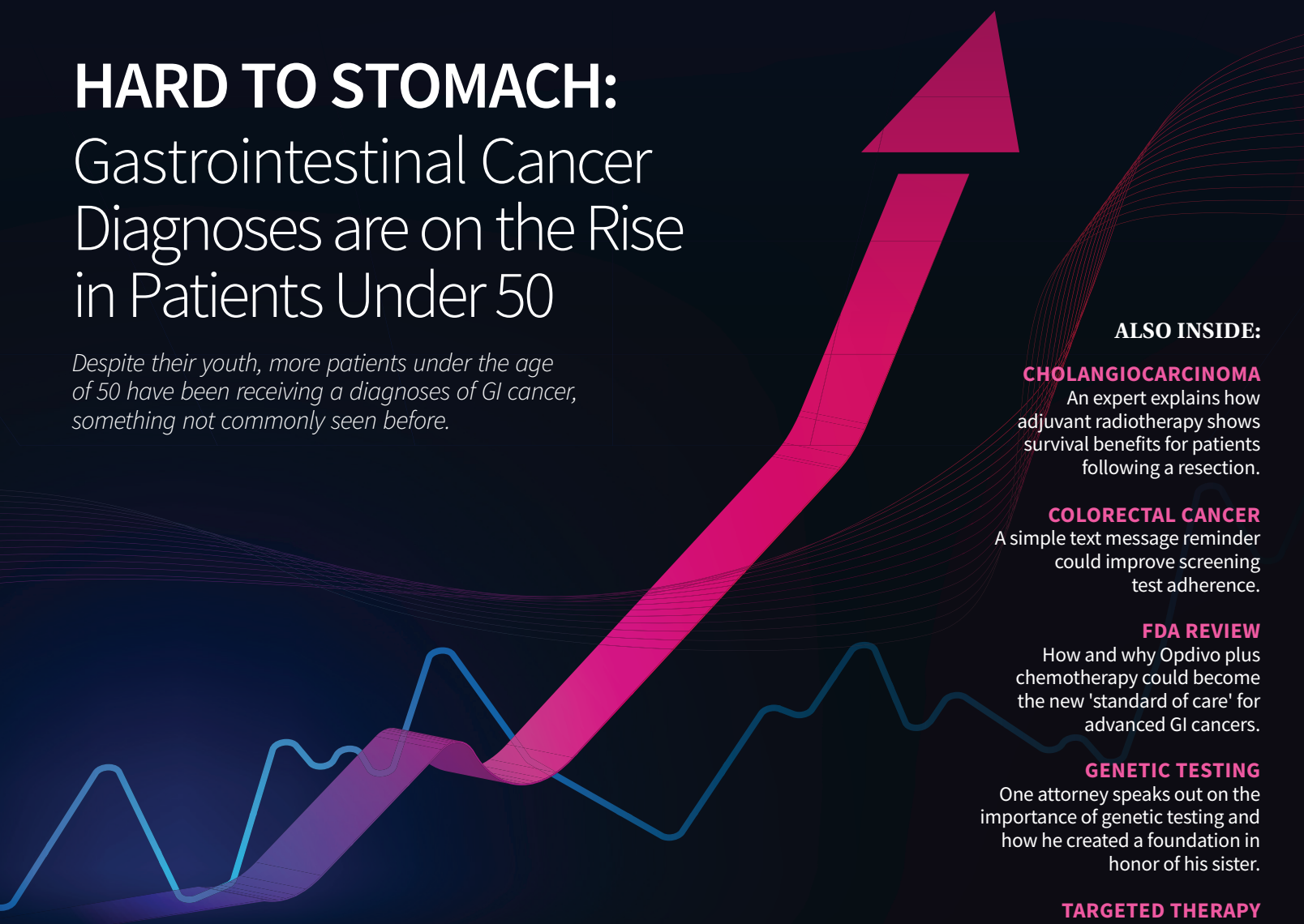
Cancer Updates, Research & Education®

HARD TO STOMACH:

Gastrointestinal Cancer Diagnoses are on the Rise in Patients Under 50

Despite their youth, more patients under the age of 50 have been receiving a diagnoses of GI cancer, something not commonly seen before.



ALSO INSIDE:

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SPECIAL ISSUE · 03.21

How do I manage chemo rash?

Skin toxicity, also known as "chemo rash," is a common side effect for patients with colorectal cancer. Luckily, there are ways to manage and lessen the symptoms of skin toxicity.

Skin toxicity resources are available for free in Fight Colorectal Cancer's resource library. Find them at fightcrc.org/skintoxicity.

fightcrc.org/skintoxicity

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GASTROINTESTINAL CANCERS · 03.21

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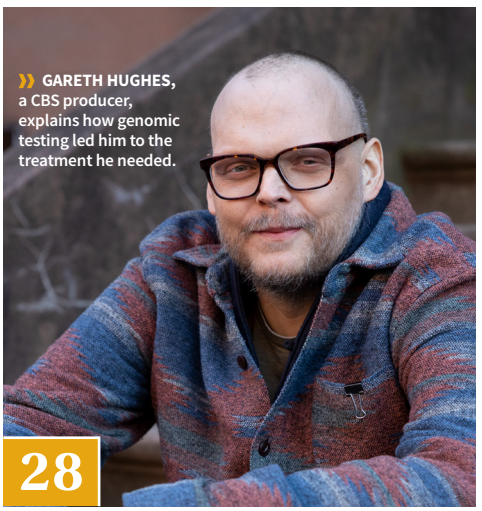

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Advances in Targeted Therapies Promise Significant Change in Treatment of Colorectal Cancer

RECENT HEADWAY IN THE study of targeted therapies has transformed how some cancer types are treated. For instance, the past several years, we have seen an influx of targeted therapies that have been shown to successfully treat patients with breast cancer, lung cancer and melanoma.

However, as one expert noted in a feature article in this special issue of *CURE*®, targeted therapies have not been as successful when used to treat colorectal cancer. But this expert also noted how researchers have learned from the past and are on the cusp of revolutionizing treatment for this patient population.

> **"One such piece of advice that stood out to me was how going through cancer treatment is 'harder than hard,' as Ramshaw puts it."**

"Compared (with) other forms of cancer, results of targeted therapy agents have not been as impressive in colorectal cancer, but we have learned from many negative trials," says Dr. Afsaneh Barzi, a gastrointestinal medical oncologist at City of Hope in Duarte, California. "With the new clinical trials, we are right on the cusp of seeing significant changes in outcomes for this population of patients."

Also in this special issue, we explore a Food and Drug Administration priority review of Opdivo (nivolumab) plus chemotherapy in the treatment of patients with certain advanced gastrointestinal cancers and, if approved, what the combination therapy would offer this patient population.

"This was the first trial that showed that if you add the immunotherapy — Opdivo in this case — it actually improved survival," says Dr. Michael Pishvaian, director of Gastrointestinal, Developmental Therapeutics and Clinical Research Programs at Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins in the Washington, D.C., area. "Our goals when trying to treat patients who (have) incurable cancers — which unfortunately, these patients fall into that category — is to help them live longer ... and to do so in a way that maintains (as high a) quality of life as possible. This trial definitely showed that the addition of Opdivo (helped patients live longer)."

And in an article, *CURE*® contributor and pancreatic cancer survivor William Ramshaw recalls how pushing through treatment reminded him of his eight-week stint gutting it out in Navy boot camp. Using his experience, he offers guidance to others on how to get through those grueling treatments.

One such piece of advice that stood out was how going through cancer treatment is "harder than hard," as Ramshaw puts it, but still doable. Ramshaw's recommendation: Take it one day at a time, surround yourself with allies, don't be afraid to ask questions and always seek out help when it is needed.

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Cancer Sometimes Does Not See Age

GASTROINTESTINAL (GI) CANCER, which includes the GI tract and other organs within the digestive system, typically affects patients aged 50 years and older. But, recently, there has been a rise in younger patients receiving diagnoses of GI cancer. In addition to this increased incidence, some studies indicate that younger patients are receiving diagnoses at a more advanced stage than older patients.

Some questions arise as GI cancers become more prevalent in younger patients. What is the reason behind this increase? Is it related to the obesity trend, other dietary/environmental factors or a combination of these? Guidelines have recently been changed to start screening for these cancers at 45 rather than 50, but should they apply for even younger individuals if risk factors are present? Will people be motivated to get screened earlier?

Beyond screening, GI cancers might behave differently in younger patients than in older patients. If that is the case, should younger patients be treated differently? There are currently no strong data to support this.

Because GI cancers are more prevalent in older populations, there is limited information about younger patients to point to specific causes and treatments, making it difficult to understand why the incidence is increasing. This represents a dilemma that epidemiologists and other researchers are endeavoring to solve.

> **"It is difficult for anyone to receive a cancer diagnosis, but when someone who is younger than average finds out they have GI cancer, they may face other challenges."**

It is difficult for anyone to receive a cancer diagnosis, but when someone who is younger than average finds out they have GI cancer, they may face other challenges. For example, there may not be as many young people to connect with who experienced a similar cancer journey, they are more likely to be uninsured, or they may not have a primary physician to evaluate and counsel them. Additionally, the financial burden of cancer treatment may be more onerous earlier in life.

It is important that we as doctors remember that although we may be biased by age, a cancer diagnosis may not. We need to adjust our threshold for when we obtain diagnostic testing. And for those young people experiencing discomfort, new GI symptoms or pain: See your doctor. If you have a family history of cancer, it is vital that you be screened according to the latest recommendations.

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MIKE KITADA

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CURE® is now accepting nominations to recognize our 2021 Class of Lung Cancer Heroes®, individuals who go above and beyond to make a difference in the lives of those affected by lung cancer. Each hero is nominated by patients, caregivers, and fellow health care professionals for their heroic contributions in the field of lung cancer, or in the individual lives of people with lung cancer.

Submit yours by June 30, 2021.

Three Lung Cancer Heroes®, along with their nominators, will be interviewed by *CURE*® and honored at a special reception to be held later in 2021. More details will be announced as they become available.

Submit your essay today at **curetoday.com/LCH21**

CURE®, Takeda, Lung Cancer Heroes®, and the advocacy community are dedicated to bringing together the lung cancer community to end the stigma, inform, connect, and empower anyone who has been impacted by lung cancer.

News & Insights From the 2021 American Society of Clinical Oncology Gastrointestinal Cancers Symposium

COMPILED *by* RYAN MCDONALD

More Counseling and Interventions May Boost Quality of Life for Young Colon Cancer Survivors

AS THE INCIDENCE OF colorectal cancer in patients under age 50 rises, overall health-related quality of life among younger survivors is declining, with longer treatment taking a toll on social and functional well-being.

Using a patient survey that assesses health-related quality of life globally, along with a cross-sectional online survey that focused on emotional, physical, social and functional well-being specific to colorectal cancer, study authors evaluated the responses of 235 patients (mean age, 33.76 years).

Patients' tumors were in either the colon (41.7%) or the rectum (58.3%). Most patients (33.23%) had received a diagnosis of stage 2 cancer and 98% were nonmetastatic, whereas 42% experienced relapse of their disease. Patients were split into two categories: six to 18 months or 19 to 36 months from initial diagnosis or relapse. In all, 189 patients (61.4%) were six to 18 months from their diagnosis or relapse, but there was no significant statistical difference between the two groups for important demographic figures such as age and ethnicity.

Although the study authors did not find a significant difference in terms of emotional and physical well-being, health-related quality-of-life scores were low across all domains, with social well-being the highest (15.15 on a 28-point scale) and emotional well-being the lowest (11.44 on a 24-point scale). Moreover, functional well-being rated near the bottom (11.84 on a 28-point scale), and physical well-being the second highest (15.15 on a 28-point scale).

Higher scores for physical and emotional well-being were observed in patients who had a longer time between diagnosis and taking the survey, whereas significantly lower scores were observed in social well-being for patients who had a shorter time between diagnosis and survey. This was also observed in functional well-being.

The authors concluded that more appropriate targeted methods, such as counseling and quality-of-life interventions, are needed to address the low overall health-related quality-of-life scores for young survivors of colorectal cancer. Further study is needed to determine the best measures, the authors said.

Findings Show Combination Therapy's Long-Term Survival Benefit in Advanced Liver Cancer

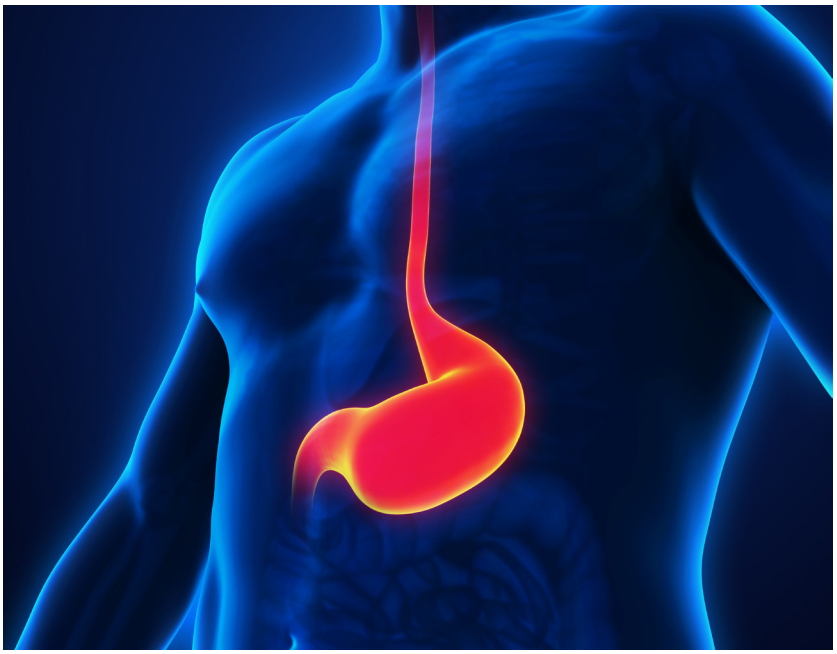
TECENTRIQ (ATEZOLIZUMAB) PLUS Avastin (bevacizumab) continues to show improved survival outcomes in patients with previously untreated advanced hepatocellular carcinoma compared with Nexavar (sorafenib).

"The median survival for (Tecentriq/Avastin) is now over 19 months. This is the longest survival seen in a phase 3 study of advanced liver cancer," lead study author Dr. Richard S. Finn, director of the Signal Transduction and Therapeutics Program at the UCLA Jonsson Comprehensive Cancer Center, said during a virtual presentation of the updated data.

Investigators in the phase 3 IMbrave150 trial, which included 501 treatment-naive patients with locally advanced or metastatic and/or unresectable hepatocellular carcinoma, assessed progression-free survival (the time from treatment to disease progression), overall survival, response rates and safety.

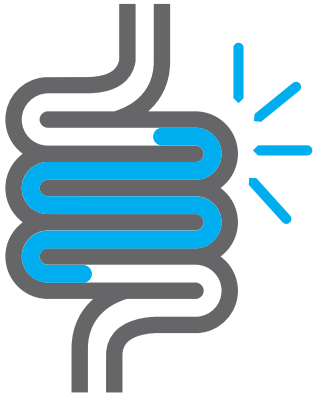
At a median follow-up of 15.6 months, 18-month progression-free survival was 24% in the Tecentriq plus Avastin group compared with 12% in the Nexavar group. The combination treatment was associated with better overall survival (19.2 months) than with Nexavar alone (13.4 months). Moreover, the Tecentriq plus Avastin regimen resulted in increased responses to therapy compared with those treated with Nexavar (30% versus 11%, respectively).

In terms of safety, all-grade treatment-related side effects occurred in 86% of patients receiving the combination versus 95% of those who got Nexavar. The rates of grade 3 and 4 (more serious or severe) treatment-related side effects were 43% and 46%, respectively.



Lenvima Plus Keytruda Performs Well Across Multiple Gastrointestinal Cancers Types

RESULTS OF SEVERAL patient cohorts from the phase 2 LEAP-005 study demonstrated that treatment with Lenvima (lenvatinib) plus Keytruda (pembrolizumab) resulted in positive antitumor and safety outcomes in previously treated patients with advanced gastric cancer, advanced or metastatic microsatellite instability-high or mismatch repair deficient colorectal cancer, and advanced biliary tract cancers.



"Among 26 patients who completed at least one baseline tumor assessment (in the gastric cancer cohort), 50% had a decrease from baseline in the size of their target lesions, and 15% of patients showed a decreased tumor size of more than 30%," study author Dr. Hyun Cheol Chung said during a virtual presentation of the data.

Among 32 patients in the colorectal cancer group who received the combination, overall response rate was 22% and the disease control rate was 47%. Median progression-free survival was 2.3 months, and median overall survival was 7.5 months. Half of those patients reported experiencing grade 3 to 5 (more serious or severe) side effects after receiving the treatment.

In the 31 patients in the biliary tract cancer group, treatment with Lenvima plus Keytruda led to an overall response rate of 10% and a disease control rate of 68%. The median duration of response to treatment was 5.3 months, median progression-free survival was 6.1 months, and median overall survival was 8.6 months. Of note, 97% of this group reported experiencing treatment-related side effects, which 48% of patients described as more serious or severe.

Novel Combination Shows Mixed Results in Pancreatic Neuroendocrine Tumors

TREATMENT WITH INLYTA (axitinib) plus the synthetic hormone octreotide acetate did not significantly improve progression-free survival (length of time during and after cancer treatment that a patient is alive but the disease does not get worse) in patients with advanced extra-pancreatic neuroendocrine tumors (NETs) compared with placebo plus octreotide acetate.

The study authors randomized 256 patients (median age, 61 years; range, 21 to 85 years) to receive either the Inlyta and octreotide acetate combination (126 patients) or placebo plus the synthetic hormone (130 patients). Measuring progression-free survival was the main goal of the study. Secondary goals included assessing overall response rates, duration of response, overall survival and safety.

Although investigator-assessed median progression-free survival favored the Inlyta group (17.2 months) compared with the placebo group (12.3 months), the authors noted that the difference was not statistically significant.

However, patients receiving Inlyta achieved a greater overall response (17.5%) compared with those who got the placebo (3.8%). Sixty-nine percent of patients in the treatment group demonstrated tumor shrinkage compared with 44% of patients in the placebo group.

Patients in both the Inlyta and placebo groups discontinued treatment because of disease progression (45.2% versus 63.8%), side effects (23.8% versus 4.6%), consent withdrawal (4% versus 3.1%) and death (3.2% versus 2.3%), respectively.

The authors noted that the occurrence of all-grade side effects was similar to previous safety profiles of Inlyta. The most common side effects included diarrhea (63.2%), weakness (52%), hypertension (50.4%) and inflammation of the mouth or gut (28.8%).

She Believed She Could, So She Did

My mom did not lose her battle with stomach cancer. She won the day she finally received a diagnosis. Could her story have turned out differently had she received treatment sooner? By LISA LORDEN

ON OCT. 25, 2016, my mom, Shirley, finally had an endoscopic ultrasound, three months after she was hospitalized with a major gastrointestinal (GI) bleed. When the doctor came back in, I could see in his eyes what I suspected: It was not good. His words were "You need to get your mom to an oncology surgeon as soon as possible."

I left and made an appointment for Oct. 28, before the results confirmed our fears: stomach cancer. I raced around pulling strings and making phone calls to get her scheduled for a port placement, a jejunostomy (J)–tube placement and a laparoscopic look at things on the inside to confirm the staging of her disease. All these things were done on Nov. 1, 2016, and we continued to pray that the cancer was contained in the stomach, leaving the possibility for surgery. We received the call the night before she started chemotherapy: Malignant cells were found in the washings of the peritoneal fluid, meaning stage 4. That meant no surgery, just chemotherapy, for as long as she could stand it. We were devastated.

To give some background, I am a nurse practitioner who works in oncology and am getting a Ph.D. in oncology research. How could my mom receive a diagnosis of stage 4 stomach cancer when I see her all the time? What did I do wrong? How could I have missed this?

I struggle with these questions on a daily basis.

> **How could I have missed this? I struggle with this question on a daily basis.**
>
> — LISA LORDEN

HOW IT STARTED

My mom's story really begins in May 2016, when she called and said she was having horrible reflux and no antacid was working. She said even swallowing was painful. I gave her an over-the-counter medication, and two days later the symptoms subsided. But I insisted she see a GI specialist, and we made an appointment that week. During the visit, I explained how rare this was for my mom and how she never even took Tums.

Although the specialist prescribed my mom Protonix (pantoprazole) and recommended Tums, he said there was no reason to do an endoscopy if she was feeling better. As a result, I decided to watch her like a hawk. Over the next month she looked more tired, but she was also nearly 78. On my birthday, June 7, she said she wasn't very hungry and she ate very little. I started to notice she looked a bit thinner, but she said all her clothes fit just fine. When I called the GI doctor and asked if we could do a scan or an endoscopy now, since she was not eating well, he told us to give the Protonix time to work and increased her dose to twice a day.

My mom turned 78 on July 7, 2016. Her party was awful due to the fact that she could not eat much. I told her that if the doctor would not agree to an endoscopy, we had to find another doctor. Within two weeks, my once vibrant and active mother — who lived alone, drove, took care of her house and was socially active — was weak and exhausted. She told me it was because of her knees. She was in denial and refused to go to the hospital. Her primary care physician said she just seemed tired, probably due to the summer heat, and needed to take it easy. But while sitting in the waiting room for an

LISA LORDEN, here with her mom, **SHIRLEY**, discusses her mother's diagnosis and journey with stage 4 stomach cancer.

PHOTO PROVIDED BY LISA LORDEN

appointment with her cardiologist three days later, my mom, with terror in her eyes, said to me, "I can't talk. I can't speak."

I pushed the emergency bell, knowing she was either having a stroke or a ministroke, but a doctor said she was in atrial fibrillation. Upon arrival at the hospital, I knew she was anemic and requested scans of the brain and lab work. Her red blood cell count was so low they gave her two units of blood right away. She was in atrial fibrillation from the lack of blood in her body. She was transported to the medical floor, where the testing began: CT scan, MRI of the abdomen, red cell scan, an endoscopy and a colonoscopy. The findings: acute gastritis.

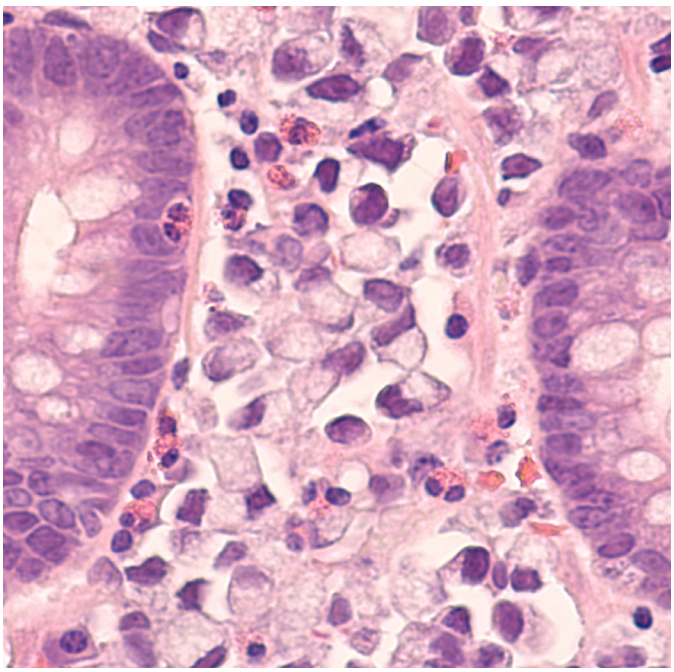
I insisted that something was very wrong and that the bleed had not just stopped on its own because her blood levels continued to drop. They said because of her age, a significant bleed is hard to recover from. While in the hospital, she received six units of blood over the next five days. The only "odd" finding on the scan was pyloric stenosis, a narrowing of the sphincter between the stomach and small intestines. They said they were not sure what that was and to follow up with a gastroenterologist.

What else could it be but a tumor? I asked if they could do a laparoscopic procedure to explore the abdomen, and they said it was not necessary because the biopsies in the stomach were all fine. Once again, my mom was just happy to go home, but I was terrified — and with good reason.

The rest of August and September had me making appointments and getting nowhere. Mom had another endoscopy after a month of my pleading. All biopsies came back fine, and doctors said the gastritis was looking better, but my mom was not looking better. She had no appetite, had lost weight and now she was vomiting after a few bites of food.

Next, she was supposed to have a procedure, during which they would place a camera in her stomach that would pass through and enter the intestines. Her GI specialist, however, was unable to do this because the stenosis had gotten worse, so he couldn't even pass a pediatric scope into the duodenum. We waited 14 days to return.

Oct. 25, the second worst day of my life.



Microscopic image of stomach cancer, that has metastasized (spread) to the colon.

TREATMENT BEGINS

At that point, we had a diagnosis and were facing stage 4 cancer of the stomach. And the only treatment option was for my 78-year-old mom to have chemotherapy until she could no longer take it. I was told on Nov. 8 that if she made it to Christmas, it would be a real miracle. Six weeks? Are you kidding me?

She started chemo with a J-tube in place and received five cans of nutrition a day, which made her feel bloated and caused diarrhea. Her chemotherapy was a combination of four medications, and it was a tough regimen. The oncologist said she might not be able to tolerate it because she was so advanced and so sick. Within a week, she was in the emergency department with a neutropenic fever and an ileus (a condition in which the bowel doesn't move its contents), so she went without nutrition for days.

My mom was getting worse, and she was scared. I prayed and begged her to transfer to another hospital, but she said that she had faith in God and that she could do this. I told her that we would do it her way, but I vowed to do everything I could to help her.

When she no longer could tolerate her J-tube feedings, they started nutrition via her port. She worked hard every day with physical therapists to get stronger, and I walked the halls counting the blocks on the floor and encouraging her to walk one more block before resting. I nagged her to do exercises in the chair. I woke her up to walk the halls or move into the chair. To keep her mind active, we watched "Jeopardy!" every night and did crossword puzzles. I brought books from home, and we read the paper every day. Slowly, she got stronger. Then Medicare said that they would not pay for her IV nutrition and that we had to try another tube feed. But every time we did, she had horrible bloating, pain and diarrhea.

Now what?

On the day that she was to be discharged, Mom asked if she could try to eat and wanted a chicken quesadilla. Not what I expected to hear. A chicken quesadilla was ordered, and I had the basin close, thinking it was not going to go well at all. But then she ate one and then half of another! Was this a miracle, or was that crazy strong chemo doing something?

The oncologist recommended changing her chemo drugs or, if we stayed on those drugs, dropping the dose. Instead, I begged to give her another chance on this regimen because she wanted to try. »

> She lived a good life, and she did not deserve to suffer for so long with no treatment. No one does, and this needs to stop.
>
> — LISA LORDEN

During chemo session No. 2, the dose was the same, and she did really well. Then it was Christmas and my mom was there with me, and I was happy, exhausted and devastated all at the same time. She was weak and struggled with activities around the house, but she fought so hard and, little by little, regained some of her strength. On Christmas Day, she was very tired and said she was short of breath, so the next day we went to the emergency department and learned that she has fluid in her lungs.

I worried that the cancer had spread to her lungs. But after she had both lungs drained, the fluid tested negative. She also had an arrythmia that needed to be controlled with medication. That day, she had 1.5 liters of fluid removed from her lungs. She ate dinner and sat up in the chair, saying how much better she felt.

LIFE IS WORTH FIGHTING FOR

On Dec. 31, 2016, Mom came home and watched the ball drop: Goodbye, 2016! After that, she gained weight, ate close to 2,000 calories a day and never missed another chemo. She never received another transfusion again.

She went back to her old self — and many days, she said, "I can't believe I even have this anymore." She made it to her 79th and 80th birthdays, and she had an amazing Christmas in 2017. My warrior mom was living her life with hope and feeling good!

But in June 2018, she received a diagnosis of bladder cancer, and she started to get a bit weaker. The chemo was changed, and she also had 10 rounds of radiation to the bladder. In September 2018, she fell, and that was the beginning of the end. She knew she was getting worse, but she said she would continue to fight and never stop chemo because that is what's "keeping me alive."

She received her last chemotherapy on Oct. 23, 2018, and died from sepsis on Oct. 29.

My mom did not lose her battle with stomach cancer. She won. She won the day she was diagnosed because she lived every day with courage and strength. She had 32 rounds of chemotherapy, 10 rounds of radiation and the most impressive stat — countless days of happiness.

A good day to my mom was seeing the sunrise, enjoying her flowers, spending time on the porch with me and watching the sunset. I cherish every second I had with my mom, and I miss her every second of every day. She was loved by so many, and she touched so many people in her life. She was a survivor.

I'm an only child. It has always been "me and my mom," and it was until the very end. The most important person in my life is gone, but she is still with me every day. My only goal is to make her proud.

THE PROBLEM WITH THIS STORY

What's wrong with this story is how long it took for my mom to receive a diagnosis. I don't know if her story could have been different. I will never know that, but what I do know is that her story is important and needs to be told. She lived a good life, and she did not deserve to suffer for so long with no treatment. No one does, and this needs to stop. Patients deserve better, more aggressive care.

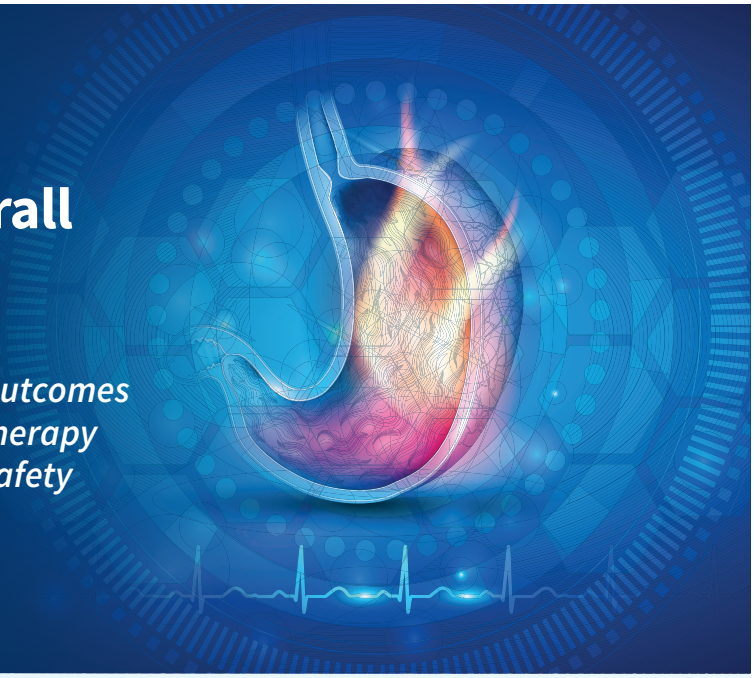
My favorite word is "believe," and I believe that my mom's story can help other people. I believe that what happened to her can turn into something good. Every time I see this quote, I think of my mom: "She believed she could, so she did!"

I love you, Mom. And I promise that I will always fight for a cure and the opportunity to help others, but most of all, I will always believe in you!

PHOTO PROVIDED BY LISA LORDEN

Bavencio Shows No Improvement in Overall Survival for Patients With Gastric Cancers

Treatment didn't extend survival outcomes compared with continued chemotherapy but did demonstrate a favorable safety profile. By COLLEEN MORETTI



PATIENTS WITH GASTRIC OR gastroesophageal cancer who received Bavencio (avelumab) after induction chemotherapy showed no improvment in overall survival compared with patients who continued with chemotherapy only, according to data published in the *Journal of Clinical Oncology*. The safety profile of Bavencio was, however, found to be favorable.

"To our knowledge, this is the first phase 3 trial of switch maintenance treatment with an immune checkpoint inhibitor in patients with advanced gastric cancers, and its results are informative for design of future trials," the authors noted.

A total of 805 patients received induction (first-line) chemotherapy, and then 499 patients were randomly assigned to 10 milligrams intravenouly every two weeks of Bavencio (249 patients) or continued chemotherapy (250 patients). Of those patients who received Bavencio, 30 had tumors that were positive for PD-L1 (a protein that cancer uses to evade the immune system); of those who continued chemotherapy, 24 had PD-L1-positive tumors.

No significant difference in overall survival was demonstrated. Median overall survival for those who received Bavencio was 10.4 months and for those who continued chemotherapy was 10.9 months. At 24 months, overall survival rates were 22.1% with Bavencio and 15.5% with continued chemotherapy.

Those with PD-L1-positive tumors, median overall survival was 16.2 months for patients on Bavencio and 17.7 months for patients on continued chemotherapy. In an analysis of these patients, those with tumors high in PD-L1 saw no overall survival benefit with Bavencio compared with the contiued chemotherapy.

Side effects occurred in 233 patients who received Bavencio and in 214 who continued chemotherapy. The most common side effects in patients who received Bavencio were increased amylase (an enzyme that converts starch to sugar), increased lipase (a protein that helps the body digest fat), physical weakness, colitis (intestinal problems), loss of appetite, hypotension and inflammation of lung tissue. For those patients who continued chemotherapy, side effects included decreased white blood cell count and peripheral sensory neuropathy (damage to nerves not in the brain or spinal cord). Overall, researchers found that Bavencio showed favorable safety in comparison.

Although the trial did not show improved overall survival in patients with gastric/gastroesophageal cancer, the authors concluded, "Results suggest potential activity in selected patient subsets and a favorable safety profile, providing guidance for future studies in this challenging disease."

Median overall survival was:

10.4 MONTHS with BAVENCIO AND **10.9** MONTHS with CONTINUED CHEMOTHERAPY

At 24 months, overall survival rates were

22.1% with BAVENCIO AND **15.5%** with CONTINUED CHEMOTHERAPY

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Opdivo with Chemotherapy Treatment Under Priority Review by FDA Shows Promise for Patients with Advanced Gastrointestinal Cancers

In clinical trials, Opdivo in combination with chemotherapy improved overall survival and progression-free survival compared to chemotherapy alone. By COLLEEN MORETTI

IN DECEMBER 2020, THE Food and Drug Administration (FDA) granted priority review to Opdivo (nivolumab) in combination with chemotherapy for treatment of several gastrointestinal cancers based on results from the phase 3 CheckMate649 trial, which showed that Opdivo and chemotherapy improved progression-free survival and overall survival.

The FDA is expected to make a decision on Opdivo in combination with chemotherapy by May 25.

To learn more about why this treatment has been granted priority review and what an approval could mean for patients, *CURE*® interviewed Dr. Michael Pishvaian, associate professor at John Hopkins School of Medicine and director of Gastrointestinal, Developmental Therapeutics and Clinical Research Programs at Sidney Kimmel Comprehensive Cancer Center at John Hopkins in Washington D.C.

Q: *CURE*®: What does it mean when the FDA grants a priority review?

A: Generally speaking, (when) a new therapy is looking highly promising and there (are) some preliminary data that (suggest) it might actually be effective for patients, the FDA wants to be able to get it out to patients as quickly as possible so (they're) not missing an opportunity. That's part of the expedited review process ... but ultimately the (drug developer) will need to present the full set of data and, in some cases, even follow up with a more definitive trial (before) the FDA gives ... final approval.

Q: Would you explain why this particular therapy was granted priority review?

A: Two big studies were presented at the European Society for Medical Oncology Virtual Congress last

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fall. One was CheckMate649, which was a trial of Opdivo with chemotherapy versus chemotherapy alone in patients with gastric and esophageal cancers. Interestingly, and in some ways surprisingly, the addition of Opdivo to chemotherapy improved patient survival, including overall and progression-free survival.

This is a pretty big change because some previous studies had mixed results with either Opdivo or its cousin Keytruda (pembrolizumab). But (CheckMate649) was a larger and more definitive study that did clearly show a survival benefit. So ... I think everybody's predicting that the treatment will get FDA (approval for use in patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer or esophageal adenocarcinoma).

Q: What would this mean for patients?

A: It means that patients are going to be able to have this drug added on to their chemotherapy regimen. We know that chemotherapy definitely improves survival, at least compared with a placebo, in patients with advanced, metastatic stage 4 gastric and esophageal cancers. The standard chemotherapies have become a doublet, as we call it — two drugs. Typically, a (fluoruracil) drug (plus) a second drug that (is a platinum-based compound). These doublet therapies have proved (beneficial) to patients.

This was the first trial that showed that if you add the immunotherapy — Opdivo in this case — it actually improved survival. Our goals when trying to treat patients who (have) incurable cancers — unfortunately, these patients fall into that category — is to help them live longer ... and to do so in a way that maintains (as high a) quality of life as possible. This trial definitely showed that the addition of Opdivo (helped patients live longer).

Q: How could this change clinical practice?

A: It really arguably should be the standard of care to receive Opdivo in addition to chemotherapy for any patient with advanced esophageal cancer.

Q: Are there any side effects that patients should be mindful of?

A: The immunotherapies have been around for 10 or more years, so we've learned a lot about them because (they're) very commonly used and the side effects have become predictable; we know roughly what percentage of patients are at risk (for side effects).

> **It arguably should be the standard of care to receive Opdivo in addition to chemotherapy for any patient with advanced esophageal cancer.**
>
> *—DR. MICHAEL PISHVAIAN*

(Approximately) 70% to 80% of patients have no side effects. About 10% to 15% of patients have moderate side effects, but they aren't typically chemotherapy-like side effects. When we think of chemo, we think of nausea, vomiting, diarrhea, extreme fatigue and hair loss. These immunotherapy side effects are (cold/flu-like) side effects. I always tell patients that if you think of when you had the flu, those are the kinds of symptoms you experience: fevers, chills, muscle aches and pains, joint aches and pains, and a rash can develop.

Then about 10% of patients can have an autoimmune reaction, which is basically when the immune system is revved up so much that it starts to attack the normal, healthy parts of the body. There can be an autoimmune suppression of some of the hormone-producing glands, such as the thyroid gland and the adrenal gland.

Then finally, importantly, about 3% of patients on these drugs can have very serious autoimmune reations (in which) the body starts to attack, for example, the lungs or the liver — so autoimmune pneumonitis, that's lung toxicity, or autoimmune hepatitis, which is liver toxicity. Really ... any organ can be affected by an autoimmune reaction, but those are the two more common serious reactions.

I tell patients (that) 10 years ago, when these drugs were first coming out, (the 3% of patients who developed these life-threatening) side effects ... did die because of (them). We learned very quickly how to suppress the severity of the side effects. Typically, we can reverse the side effects fairly quickly by giving steroids or other immune inhibitors and shutting down the immune system. Now, thankfully, most patients do not die from the side effects, even though 3% of them can still get very severe side effects.

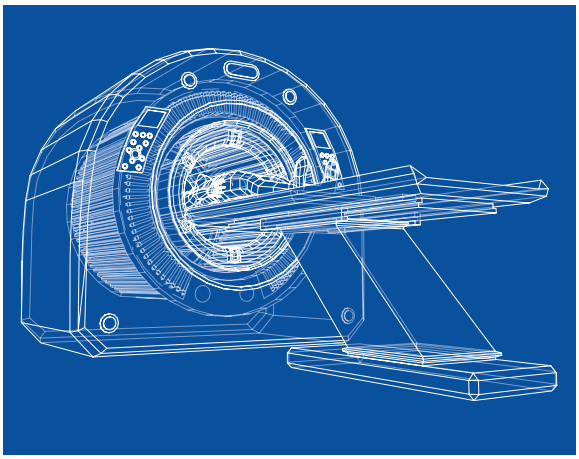
Adjuvant Radiotherapy Shows Survival Benefit for Patients Who Had Resection for Distal Cholangiocarcinoma

Following resection with radiotherapy lengthened life for patients compared with lack of the additional treatment.

By COLLEEN MORETTI

NEW FINDINGS SUGGEST THAT receiving radiotherapy after cancer treatment could boost survival in some patients with cholangiocarcinoma, or bile duct cancer. Improved survival rates were associated with adjuvant radiotherapy for patients who underwent distal cholangiocarcinoma resection, regardless of nodal involvement or resection margin status, according to data published in *Cancer*.

"Because this is a disease with a very poor prognosis, we're always looking for additional treatments that may help improve the results, over and above what we can achieve with surgery alone. Those options include chemotherapy and radiation, but there's some uncertainty as to the role of radiation — whether it actually confers a survival benefit or not," Dr. Hari Nathan, one of the study's authors, said in an interview with *CURE*®. "(Although) we want to do anything that might be helpful, we don't want to do things that don't have evidence for increasing survival. So, we wanted to look again at the existing outcomes of patients on a national level to see what we could observe in terms of differences in survival for patients who received radiation therapy versus those who did not." Nathan is an associate professor at Michigan Medicine.



Previously, distal cholangiocarcinoma had poor five-year survival rates, and chemotherapy has been the standard treatment. Adjuvant radiotherapy has been questionable because of the lack of conclusive evidence for a survival benefit, so researchers sought to analyze data for patients surviving more than six months after resection of distal cholangiocarcinoma.

Using the National Cancer Database, researchers identified 6,317 patients who underwent pancreatoduodenectomy, where the head of the pancreas, duodenum, a portion of the stomach and other nearby tissue are removed, for nonmetastatic distal cholangiocarcinoma. In total 2,162 received adjuvant radiotherapy, and 4,155 did not. In the study's matched groups, for selection bias, 1,509 patients received adjuvant radiotherapy and 1,509 did not. Rates of node-negative, node-positive and unknown node disease status were 39%, 51% and 10%, respectively.

Adjuvant radiotherapy was associated with a significant survival advantage compared with lack of the treatment (median, 29 versus 27 months; five-year survival, 28% versus 25%), but the benefit was not seen in the unmatched cohort (28 versus 29 months; five-year survival, 28% versus 29%). In a multivariable analysis, older age, higher comorbidity score, advanced tumors, node-positive tumors and positive margin status were all associated with inferior survival outcomes.

Patients in the matched group with node-negative, node-positive or unknown node disease who received adjuvant radiotherapy all had survival benefits. Similarly, patients who received adjuvant radiotherapy had improved survival regardless of whether resection margins were clear or not.

"When delivered by experts, radiation therapy is generally very well tolerated," Nathan said, adding that, like any medical treatment, it can cause side effects. "Patients should discuss (potential side effects) with their radiation oncologist and, of course, every treament decision to some degree should be individualized."

The results suggest that adjuvant radiotherapy should be strongly considered for those who underwent distal cholangiocarcinoma resection, Nathan said. "It's a retrospective study, and (it is possible) that, for example, healthier patients might have gotten radiation or patients with other favorable characteristics might have gotten radiation, skewing the results in their favor. We try to account for that using statistics, but you can't ever account for that completely," he concluded.

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WhatsApp Text Message Reminder Improves Adherence to Long-Term Screening for Colorectal Cancer

People who received a text message about their upcoming screening test were more likely to pick up, complete and return the kit. By COLLEEN MORETTI

A TEXT MESSAGE REMINDER MAY be pivotal to helping people adhere to colorectal cancer screening, according to data presented in *Cancer*.

The fecal immunochemical test, which uses antibodies to detect blood in stool, is a cost-effective, noninvasive way to check for the disease. The test is typically done once a year at home, which requires the person to schedule, pick up and complete the test kit and then send it back to the health care provider or lab.

Although it's low in cost with high sensitivity, research shows there is poor longitudinal adherence. Therefore, researchers in Hong Kong sought to discover if a text message reminder using WhatsApp, a free-to-use messenger application, would improve this poor long-term adherence.

Previously, conventional mail, calls and other message services have seen success but are not cost-effective.

"Because an inverse relationship exists between fecal immunochemical test adherence (and) colorectal cancer--related mortality, it is of clinical importance to implement effective strategies that optimize longitudinal fecal immunochemical test adherence," the authors wrote.

The study included 500 participants, of which three people were excluded (one died and two underwent colonoscopy). They were selected randomly to either receive a text message reminder or standard of care, meaning no text message. Most participants were men, with a mean age of 57.

A WhatsApp reminder, which shared screening benefits, the pickup date and hours of operation at the pickup location, was sent to 249 participants one month prior to their test pickup date. The remaining 248 participants received no text message reminder. Both groups received a phone call reminder to drop off their completed test if they had not already.

The researchers discovered that participants who received a text message reminder about their fecal immunochemical test were more likely to schedule, pickup, complete and return the test kit compared with participants who did not receive a text.

Out of those who received the reminder text, 200 participants (80.3%) went to pick up their test compared with 147 participants (59.3%) who did not receive a text message reminder. Not only was there a higher rate of pickup for those who received a reminder, but there was also a higher rate of returning the completed kit: 199 participants (79.9%) compared with 142 participants (57.3%).

Two years after participants were randomized to this intervention, those who remained eligible (452 participants) crossed over to another intervention. A text message reminder was sent to 225 participants, whereas 227 participants received no reminder. Those who received the text message, again, showed significantly higher rates to not only pick up the test (178 participants, or 79.1%, versus 120 participants, or 52.9%, respectively), but also return it (119 participants, or 52.4%, versus 76 participants, or 78.2%) compared with participants who did not receive the text message reminder.

Interestingly, the WhatsApp text message reminder was most effective with men, those younger than 65 and those with a family history of colorectal cancer. Researchers observed that the reminder did not improve adherence for those over the age of 65.

"This observation suggests that proficiency with smartphone applications may influence the effectiveness of such a reminder strategy," they wrote.

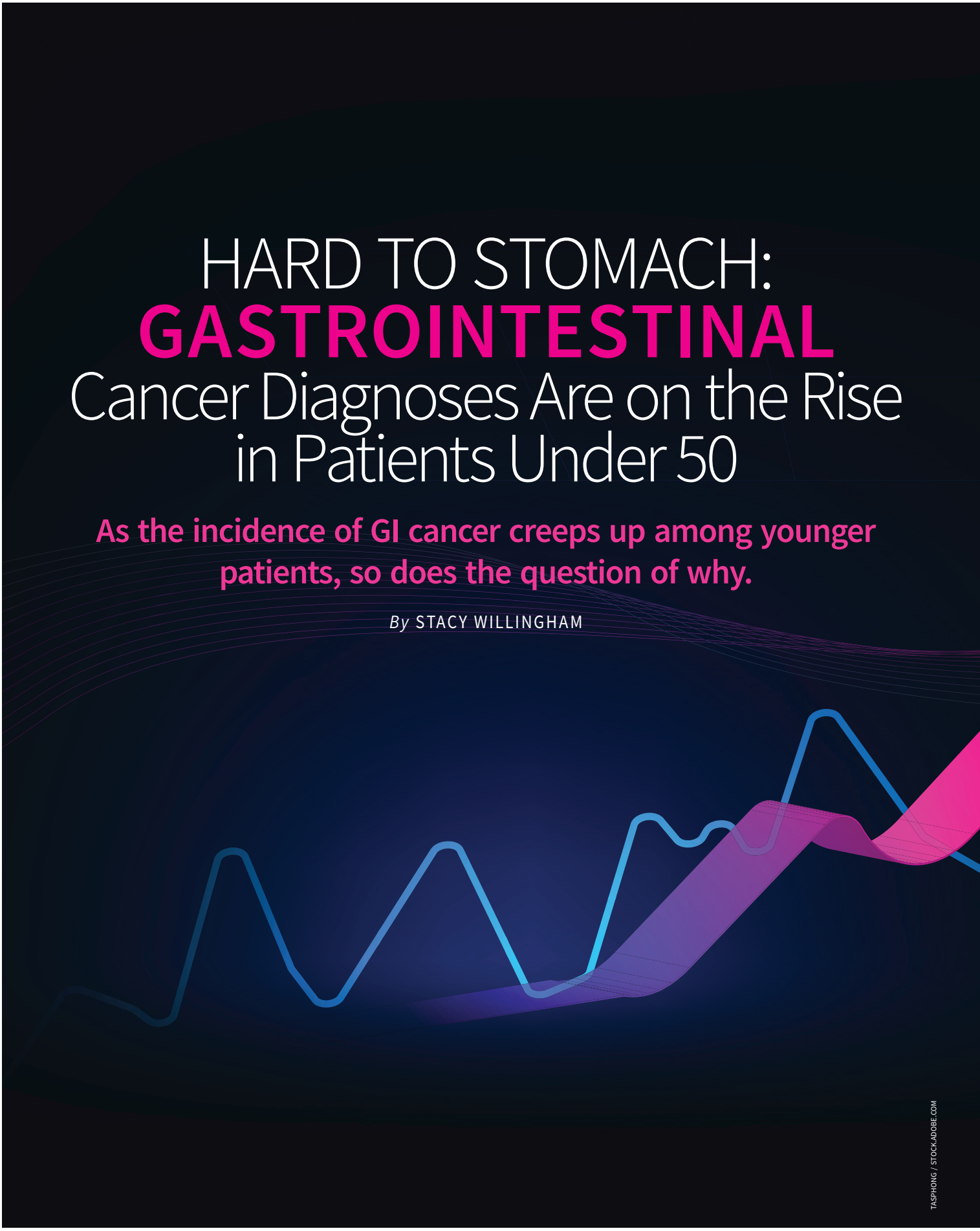
The researchers suggested that this routine in colorectal cancer screening should be considered further, not only because it worked but also because it is cost-effective. However, they noted it might not be popular in other countries.

"Further studies would be needed to investigate the acceptability of different mobile messengers among screening program organizer and their target population," they concluded.

HARD TO STOMACH: GASTROINTESTINAL Cancer Diagnoses Are on the Rise in Patients Under 50

As the incidence of GI cancer creeps up among younger patients, so does the question of why.

By STACY WILLINGHAM



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In April of 2019, Colt Blunt arrived to a routine physical prepared with notes describing some gastrointestinal symptoms he had been experencing, including heartburn, bloating, abdominal pain and general discomfort.

"My symptoms weren't that bad, but they were new," says Blunt, a forensic psychologist in Minnesota. "Luckily, I have a fantastic primary care doctor, so he took me seriously. He said it was probably just acid reflux, put me on some proton pump inhibitors and said if I wasn't perfectly back to normal after 10 days, he would send me for an endoscopy."

Although the medication helped, it didn't eradicate Blunt's symptoms, so the following week, he went in for an endoscopy. At 37 years old, Blunt was young and otherwise healthy. However, because his family has a history of cancer, when the endoscopy visualized an ulcerated area of his cardia, he was concerned about the risk. »

"I asked my (gastrointestinal) doctor 'What are the chances that this is cancer?' and he said, 'One in a million,' " Blunt says. "When I asked him why, he said that he had just diagnosed a 37-year-old with stomach cancer the week before, and he sure as hell wasn't going to diagnose another one a week later."

However, on June 20, 2019, that's exactly what happened. After his endoscopy, Blunt received a diagnosis of stage 3 gastric adenocarcinoma of the upper cardia (just below the esophagus). Although gastric cancer at Blunt's age is rare, his experience is representative of a growing trend — an increasing number of patients under the age of 50 are receiving a diagnosis of gastrointestinal cancer.

AN UNSETTLING TREND

"I used to always be younger than all of my patients, and now I'm seeing patients younger than myself," says Dr. Travis Grotz, a surgical oncologist in the Division of Hepatobiliary and Pancreatic Surgery at Mayo Clinic in Rochester, Minnesota. "It is crushing when you see a young mother or father dealing with something so serious."

"Gastrointestinal (GI) cancer" is a term used for the group of cancers that affect the gastrointestinal tract and other organs contained within the digestive system, including the colon, rectum, liver, stomach, pancreas and esophagus. As with many cancers, GI cancer mostly affects older populations. For example, the average age of people who receive a stomach cancer diagnosis is 68; for colon cancer, the average age at diagnosis is 68 for men and 72 for women. Why, then, is incidence for GI cancers rising in younger patients?

Rebecca Siegel, senior scientific director at the American Cancer Society, first set out to answer that question, in regards to colorectal cancer, in 2007.

"I was analyzing data from a colorectal cancer report, and for some reason, I decided to analyze trends by age," Siegel says. "In the oldest age groups, incidence and mortality (are) declining rapidly and (have been declining) for a long time now. … But when I looked at rates in adults under 50, I noticed that incidence was actually increasing — and by a statistically significant amount."

What's more, Siegel clustered that data from adults under 50 into several smaller age groups — 20 to 29, 30 to 39 and 40 to 49 — and found that incidence rates were increasing across all of them. Similar studies are taking place across other GI cancers, too, with very similar findings.

One study was co-authored by Dr. Don Codipilly, a gastroenterology fellow at Mayo Clinic, in January. When analyzing data from patients with esophageal adenocarcinoma between 1975 and 2015, Codipilly and colleagues found that not only has esophageal adenocarcinoma incidence increased in patients under age 50, with an annual change of 2.9%, and presented at more advanced stages than older patients, but younger patients with esophageal adenocarcinoma also experienced poorer five-year disease-free survival (the length of time after primary treatment for a cancer ends that the patient survives without any signs or symptoms of that cancer) compared with older patients.

"Obviously, this is an unsettling trend because with cancer, we would hope that incidence would be going down," Codipilly says.

Because GI cancers are more prevalent in older populations, limited data are available on younger patients, making it difficult to ascertain why incidence is rising among people under the age of 50.

"There are known risk factors for colorectal cancer, such as excess body weight and smoking, but all of those studies are based on people who are much older," Siegel says. "All of this is a really new area, and (increasing incidence in younger populations) doesn't seem to be fully explained by those risk factors that we currently know of."

For example, Siegel says that they are not seeing the same increase among racial and ethnic groups; the largest increase is in non-Hispanic White patients, which suggests that it isn't just excess body weight contributing to the rise, because obesity has been increasing in all of these groups. The trends are also "remarkably similar" between men and women, which suggests that it is not hormonal.

However, researchers are learning more by the day, such as the role gut bacteria may play in the development of certain cancers.

LAURIE FALK-MCVEAN

« **COLT BLUNT** discusses receiving a diagnosis of GI cancer and how his age affected his journey.

LAURIE FALK-MCVEAN

"I have been very impressed with the increasing literature suggesting that the bacteria in our GI tract may play important roles in the development of cancer," explains Grotz. "This may be particularly true in young patients. As a result, this has widespread implications of how we manage antibiotics."

BEING PUSHED TO THE SIDE

Even with an increasing number of younger patients receiving a diagnosis of GI cancers at more advanced stages, obstacles to getting that diagnosis still remains.

"If a young person who is 20 or 30 (years old) goes to their doctor with a GI complaint, cancer is not coming to their or the physician's mind," notes Codipilly.

This is exactly what happened when Matt Budgell first started experiencing chronic stomach pain in February 2019.

"I wasn't getting enough hours at work to get health insurance through my employer, so I just started getting used to dealing with the discomfort. Cancer was the furthest thing from my mind," says Budgell, who was 26 years old at the onset of his symptoms. "When I finally got in to see a gastric specialist, they said, 'You're young. You probably just have an abnormal amount of acid or an ulcer in your stomach. Take some Prilosec OTC and you'll be good to go.' I tried that, and it didn't do very much at all."

After having his endoscopy appointment continually rescheduled — once, Budgell says, because they gave his appointment to somebody else who "needed to be seen right away" — he was finally given answers on Jan. 10, 2020, almost a year after his symptoms began. At age 27, he was told he had stage 3/4 gastric cancer.

"There is no doubt in my mind that my age played a role in why it was so hard for me to get an appointment," Budgell, who initially received treatment in his home state of Hawaii and later California, says. "They push young people off to the side. They expect you to be fine. And then all this time passes, and finally, you find out that you're not going to be fine at all."

Siegel highlights that later diagnoses like that of Budgell play a critical role in why cancers in younger patients are more advanced — so, as with any cancer, early detection is important. However, because younger patients tend to be healthier than those over 50 years of age and are less likely to have comorbidities, they can also handle more aggressive treatments.

"A lot of our current treatment regimens (for GI cancer) are targeted at an older population, but younger people can probably withstand more aggressive treatment or major surgeries," Codipilly says. "That could lead to more complications, but it could also lead to greater rates of cure." »

MATT BUDGELL says his age played a part in why his diagnosis took so long.

Immediately after getting his diagnosis, Budgell had an open partial gastrectomy to remove the tumor, 60% of his stomach and a piece of his pancreas, followed by four months of chemotherapy. Blunt, too, underwent an aggressive treatment comprised of an open full gastrectomy (a complete removal of the stomach) and eight rounds of chemotherapy.

"I didn't want (a doctor) who was going to treat me like I was medically fragile," Blunt says. "I wanted an oncologist and a surgeon who were willing to look at me as an individual, not as a group statistic."

> **"I wanted an oncologist and a surgeon who were willing to look at me as an individual, not as a group statistic."**
>
> — *MATT BUDGELL*

For both of them, despite the advanced stage of their cancers, the aggressive approach paid off. Budgell's most recent follow-up PET scan and endoscopy looked clear, and Blunt has been NED, or no evidence of disease, on all of his scans since August 2019. Now the biggest hurdle involves finding the best way forward — changing their diets and dealing with psychological after effects.

"My diet has been completely overhauled. I used to eat whatever I wanted and never gained any weight, so it felt like it didn't matter, but after this experience, I eat really clean," explains Budgell. "For me, the recovery from the surgery was not as bad as the psychological damage and recovery that had to take place."

"It took me almost a full year to figure out how to eat enough to get all my calories in," notes Blunt. "I can't eat dairy and sugar like I used to; meals, in general, have to be smaller than they used to be … but I'm back in the gym, back to running, back to working full time, and I'm feeling pretty healthy. I'm still learning things about my new normal, but anybody looking at my life from the outside who doesn't know what I've gone through probably thinks I'm living a pretty normal life."

However, although young individuals may be better able to withstand treatment, as well as bounce back quicker after treatment, their age can also come with some disadvantages.

"Young folks are not usually as financially stable as older patients," Siegel says. "They often have young families to

PAWEL NUCKOWSKI

care for and are in the beginning or middle of their career, and a lot of drugs they are receiving are very expensive with high out-of-pocket costs."

"Being a young adult and not dealing with cancer, it is already hard enough to get by and make ends meet," Budgell says. "But when you're diagnosed, you have to think about treatment and taking time off because you don't feel well, (but) your expenses don't just go away even though you're sidelined by cancer."

KEEPING YOURSELF SAFE

Experiences like those shared by Blunt and Budgell underscore the unique challenges young patients with GI cancer face, as well as the importance of both patients and doctors taking all symptoms seriously, despite the age of the patient.

To get ahead of a potentially serious diagnosis, Grotz suggests, patients should have health insurance whenever possible and bring up every symptom to their doctor, no matter how benign that symptom may seem. If patients feel that their doctors are discounting their concerns, they should advocate for themselves and find a new doctor, if necessary. They can even empower themselves with knowledge and point out the statistics of rising cases of GI cancers, as well as others, among young individuals.

"All of us should be going to the doctor at least once a year," Blunt says. "Listen to your body, and if something feels off, talk to somebody about it. If you have a doctor that brushes you off and says it's nothing, then that's a bad doctor — get a new one. If I had a different doctor who didn't take me seriously, I would probably be dead. It would have been caught too late."

Siegel also stresses the importance of knowing your family history and relaying that information to your doctor.

"There are a lot of places to fall through the cracks, but knowing your family history is a low-hanging fruit," she says. "We could make a huge impact if everybody knew their family history and was screened according to guidelines."

Although there are no strict screening guidelines for many GI cancers, Siegel's research contributed to the American Cancer Society lowering its recommended age to start screening for colorectal cancer — from age 50 to 45.

"Reducing the age recommendations is huge," Siegel says. "However, while colonoscopy is the most common test, for even younger people … there are home tests that are very effective. The best test for you is the test that you do."

JACOB LUND / STOCK.ADOBE.COM

Finding a Community Through Cancer

A CANCER DIAGNOSIS CAN BE isolating, no matter your age, stage or cancer type. And because gastrointestinal (GI) cancer typically affects older populations, receiving a diagnosis as a young adult comes with a unique set of challenges.

"A lot of times, folks with cancer can feel like they're doing it on their own," explains Dr. Don Codipilly. "But there are tons of people out there who have gone through similar issues."

For that reason, patients should never underestimate the importance of finding a community of other patients with cancer and survivors who understand what they're going through. Codipilly suggests starting by asking a doctor to recommend local support groups; if there aren't any available locally, many national groups are able to connect patients from across the world over the internet.

Both Colt Blunt and Matt Budgell, two young adults with GI cancer, have been involved with Debbie's Dream Foundation since receiving their diagnoses. The nonprofit organization is dedicated to raising awareness about stomach cancer, funding research and providing support to patients, families and caregivers.

"I became involved with Debbie's Dream Foundation after searching for cancer survivor stories on Google shortly after my diagnosis," Blunt says. "Through Debbie's Dream Foundation, I've met other survivors who I've been in frequent contact with since."

Since finding the foundation, Blunt has also started advocating and mentoring, as well as helping to open a local chapter of Debbie's Dream Foundation in his home state of Minnesota.

Budgell took his advocacy a step further by founding his own nonprofit, The Love for Life Foundation.

"I didn't connect with any other young adults with cancer until after my treatment was over," notes Budgell. "After I started the foundation, I started realizing how much of a benefit that human connection is after the cancer experience, so I can only imagine the impact it would have made on me during the experience itself."

Budgell describes the foundation as his way of "letting other young adult cancer patients and their partners, caretakers and families know that they are not alone on their journey."

In addition to providing resource navigation, mentorship and human connection to young patients, The Love for Life Foundation provides rent relief funds for qualified applicants.

"I was making $300 a week on disability (during my treatment), and that was not enough to make it," Budgell says. "If it (weren't) for the support we got from GoFundMe and other cancer nonprofits, we would have been in real trouble. I was blessed with the support I received, and I felt like it was my responsibility to pay it forward … and create an extension of that same love and support for others."

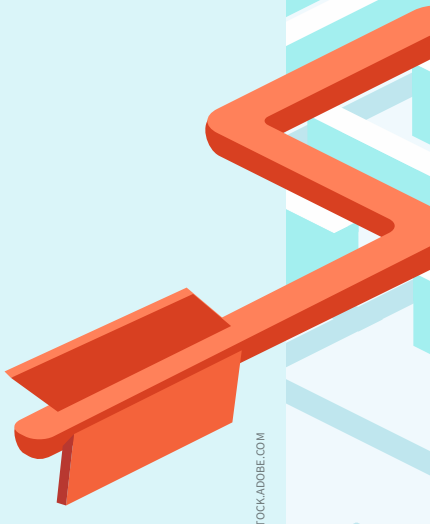
Overcoming Obstacles to Targeted Therapy in Colon Cancer

The identification of rare genomic alterations in patients with colorectal cancer gives oncologists the opportunity to treat patients who otherwise might not have many options.

By HEATHER STRINGER

When Mia Balko, 48, started experiencing an ongoing cough in early 2019, her primary care doctor treated her with medication for acid reflux disease, but the cough persisted. Then she noticed that her abdomen was becoming increasingly distended and firm, and she asked to see a gastroenterologist.

Balko, who lives in Waco, Texas, was shocked when she later learned that the cough had been triggered by stage 4 colon cancer. The disease had spread to her abdomen and caused fluid retention, which in turn pressed on her lungs. Balko initially received two different chemotherapy regimens over the course of a year, but despite each treatment, the disease continued to grow. »



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MIA BALKO's health and wellness improved after being on a targeted therapy treatment.

The cancer tested positive for a specific gene mutation known as KRAS G12C, which made Balko eligible to participate in a clinical trial at The University of Texas MD Anderson Cancer Center in Houston for a new targeted therapy known as AMG 510 (sotorasib). She started taking eight pills daily that contained a small molecule equipped to bind to a region of the KRAS G12C protein. Initially the only side effect was headaches, but once she started taking the medication before bed, the headaches disappeared. After nearly a year on the new targeted treatment, her scans showed that the cancer was stable.

"My quality of life improved when I switched to the targeted therapy," Balko says. "I had a lot more stamina to work and do activities I enjoy."

Although a recent scan showed a new lesion on her liver, she is grateful she can continue taking AMG 510 as she adds a new chemotherapy treatment to her regimen to address the growth.

For years, the only main targeted therapy available to patients with colorectal cancer was a medication that blocked the function of a protein called epidermal growth factor receptor (EGFR), but this treatment was not effective for patients with the KRAS mutation, which is present in approximately 40% of colorectal cancers. Now researchers are uncovering new treatments that are improving outcomes for people with colorectal cancer who have this mutation and other genetic aberrations, including the BRAF mutation and HER2 amplification.

"Compared (with) other forms of cancer, results of targeted therapy agents have not been as impressive in colorectal cancer, but we have learned from many negative trials," explains Dr. Afsaneh Barzi, a gastrointestinal medical oncologist at City of Hope Comprehensive Cancer Center in Duarte, California. "With the new clinical trials, we are right on the cusp of seeing significant changes in outcomes for this population of patients."

Colorectal cancer is the third-leading cause of cancer deaths in the United States, and Barzi notes it is critical for patients to receive molecular testing at diagnosis to identify potential genetic targets. "Sometimes doctors wait to do this testing until patients have failed on standard therapy, but this is too late," she says. "We need this information early on to identify potential clinical trials."

For patients who do not have the KRAS mutation, which

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is known as KRAS wild-type, EGFR inhibitors combined with chemotherapy can slow progression of the disease, but more recent studies have shown that there is one more element to consider for these patients: the cancer's location.

"When scientists analyzed the study results, they discovered that EGFR inhibition with first-line chemotherapy only worked with people who had left-sided colon cancers," says Dr. Alfred Neugut, co-director of the Cancer Prevention Center at New York Presbyterian Hospital and Columbia University Medical Center's Herbert Irving Comprehensive Cancer Center. For right-sided tumors, the better option for first-line treatment is chemotherapy plus Avastin (bevacizumab).

NEW STRATEGIES FOR TREATING BRAF AND HER2 CANCERS

The BRAF mutation — which occurs in approximately 10% of colorectal cancers — is another biomarker that has historically been difficult to target in patients with colorectal cancer, but researchers have started to uncover new ways to improve outcomes for this population.

"More than a decade ago, we recognized that this group of patients was not responding to traditional therapies, so initially we tried targeting the BRAF mutation," notes Dr. Scott Kopetz, a professor in the department of gastrointestinal medical oncology at MD Anderson. "This strategy had worked in patients with melanoma, but we found that this was not the case for people with colorectal cancer."

Researchers discovered that when they used a drug to block a receptor on BRAF-mutated cells, the cells increased EGFR signaling to compensate and continue cancer growth. Then Kopetz launched clinical trials in which patients received either one or two BRAF inhibitors in addition to an EGFR inhibitor, and this was more successful. In April 2020, the Food and Drug Administration (FDA) approved Braftovi (encorafenib), a BRAF inhibitor, in combination with Erbitux (cetuximab), an EGFR inhibitor, for patients with metastatic colon cancer. Findings from the recent BEACON CRC study showed that these combinations increased overall survival by more than four months. The most common side effects included diarrhea, acne and nausea.

Now researchers are exploring benefits of adding chemotherapy to this regimen or combining BRAF inhibitors with immunotherapy. Mary DeForest, 59, recently enrolled in a clinical trial for a combination of Braftovi and Erbitux plus the immunotherapy drug Opdivo (nivolumab) to treat stage 4 colon cancer, and she has been impressed by the results. After four months on the combination, the tumor in her liver has shrunk 75% and the cancer in her colon decreased 25%. "I feel so good that I don't think about having cancer anymore," DeForest, from Bay City, Texas, says.

Another promising target in colorectal cancer is the HER2 amplification, which means the cancer has too many copies of the HER2 gene. The amplification occurs in approximately 3% to 5% of colorectal cancers, and clinical trials combining two HER2-targeted therapies have shown that this strategy can have impressive results, according to Dr. James Cleary, a senior physician at Dana-Farber Cancer Institute in Boston.

One of Cleary's patients has been taking a combination of Herceptin (trastuzumab) and Tykerb (lapatinib) for four years with an excellent quality of life, and now there is a second option for her if the cancer starts to grow. »

MARY DEFOREST, with her daugther, **LISA HAKEMACK,** and husband **ERNEST DEFOREST.**

PHOTO COURTESY OF DEFOREST

> I had no side effects from the immunotherapy, and I've had clean scans ever since.
>
> — *RODNELL WORKMAN*

RODNELL WORKMAN was among the few patients eligible for immunotherapy treatment.

Enhertu (trastuzumab deruxtecan) is an antibody-drug conjugate that binds to cells with the HER2 amplification and then delivers a toxin into these cancer cells. Results of a recent study showed that, among patients with the highest levels of HER2 expression, the response rate to this drug was 45% and the median progression-free survival (the time from treatment to disease progression or worsening) was seven months.

> **Seeing (patients with colorectal cancer) with these rare genomic alterations benefit from nontraditional therapies gives me hope that additional targetable alterations can be found and exploited, and, hopefully, this is just the beginning.**
>
> *— DR. JAMES CLEARY*

IMMUNOTHERAPY FOR COLON CANCER

Genomic testing of cancer cells can reveal not only the presence of KRAS, BRAF and HER2 alterations but also the level of microsatellite instability (MSI). People who are MSI-high are deficient in the mismatch repair (MMR) proteins that find mistakes in DNA. These MSI high cancers accumulate DNA mutations that are felt to make tumors more recognizable, which is good news now that immunotherapy is an option for treatment.

"Immunotherapy uses the body's own immune system to fight off cancers, and tumors with more mutations are easier to identify as invaders," Cleary says. "The challenge is that only about 3% to 4% of people with metastatic colon cancer are MSI-high, so not many patients can benefit from immunotherapy at this point."

Rodnell Workman, 47, was among the patients with stage 4 colon cancer who were eligible for immunotherapy. His symptoms began in 2016, when he felt as though he had the flu and later discovered that his appendix had ruptured. The surgical team identified abnormalities on his appendix and a colonoscopy showed that he had a large mass in his colon. Biomarker testing revealed that he had Lynch syndrome, an inherited condition associated with high

FABIOLA GARCIA

levels of MSI and increased cancer risk. The doctors prescribed chemotherapy to shrink the tumor before removing it surgically, and they also recommended three months of the immunotherapy Keytruda (pembrolizumab) to ensure that the cancer was eradicated.

"I had no side effects from the immunotherapy and I've had clean scans ever since," says Workman, who lives in New Jersey.

Although Workman received immunotherapy after chemotherapy, in June 2020 the FDA approved Keytruda as a first-line treatment for patients with colorectal cancer that is MSI-high, MMR deficient or unresectable. Researchers also have started to investigate whether immunotherapy in combination with Stivarga (regorafenib), which inhibits growth of blood vessels needed for tumor growth, could benefit the many patients with tumors that are not MSI-high.

PROMISING TARGETS ON THE HORIZON

Although oncologists have more targeted therapy options for patients with colorectal cancer than in the past, the treatments are still limited to a somewhat small percentage of patients who have certain mutations, says Dr. Suneel Kamath, a medical oncologist who specializes in the treatment of gastrointestinal cancers at Cleveland Clinic in Ohio. "The biggest area of need is finding more mutations and developing drugs to target them," he says.

For example, fibroblast growth factor receptor (FGFR) mutations in bile duct and bladder cancer have also been found in colon cancer. Clinical trials are underway to test whether Pemazyre (pemigatinib), an FGFR inhibitor that targets this mutation, blocks tumor growth in people with metastatic colon cancer.

Moreover, mutations in the RAS gene family have been known to be bad actors for decades — associated with more aggressive behavior in many tumor types — and were considered "undruggable" until recently.

Cleary said he hopes to see more studies that explore repurposing targeted treatments for other forms of cancer to help people with colorectal cancer. As part of one study, Cleary and his Dana-Farber colleague Dr. Harsh Singh treated two patients with colon cancer who tested positive for gene translocations seen in lung cancer: ROS1 and ALK. They prescribed targeted therapies that have been effective in lung cancer, and the results were encouraging. The treatment was beneficial for seven months for the patient with the ALK translocation, and the patient with the ROS1 translocation continues to do well after more than a year of targeted treatment.

"To me, this was very exciting," Cleary says. "Seeing (patients with colorectal cancer) with these rare genomic alterations benefit from nontraditional therapies gives me hope that additional targetable alterations can be found and exploited, and, hopefully, this is just the beginning."

A New Frontier: Identifying Traces of Colorectal Cancer in the Blood

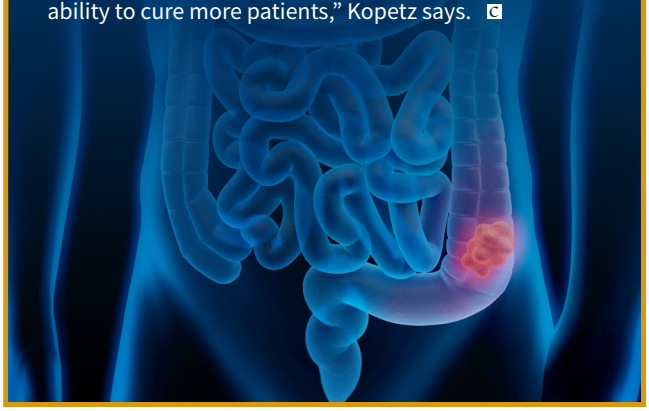
FOR PATIENTS WHO have undergone surgery to remove colon cancer, one of the significant stressors is waiting to see if CT scans show that the cancer has recurred. Now, new technology to detect cancer much earlier may alleviate the agonizing wait and lead to better outcomes.

In 2020, Medicare recommended coverage for a new test that detects small amounts of circulating tumor DNA (ctDNA) in the blood of patients who previously received a diagnosis of certain types of cancer. The Signatera test, developed by Natera, is being used in a clinical trial looking at how well the ctDNA testing works to predict the benefit of chemotherapy treatment after surgery for stage 3 colon cancer.

"In early stage 2 colon cancer, for example, we do not typically recommend chemotherapy, but what if the test came back positive for cancer in the blood?" Kopetz said. "Then we might suggest chemotherapy."

In patients with stage 3 disease, chemotherapy is usually prescribed, but a negative ctDNA test result might indicate that this treatment is not needed, Kopetz explains. The new blood test detects unique mutations in a patient's tumor and has been shown in clinical studies to identify residual disease up to two years earlier than standard imaging.

"The challenge now is learning what to do with the information we gather from the test, but ultimately I think this technology will dramatically accelerate our ability to cure more patients," Kopetz says.



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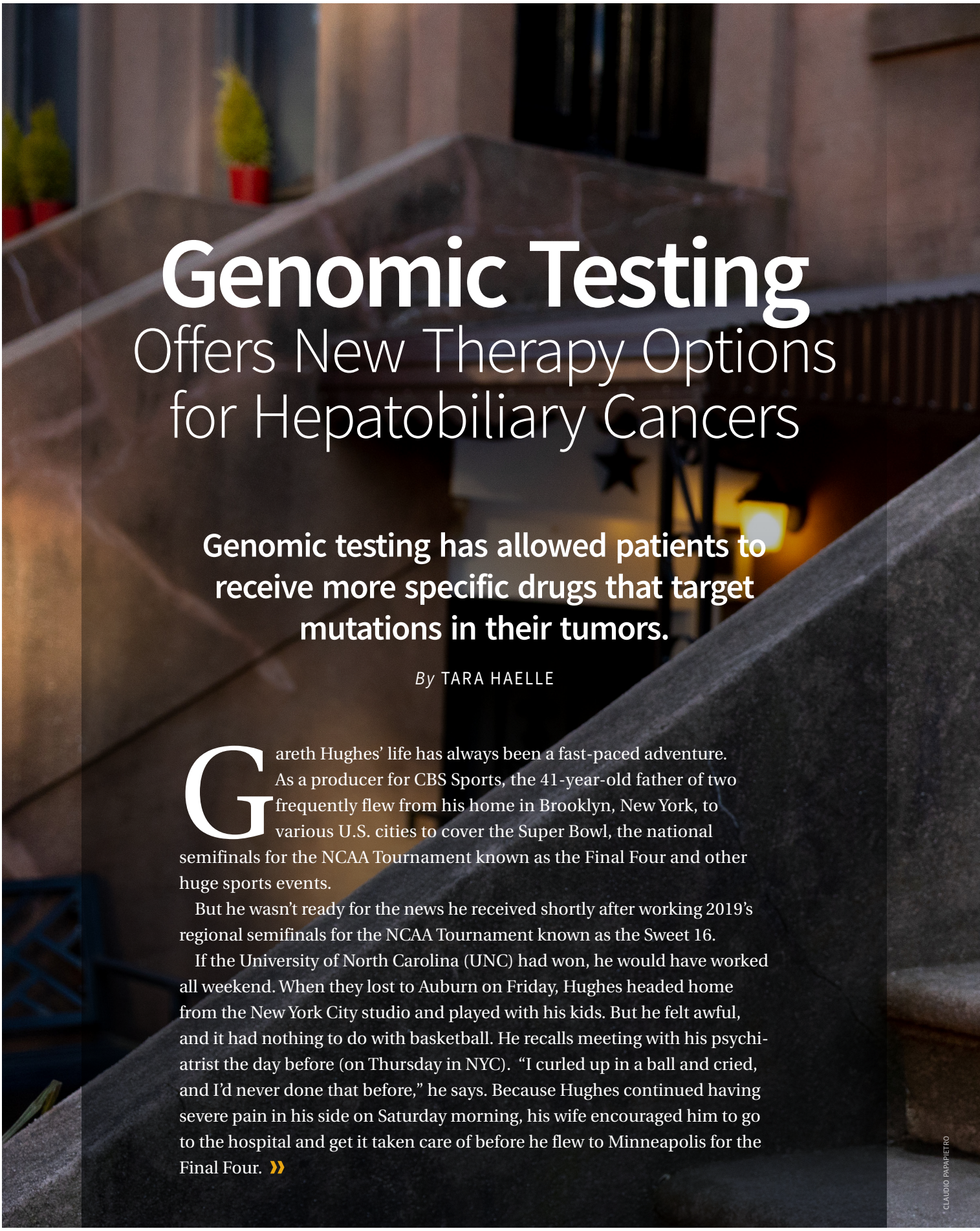

Genomic Testing Offers New Therapy Options for Hepatobiliary Cancers

Genomic testing has allowed patients to receive more specific drugs that target mutations in their tumors.

By TARA HAELLE

Gareth Hughes' life has always been a fast-paced adventure. As a producer for CBS Sports, the 41-year-old father of two frequently flew from his home in Brooklyn, New York, to various U.S. cities to cover the Super Bowl, the national semifinals for the NCAA Tournament known as the Final Four and other huge sports events.

But he wasn't ready for the news he received shortly after working 2019's regional semifinals for the NCAA Tournament known as the Sweet 16.

If the University of North Carolina (UNC) had won, he would have worked all weekend. When they lost to Auburn on Friday, Hughes headed home from the New York City studio and played with his kids. But he felt awful, and it had nothing to do with basketball. He recalls meeting with his psychiatrist the day before (on Thursday in NYC). "I curled up in a ball and cried, and I'd never done that before," he says. Because Hughes continued having severe pain in his side on Saturday morning, his wife encouraged him to go to the hospital and get it taken care of before he flew to Minneapolis for the Final Four. »

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GARETH HUGHES discusses how his fast-paced life turned upside down.

« **GARETH HUGHES** knew by the look on his doctors' faces this wasn't a classic gallbladder problem.

Given his youth and health — he'd quit drinking three years earlier — the doctors jumped to the obvious conclusion: time to take out his gallbladder. But after an ultrasound, X-ray and additional imaging at the emergency department, the doctors changed their tune. "You could tell by the look on their faces that this was not going to be as easy as classic gallbladder problems," Hughes says. The doctor sat on his bed and explained that there were spots on his liver, either from an infection or cancer. And infection didn't seem likely.

After a CT scan and biopsy, Hughes knew he wouldn't be covering the Final Four that year. Instead, he and his wife wrangled with news that changed their lives.

"You go from that Friday night, sitting on the stoop, listening to the music and playing buddy ball, a game we made up, with my 4-year-old son, and by Saturday evening, I've been admitted to the hospital and (I don't know it yet), but my life is never going to be the same," he says.

By the time he was discharged, it was clear that it was cancer. At an appointment with an NYU Langone Health oncologist, while fielding text messages from work about the Final Four set he'd worked a month to build, Hughes received an official diagnosis of intrahepatic cholangiocarcinoma — cancer of the bile ducts inside his liver. "It was a very strange moment where work and life collided," he says.

After the appointment, he and his wife just rode the Second Avenue bus for a while, crying, talking and texting the news to friends. "In that initial moment you're so lost. You don't know anything," he says.

The cancer hadn't metastasized beyond Hughes' liver, but it had gone too far for resection surgery. He had a grapefruit-sized tumor with satellites on the right side and two dots on the left — dots that essentially ruled out surgery because the risk of recurrence would be too high. He would begin chemotherapy treatment, the first-line standard of care for cholangiocarcinoma. Instead of receiving gemcitabine and cisplatin, however, Hughes sought a second opinion at Memorial Sloan Kettering Cancer Center in New York City, which prompted him to choose a pump that delivered floxuridine directly to an artery in his liver while he received gemcitabine and oxaliplatin. He also underwent testing to see if his tumors contained any mutations.

Hughes, like most Americans, had never heard of cholangiocarcinoma. He had also never heard of the FGFR2 fusion mutation, a gene alteration present in his tumor that broadened treatment options beyond standard chemotherapy — and an example of why doctors are increasingly encouraging people with hepatobiliary cancers to get genomic testing.

HEPATOBILIARY CANCERS VARY GREATLY

Hepatobiliary cancers include those in the liver, bile ducts and gallbladder. According to the National Cancer Institute, more than 42,000 people in the U.S. receive a diagnosis of liver or intrahepatic cholangiocarcinoma each year — a rate that has tripled since 1980 and continues to increase due to rising rates of hepatitis B and C infections, cirrhosis from alcohol consumption, and obesity and type 2 diabetes, which contribute to fatty liver disease. In addition, nearly 12,000 others,

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according to the American Cancer Society, are diagnosed with gallbladder cancer or extrahepatic cholangiocarcinoma, which occurs in the bile ducts outside the liver. The two extrahepatic types are perihilar, occurring in the bile ducts just outside the liver, and distal, occurring in the portion of the bile duct nearest the small intestine. Cholangiocarcinoma is rare — a couple of cases per 100,000 Americans each year — but intrahepatic cholangiocarcinoma is increasing, possibly due to increased detection as scans are done more readily and often.

Only surgery can cure hepatobiliary cancers when they're caught early enough, but most patients don't experience symptoms until the cancer has spread far enough to rule out curative surgery. Recurrence is common even after completely resecting a tumor that has spread, and post-surgery treatments vary greatly depending on where the cancer is.

For unresectable liver cancer, on the other hand, first-line treatment usually includes either the combination of the immunotherapy drug Tecentriq (atezolizumab) and the targeted drug Avastin (bevacizumab), or Nexavar (sorafenib) or Lenvima (lenvatinib), both targeted drugs. Second-line treatments include a range of immunotherapy and targeted drugs, including oral tyrosine kinase inhibitors, that have become available.

"With hepatocellular cancers, there has really been a sea change," says Dr. Milind Javle, a professor of gastrointestinal oncology at The University of Texas MD Anderson Cancer Center in Houston. "Several agents (have been) approved in the last five years, whereas for a decade we had nothing other than sorafenib." Those approvals include the immunotherapy drugs Keytruda (pembrolizumab), Opdivo (nivolumab) and Yervoy (ipilimumab) as well as the targeted drugs Stivarga (regorafenib), Cabometyx (cabozantinib) and Cyramza (ramucirumab).

> **"In that initial moment you're so lost. You don't know anything."**
>
> — *GARETH HUGHES*

For unresectable gallbladder and biliary cancers, however, not many options exist after first-line treatment with chemotherapy, nearly always gemcitabine and cisplatin. Without formal guidelines, most doctors use FOLFOX — folinic acid plus the chemo combo of fluorouracil and oxaliplatin — for second-line treatment of gallbladder cancer and cholangiocarcinoma.

Yet much of that is changing by the day. An increased understanding of tumor mutations across all hepatobiliary cancers is rapidly transforming patients' treatment options, and doctors are increasingly encouraging patients to undergo genomic testing as the landscape of therapies expands to include more targeted drugs for these cancers.

GENOMIC AND GENETIC TESTING

Two types of testing that look at the genes are informative, says Dr. Kenan Onel, director of the Center for Cancer Prevention and Wellness at the Tisch Cancer Institute at Mount Sinai in New York City. Genetic testing looks at a person's innate genetic code to see if they have any germline, or inherited, mutations that increase the risk of cancer developing. These mutations include ones familiar in other cancers, such as in the BRCA1 and BRCA2 genes.

Genomic testing, also called molecular profiling, on the other hand, looks only at the genes in the tumor itself that are not inherited, with the goal of finding mutations that can be targeted with specific drugs. No germline mutations have yet been linked to all gall bladder or bile duct cancers, Onel says, so genetic testing offers little insight for people with these cancers. But genomic testing, particularly with a method called next-generation sequencing, is already standard of care for biliary cancer and rapidly becoming so for liver cancer, Javle says.

"For both cancers, increasingly we are understanding that there are subgroups of the patients that have specific genomic alterations that render them more likely to respond to a specific treatment or more likely to be resistant to other treatments," explains Dr. Lewis Roberts, a professor of medicine at Mayo Clinic who specializes in liver, biliary and gallbladder cancers. "That is perhaps more the case with bile duct cancer than with liver or gallbladder cancer."

Only one targeted drug has been approved by the Food and Drug Administration (FDA) for cholangiocarcinoma — Pemazyre (pemigatinib). It was approved in April 2020 for advanced intrahepatic cholangiocarcinoma containing FGFR2 fusion or rearrangement mutations, the one Hughes had, after first-line standard chemotherapy. But additional targeted drugs may be coming soon as scientists learn more about genomic targets in biliary tumors, and more are available in clinical trials — the direction Hughes ultimately took.

When his genetic and genomic testing results came back, Hughes learned he didn't have any germline mutations that predisposed him to cancer, which also meant this cancer was unrelated to the testicular cancer he had at 11 months old that was cured by removal of one testicle. He also learned he hadn't brought this cancer on himself with »

drinking, a fear he'd harbored since hearing the news. His doctor told him to "accept that this is random."

The most important news from the testing was his having an FGFR2 fusion mutation, found in 15% of people with intrahepatic cholangiocarcinoma. That left open a door for oral therapies if chemotherapy failed. "From the get-go, they're mentioning surgery, and that's what I had in my head," Hughes says. "What I should have had in my head were these pills."

Hughes remained on the triplet chemotherapy regimen from May 2019 until Thanksgiving 2019, when scans showed the tumors were shrinking but his liver function had plummeted. While trying to kill the malignant cells, the chemotherapy had also killed too many healthy cells. Hughes had also developed a common allergy to oxaliplatin. While Hughes was on a long break from chemotherapy, his pain worsened, his pain medications increased, and he frequently visited the emergency department with pain and tumor fevers. By January 2020, his tumor markers had skyrocketed. He restarted chemotherapy, but because it continued to injure his liver, he stopped it in March 2020. It was time to try FGFR inhibitors.

> **Just knowing you have certain mutations gives us some idea about your likely outcomes because patients with different mutations seem to respond differently.**
>
> *— GARETH HUGHES*

GENE TARGETS IN CHOLANGIOCARCINOMA AND GALLBLADDER CANCER

An estimated 40% of patients with cholangiocarcinoma have tumor mutations that could potentially be treated with targeted therapies, but low enrollment in clinical trials has slowed progress in learning about effectiveness of these treatments.

Trials are currently investigating the FGFR inhibitors Balversa (erdafitinib), derazantinib, ponatinib, pazopanib, and Debio 1347, and researchers are testing Pemazyre or infigratinib against chemotherapy for first-line treatment. Another potential target in intrahepatic cholangiocarcinoma is the IDH1 mutation, occurring in approximately 10% to 20% of these tumors. IHD1 encodes an enzyme that can "turn off" the expression of certain cancer protection genes. Recent clinical trials showed improvements in progression-free survival with the IDH1 inhibitor Tibsovo (ivosidenib) in patients whose tumors harbor this mutation. Even the less common BRAF V600E mutation, which occurs in 5% of patients with cholangiocarcinoma, has shown some response in a trial testing the combination of the BRAF inhibitor Tafinlar (dabrafenib) with the MEK inhibitor Mekinist (trametinib). And tumors with HER2 mutations responded to the drug Nerlynx (neratinib) in a 2019 clinical trial.

Genomic testing can also benefit patients by offering insight into whether they'll respond better — or more poorly — to different therapies. For example, some research suggests tumors with the IDH1 mutation respond to the TKI inhibitor Sprycel (dasatinib) even though it's not specifically an IDH1 inhibitor. Meanwhile, tumors with FGFR2 mutations did not respond to Pemazyre if they also had TP53 mutations. Three mutations that occur in 15% to 20% of both intrahepatic and extrahepatic cholangiocarcinoma — KRAS, TP53 and ARID1A — lack approved drugs that target them, but emerging research still offers some hope. The ARID1A mutation may be susceptible to a group of drugs called poly (ADP-ribose) polymerase, or PARP, inhibitors, and recent results from a lung cancer trial heralded the first drug to successfully target KRAS, called sotorasib. Scientists have long sought drugs targeting KRAS mutations, which occur in several cancers, so sotorasib may offer benefit for other cancers with these mutations, too.

Though no targeted therapies for gallbladder cancer have been FDA approved yet, a number of mutations could soon have targeted drugs. One recent study by Javle found that 87% of 760 people with gallbladder cancer had a mutation that a drug may potentially target. The most common mutation was CDKN2A, followed by ERBB2, PIK3CA, MDM2, CCNE1, STK11, ERBB3, ATM and PTEN. Similarly, a recent study by Dr. Chirag Nepal and colleagues analyzed sequences from 92 tumors and found nearly a third (29%) had mutations in the TP53 gene, another gene that has attracted researchers' attention because it's so commonly mutated across many cancers. The researchers also found ELF3, ERBB2, CDC27, TGFBR2, PIK3CA, KIR2DL4, KIR2DL3 and ARID2 gene mutations, any of which might eventually help determine the most optimal therapies for tumors with these mutations.

With all these targets to investigate and all the experimental therapies out there, it takes additional research to discover what therapies might work against tumors with different mutations. Hughes started first with Balversa, the only other FGFR inhibitor approved by the FDA. However, because it's approved only for advanced urothelial cancers with FGFR2/3 mutations, Hughes took it off-label. The most common side effect of FGFR inhibitor drugs is high phosphate levels in the blood, followed by fatigue, hair loss, diarrhea, constipation, losing nails, inflammation of the mouth and dry eye. Hughes vomited for a week after starting Balversa, took a brief break and started it again. It worked.

His tumors shrank by half until June, when treatment-related hand-foot syndrome(HFS) caused such painful sores on his feet that he couldn't walk, and he had to stop the

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drug. "I became comfortable with the idea that taking breaks was going to be an important part of treatment," Hughes says. "You have to build in breaks to give your body time to recover." Hughes continued Balversa until October, when it was not longer working and the tumors began to grow again. He then enrolled in a trial for another FGFR inhibitor that didn't even have a name yet. But he stopped that drug after just three weeks because his tumor marker doubled.

Fortunately, he qualified for a phase 1 trial with RLY-4008, a drug that targets FGFR2 mutations. Hughes began in December, and after one dose reduction so he could better tolerate it, his main tumor had shrunk 27% by the day after the Super Bowl. "Other drugs you feel drugged and stupid, but this one has kept me feeling normal," he says, adding that he's optimistic about his response so far. This drug still causes HFS and requires him to take breaks, but it isn't as rough on his liver function.

Hughes wouldn't have had access to this drug without genomic testing revealing the FGFR2 mutation and his choosing to enroll in a clinical trial.

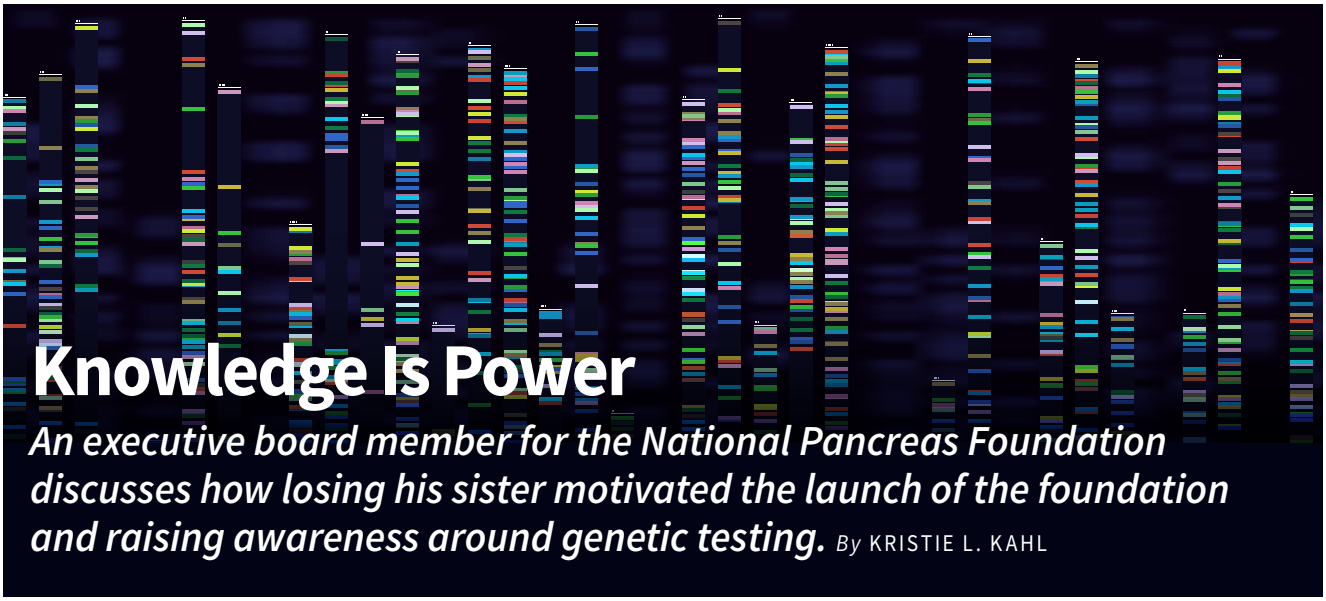
"We should consider every patient as potentially someone who should be participating in a clinical trial," Roberts says. "At every stage of cancer, there are trials that people can participate in that could potentially help them (and) increase the knowledge that we have and allow us to be offering better treatments over time." The many trials investigating genomic targets also make Roberts optimistic about future treatments for hepatobiliary cancers.

"These biliary tract cancers are some of the most lethal cancers we have," says Roberts, but FGFR inhibitors are already showing success in slowing them down — and that's only one target. "Just knowing you have certain mutations gives us some idea about your likely outcomes because patients with different mutations seem to respond differently, and patients who respond to these treatments have substantially improved outcomes," he says. "I think many of us are quite hopeful that with time, we'll be able to continue to make progress and develop better and better treatments and cover a larger proportion of tumors with personalized treatment."

That's certainly Hughes' hope as he's come to accept the ups and downs of trying different therapies.

"My treatment has moved into a chronic phase, and that's the most likely way I'll be living with it for the rest of my life," he says. "There's a small possibility that things could break right and things could shrink. I don't think the odds of that are that great."

He prefers his odds with the new targeted drugs in development, such as RLY-4008. "I have this dream," he says, "of this drug acting as my chronic answer."



Knowledge Is Power

An executive board member for the National Pancreas Foundation discusses how losing his sister motivated the launch of the foundation and raising awareness around genetic testing. By KRISTIE L. KAHL

ALTHOUGH EARLY DETECTION IS important in improving survival rates in pancreatic cancer, genetic testing may be just as important as informing family members of their risk and allowing them to get screened sooner.

In an episode of *CURE*® *'s Speaking Out* video series, Tom Birsic, an executive board member for the National Pancreas Foundation since its inception, discussed his family's journey with pancreatic cancer and how the organization has raised awareness around genetic testing and early detection.

Q: *CURE*®: Can you talk about your relationship to pancreatic cancer?

A: Birsic: So, I first became aware of pancreatic cancer a little over 24 years ago when my sister, Joan Birsic-Dawson, originally received a diagnosis of pancreatic cancer. And I come from a very large family — there were nine of us — and we had lots of accomplished people in the family. We had doctors and lawyers, and Joan was the best among us. Joan had a master's degree in pediatric nursing. And she would, in addition to being a mother of two lovely young girls, volunteer time to go into the roughest neighborhoods in Pittsburgh and take care of expectant single mothers and (single) mothers who ... just had babies. And she did this on her own time. She was just a wonderful person.

So her diagnosis was a shock to all of us. We'd never heard of (it). A doctor came out, told all of us that she had pancreatic cancer and ought to get her affairs in order because there was really nothing that could be done. And it was really mind-boggling and unbelievable to us. So from that point on, the doctors in (our) group started exploring the credibility of the diagnosis and the prognostication ... that nothing could be done. And my wife, Patter, who's nearly 100% Irish and very stubborn, got very angry and decided (that) we all ought to do something. (We ought to create) a foundation ... to try to raise money to make sure that (something was) going on and could be done for other people that had a diagnosis of pancreatic cancer. And so, we found Joan a trial that was going on at Johns Hopkins, but she passed away. That's when we got the (National Pancreas) Foundation going full steam.

Q: Since Joan's death, what steps have you taken personally for early detection?

A: After being bugged ... by my wife, Patter, who (is) the co-founder of the National Pancreas Foundation, to get genetic testing for about a dozen years — and I ignored her for many, many, many years (and ignored) the advice of great doctors on our boards like Dr. Randy Brand — I (learned) that one of my adopted sisters, and my first cousin, got a genetic test and found that she had the BRCA1 gene mutation ... and that sort of turned the light on for me.

My grandfather, at age 92, died of pancreatic cancer. My sister died of pancreatic cancer. My first cousin had the BRCA1 gene mutation, which (increases risk of) pancreatic cancer (by eightfold) and for women (is) a horrendously high-risk factor for breast cancer and for ovarian cancer.

So I decided to call up my good friend Dr. Randy Brand and schedule an appointment. And I found out that I had the BRCA1 gene (mutation). For somebody who was resistant for so long, I realized knowledge is power here. And one of the most stunning things about (pancreatic cancer which), I still remember to this day ... is that it's really hard stuff. It's a really tenacious, ferocious and hard cancer because it sneaks up on you. And by the time you properly diagnose it, it's nearly too late. And so the »

> **For someone who was resistant for so long, I realized knowledge is power here. And one of the most stunning things about (pancreatic cancer which), I still remember to this day … it's really hard stuff.** —TOM BIRSIC

statistics are really not with people once they get a diagnosis. It's like every cancer: The sooner you discover it and you can detect it, the better off your odds are.

There's research now that confirms that you're better off knowing. So early detection has been really important. And an important part of that is understanding your own genetics. After (I got the test and heard) the "I told you so's" … I worked with Dr. Brand and his team to put together a package for all my siblings and my nephews and nieces, including my own daughter. This is the gene mutation that Angelina Jolie had, and you have to make decisions. Knowledge is power (when it comes to) health. That was my first early-detection message.

It was great because Dr. Brand's team (spanned) the country, (so there were) different centers where people could get tested and (receive) the package of materials and information. It was just really, really wonderful. … As a result of (all) that, I decided that I'm doing a yearly endoscope, a procedure where they essentially (use a scope to) look at your pancreas and figure out if there's anything going on, which is right now the best we have, as I understand it.

Q: You've touched on this a bit already, but why was genetic testing so important to you?

A: Knowledge is power, and … your best odds are catching this thing early and if you understand, as we do from our own personal experience in our family, that by the time people get diagnosed with this … they'll feel a pain in their side. They'll think they have a gallstone. They go in, they get it checked, and pretty soon you've got 18 months to live. That's the standard.

Genetic testing tells (you that) your odds are much greater of getting this thing, and you need the impetus to be really tuned in to early detection. That is really heightened when you understand both your genetic profile and … what's available in terms of early detection. That's part of what the National Pancreas Foundation is really doing now — being a real information resource for people who are in this position. And where does one go for knowledge and for information? That's where we're putting a lot of our emphasis. And we're putting research dollars into early detection (because) it's really the holy grail for most of us that have been involved in this fight against pancreatic cancer.

Q: What hesitation do people have regarding genetic testing, and what would you say to them?

A: I understand the hesitation because, as I said myself, given my own family history — knowing my grandfather died of pancreatic cancer, my sister Joan died of pancreatic cancer — I was (still) reluctant to just take that simple step to do the genetic testing that Patter had been encouraging me to do for five or six years before I actually did it. I just think human beings are wired, in some sense, to just say, "Leave well enough alone. I feel fine. What good would it do me? I'd rather not know." Those sorts of things. I did (an at-home genetic) test … that didn't show anything. Those things create an inertia, a status quo of "I'll put it off. I won't do it." But it's such a simple procedure, and you gain so much by doing it. If you don't have a genetic issue, that's great. If it's not in your family, that's great. But that doesn't mean that there isn't something there lurking. (So) you might as well (do it). It's very easy.

Q: How can someone start a conversation about their family history of pancreatic cancer?

A: I think that's a great question. It goes to another core mission of the National Pancreas Foundation, and that is awareness. People underestimate the mission of awareness, right? You say, "OK, we principally want to raise funds for research into early detection and cures of pancreatic cancer and pancreatitis," but awareness is also important. This disease is a tough one. It sneaks up on people. It just comes at them out of the blue, right? And they don't want to think about that — until it's too late. And it becomes a very tragic thing, right?

It's good to understand what's been going on in your extended family. What are people suffering from? (Have) people died from it?

In this day and age, especially with younger people today, with all the resources available and all the increases in science, it's amazing.

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Cancer Is Like Boot Camp

Sometimes the only way to get over something is to get through it. A survivor and Navy veteran shares his strategies for gutting out cancer treatments. By WILLIAM RAMSHAW

YEARS AGO, I REMEMBER gutting out eight weeks of Navy boot camp. Because it was summer, most days in San Diego were in the 90s or higher. Those weeks seemed like years. The days crawled by. Minutes seemed like hours.

Each day we were up before dawn to clean our barracks from the overhead to the deck, stem to stern, scrubbing out hidden crevices with a toothbrush and making our racks the Navy way, only to flunk our barracks inspection once again. In addition to the demeaning insults and getting shoved into lockers, depending on how the inspectors felt that morning, the consequences ranged from pushups and situps to far worse. Soon, we became dull to being screamed at with expletives nonstop.

I think you get the idea.

So I suppose gutting out cancer treatments is much like pushing through that time at boot camp. It feels like our treatments will never stop. Our days are stacked with appointments, first with our oncologist and then with some specialist to deal with yet another complication from our treatments. In between, we're on the phone to schedule or reschedule our appointments for next week with seemingly daily trips to our pharmacy to pick up meds with names we cannot pronounce.

Too awake to sleep, we spend hours watching beyond-asinine reality TV shows. Anything to keep our minds off all that is being done to us. Instead of lying in bed hoping for our pain meds to kick in, we hope for a day when sleep will come as easily as it once did. Well-meaning friends and family wear worry on their faces, too afraid to think about the obvious question of whether we will make it. Not only does this overwhelm us, but it overwhelms our caregivers who are putting everything they have and more into keeping us alive. It's craziness.

So what can we do to get through this?

TAKE IT A DAY AT A TIME

When facing cancer, it is all too easy to let everything — none of which we can control one bit — overwhelm us. Today's problems are enough for today. Spending endless time worrying about tomorrow's problems does us no good. We have no control whatsoever over what tomorrow brings. It only leads to despair and worse depression. Live today to its fullest. Forget about tomorrow.

LOOK FOR ALLIES

For me, those who have gone through cancer have been the biggest help.

Our friends and family try to help us, but not having been put through the cancer mill themselves, they often struggle to understand what's happening to us. How sunny days can be blue. Why we don't feel like eating our once-favorite foods, like pizza or ice cream. Why we don't feel like talking about anything.

Thus, it is often someone who has been through what we're going through who can guide us. This is but one reason why I decided to go public about my own experiences with facing pancreatic cancer.

BE HONEST

Be forthcoming with your friends and family and, most importantly, your doctors. No one can help us if we're not truthful about how we're feeling both physically and mentally. Thanks to endless self-help books, many of us have a bent for staying positive even when things are worse than awful. Don't get me wrong. There is nothing wrong with positivity if it's real.

But faking it doesn't help. If you're feeling bad, say so. If someone is getting on your nerves, say so. But beyond saying so, say why. This has been hard for me and continues to be hard even today. It's one thing to be honest, but if we don't explain why to those who are trying to help us, they can walk away feeling hurt and, worse, become unwilling to lend a hand.

PUSH THE BOUNDARIES

Our doctors mean well, but there's a limit to what they can do. Some cancers respond well to treatment; others don't. It can be frustrating to be in treatment and have it go sideways. It can be more than frustrating not knowing why a particular treatment has been prescribed over another.

Because we're in a life-or-death situation, rather than nod our heads up and down when our doctor says something we don't understand, we need to learn to not be afraid to ask questions. If necessary, we may need to challenge their nonanswers or maybe seek a second opinion. It's our lives, not theirs. How can we participate in our treatments if we don't understand them?

Push the boundaries.

UPHILL BUT DOABLE

Gutting out cancer treatments is harder than hard, uphill all the way. But like much of life, it's doable if we take it a day at a time, look for allies, push the boundaries and seek out help if we need to.

These are just a few of the things I've learned after being put through the pancreatic cancer gauntlet and coming out the other side.

Laughing Off Cancer

After pinning his hopes for survival on a self-developed laughing system, one survivor lived to share why he believes cancer can die from laughter. By ROBERT BAILEY

MEDICAL DISCLAIMER:
This content is not intended to be a substitute for professional medical advice, diagnosis or treatment.

I WAS NEVER TOLD THE actual stage of my cancer. I didn't stick around long enough to find out.

Please, however, follow your doctor's full treatment plan, and use what I'm about to tell you only as a supplementary approach to dealing with cancer. For those who refuse to accept defeat, it might work. Or it might not. I designed this program and followed it and now I'm healthy as a horse! Read on to decide if it resonates with you.

AN IDEA IS BORN

On Dec. 3, 2018, I received a cancer diagnosis. A tumor in my colon with cancer was spreading to my kidneys. I was told my tumor could break at any time. Even with chemotherapy, this type of cancer returns every two years. They scheduled more tests, but I declined. I decided to fight this disease myself. As a hack energy scientist and natural healer, I had a good idea of what needed to be done.

Growing up, I heard a story of a man who healed himself from a serious illness by watching hours of comedy in his hospital room. This story stuck with me. The whole idea of laughter as a potential medicine intrigued me. I shared this man's self-healing story many times.

In 2017, long before my cancer diagnosis, I was testing laughter as a manifestation tool. I love to experiment. I'm a scientist at heart. I spend a lot of time creating and developing effective manifestation tools. And using the power of sincere laughter to reach and secure physical goals proved successful.

Because the tool was effective, I upped the ante. I'd long suffered from a serious addiction. I don't want to elaborate, but trust me, it was serious. On my hands and knees with my forehead touching the floor, I used prolonged bouts of deep sincere laughter, laughing directly at everything to do with my addiction, its desires and my deep desire to heal it. I got on my hands and knees for 10 minutes, five times a day, six days a week.

It took 23 days of sincere laughter while in the prayer position to break this decades-old chemical addiction.

MY MINI TESTIMONIAL

In 2018, when I learned I had cancer, I was really sick. I had ignored symptoms for months. Now I had severe pain in my gut, I was passing blood, and I was experiencing rapid weight loss. I experienced extreme night sweats and, during the day, sickness came in waves. The cancer was spreading.

Because I refused treatment, the medical community gave me only six to eight months to live.

I believed I could do better. I'd spent the past 16 years studying the human energy body. My healing my own cancer was like asking a mechanic to fix his own engine. I felt I knew what I needed to know.

It would be my self-developed laughing system on which I'd pin my hopes for survival. In truth, I saw my cancer as a challenge — a challenge I could possibly beat. I believed cancer could be beaten, but could I beat my cancer? My plan was this: one large glass of freshly juiced carrots daily; a healthy diet free of most unnatural sugars; and deep honest belly laughter.

To be successful, I knew I'd have to protect my attitude. I permanently shut off the television. I removed myself from anything and everyone negative. And while on my hands and knees, I sincerely laughed at everything about my cancer for 10 minutes, five times a day, six days a week. I laughed at my having cancer and my deep desire to heal it. I had experience with this "prayer position" laughing system. You're going to need faith to try it.

Following this program wasn't always easy. I often had to push to get laughing sessions done. I cried at times, not being sure this would work. It worked for addiction, but this was cancer. I prayed to Jesus while mentally preparing to say goodbye to my kids. Psychologically, I was in a fight for my life.

ONE MONTH (OR SO) LATER

I did this for 37 days before burning out. My goal was 40 days, but I just couldn't go any longer. In truth, I was feeling better by the 10th day. By day 37, I felt healthy. The sickness had gone. The pain in my gut completely disappeared. I had stopped passing blood and regained the weight I had lost —without any medical treatment. »

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> **It would be my self-developed laughing system on which I'd pin my hopes of survival. In truth, I saw my cancer as a challenge.** — *ROBERT BAILEY*

A number of tests were done three months after my diagnosis in March 2019 and again in June 2019. They came back normal. My general practitioner said my kidneys were functioning fine.

WHAT?

It's now been 24 months since diagnosis, and I've passed two medical exams. My general practitioner (I don't have a cancer doctor) says there's no sign of cancer but he can't be sure. Because I've refused treatment, he won't do decisive testing, leaving it to me to pay for a private scan to discover if the tumor's gone.

I was originally told my tumor could break at any time. It's been two years. I don't need the radiation. Except for a preexisting blood pressure issue, my doctor considers me healthy. I consider me healthy as a horse!

LAUGHTER AS MEDICINE

For those unable to kneel, you can still use the prayer position. Place your right hand over your left knee and place your left hand dead center against your forehead. It's not as powerful, but it still does the job.

The way I understand it, laughter raises core vibration, sparking the body's natural healing ability. The happy vibration is a healing vibration. With a higher core vibration, the body is better able to fight the invading disease. Just my opinion. This prayer-position laughter system is not yet proved in the lab.

For that reason, please follow your doctor's full treatment plan. Use laughter as only a secondary approach. You may know within three weeks if this system will work for you. Even though five bouts of laughter daily won't interfere with cancer treatments or medications, consult your doctor first before starting this program. C

"Against the assault of laughter, nothing can stand." — *Mark Twain*

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to read more stories like this one from patients and survivors

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 Mt. 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 $2.9 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.

Due to COVID-19 the 2020 program has shifted - all 2020 teams will continue fundraising and training this year and will hike in early 2021.

Patients, caregivers, myeloma loved ones, and others impacted directly by multiple myeloma will take on the Alaskan Kenai Peninsula, summit Mount Washington, explore the terrain of Greenland, and more! 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**

LEARN MORE ABOUT OUR CLIMBS!

2020 TREKS IN 2021!

Mount Washington Hike
July 9-12, 2021

Greenland Trek
To be determined

Alaskan Kenai Peninsula Trek
June 20-26, 2021

Kilimanjaro Trek
March 6-16, 2021

Machu Picchu Trek
May 1-11, 2021

New 2021 hikes & dates coming soon!
Email **teammanager@themmrf.org** to get on our waitlist!

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

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