Pancreatic Cancer Experts, Patients Applaud New KRAS Inhibitor Therapy

Hope for pancreatic cancer patients and oncologists: “We’re at the beginning of a paradigm shift.”

June 24, 2026 By Fred Hutch News Service and Diane Mapes

“She was only 61 and very healthy,” said Allan Knight of his mother Judy, who was diagnosed and died of pancreatic cancer in 2007. “I did one search and the survival rates were in the single digits. I had no hope, no optimism.”

It’s an all-too-familiar story for patients and families diagnosed with pancreatic cancer. Five-year overall survival rate for this cancer is 13% and that represents a doubling of survival time over the last decade.

“It’s hard to talk about,” said Knight, a 45-year-old Seattle financial planner who began volunteering for the Pancreatic Cancer Action Network a decade after his mom died; he now chairs the Puget Sound affiliate. “It’s been a mysterious killer for years. There was never any talk of a cure.”

There still isn’t talk of a cure, but there is a lot of talk about new pancreatic cancer therapies and how they may finally move the needle in what’s been an unforgiving, intractable disease. Phase 3 clinical trial results for Revolution Medicines’ new oral agent daraxonrasib recently rocked the 2026 annual meeting of the American Society of Clinical Oncology (ASCO) with news that it had almost doubled life expectancy in the metastatic patients who took it compared to similar patients who had chemotherapy. The results led to a 30-second standing ovation and a concurrent publication in the New England Journal of Medicine; the U.S. Food and Drug Administration has already granted the drug expanded access.

“Brilliant people have been working on this problem and now there’s something really tangible,” Knight said of the targeted investigational drug that’s expected to gain full FDA approval and become standard of care for patients with pancreatic cancer that has spread after treatment with chemotherapy. “I’m absolutely hearing the buzz in the community. They’re very excited.”

Fred Hutch Cancer Center clinicians, researchers and patients are also excited that science has finally figured out a way to drug the heretofore undruggable KRAS (pronounced “KAY-ras”) gene that’s mutated in over 90% of pancreatic cancers and also drives other aggressive cancers.

Medical oncologist Dr. Andrew Coveler, director of Fred Hutch's Pancreatic Cancer Specialty Clinic.Courtesy of Fred Hutch News Service

"It's fantastic, obviously," said Andrew Coveler, MD, director of Fred Hutch's Pancreatic Cancer Specialty Clinic. "It's a paradigm-shifting treatment. It's going to probably change treatment from chemotherapy to agents that target the mechanism that causes pancreas cancer. It really brings a whole new world of targeting to this disease and to other cancers, as well."

Why is pancreatic cancer so hard to treat?

Though pancreatic cancer has two distinct types, roughly 90% are classified as pancreatic ductal adenocarcinoma, or PDAC, a disease that's fraught with challenges.

To start, symptoms are vague and mimic other conditions like gastritis, gastroesophageal reflux disease (GERD) or irritable bowel syndrome (IBS), causing delays in diagnosis. There's also no approved screening or early detection test as there is with colorectal, breast, prostate and lung cancer. As a result, most cases are diagnosed at an advanced stage, too late for a surgery such as the Whipple procedure. Pancreatic tumors also tend to metastasize early, and metastatic pancreas cancer is treatable, but not yet curable.

Even those who qualify for surgery face a daunting recovery. The pancreas is located under multiple other organs, so surgeons have to, as one patient put it, "unpack you like a suitcase" just to get at it, making for an hours-long operation. Its tucked-away location also makes it difficult to obtain biopsies, which are necessary to identify the type of cancer and more importantly, its

potential biological targets.

Unfortunately, “around 90% of patients have metastatic disease already, we just can’t see it,” said Fred Hutch surgical oncologist Jonathan Sham, MD. “It’s micro-metastatic. It might be a couple hundred cells hiding within the liver or lungs. CT and PET scans can’t see it.”

Even circulating tumor DNA, or ctDNA, is limited, Sham said, due to minimal shedding, i.e., there’s usually more tumor microenvironment (dense stroma) than there are cancer cells.

“Pancreas cancer doesn’t seem to release the same amount of DNA as other cancers, meaning that even in the setting of a visible tumor we can easily see, we don’t detect ctDNA,” Sham said.

The biggest challenge, though, has been cracking the mutated KRAS gene, a member of the RAS gene family, which drives most pancreatic cancers.

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>
> — Dr. Andrew Coveler

The most frequently mutated oncogene in cancer, KRAS acts as an on-off switch to regulate cell growth and division. Mutations in KRAS lock its protein in the “on position” so the cancer keeps proliferating, crowding out and killing healthy cells. Finding a molecular foothold to inhibit KRAS mutations has been nearly impossible due to its slick impenetrable surface (researchers refer to it as a “greasy ball”). Only in recent years have scientists discovered how to create KRAS inhibitors, which block the signal.

Seattle engineer Diego Gabrieli was diagnosed with pancreatic cancer after suffering intense stomach pain that kept waking him up in the middle of the night. Photo courtesy of Scott Warrender

What’s it like to be diagnosed with pancreatic cancer?

As with many pancreatic cancer patients, Diego Gabrieli’s diagnosis was delayed.

When the retired Seattle engineer first went to a gastroenterology clinic in November 2024 for the sharp stomach pain waking him up each night, he was told he had gastritis and prescribed medication. After taking it for more than a month without relief, Gabrieli, 63, insisted on a CT scan. An hour after the scan, his doctor called and advised him to check into an ER for further tests.

They'd found necrosis.

"I spent two nights there," he said. "They diagnosed me with stage 2 pancreatic cancer."

Referred to Fred Hutch, Gabrieli saw gastrointestinal oncologist Rachael Safyan, MD, who began his treatment in January 2025. He first did two months of a powerful chemotherapy to shrink the tumor, but when that didn't work, he switched to a "much harder" chemo regimen.

"It's a regimen that the vast majority of people cannot do," he said. "I have chronic neuropathy in my feet from it."

This time, the chemo worked, and surgery was scheduled in September 2025. Gabrieli didn't have the Whipple but had most of his pancreas removed along with his spleen and 18 lymph nodes.

And for a while, all was well. Then his tumor markers started to climb. As did his level of stomach pain. He had radiation to help with the pain and is currently back on chemotherapy. The new KRAS inhibitor could mean a long-awaited reprieve for Gabrieli and patients like him.

"I don't know how long I can take the chemotherapy," he said. "It's taking its toll."

"Horrible pain" was how it started for retired contractor Ron Stanford, 62, of Lynden, Washington, in June of 2022, first in his back and then his stomach. He saw a chiropractor initially, then switched to his primary care physician who advised a scan ASAP.

"He said 'it's your pancreas' right off the bat," he said. "He may have saved my life by diagnosing it correctly."

Stanford also did chemotherapy to shrink the tumor, then believing his cancer was inoperable, went looking for other options, even consulting with a clinic out of state. They confirmed he was not a good candidate for surgery.

"Then Dr. Sham from Fred Hutch said, 'Wait a minute, I think I can do it,'" Stanford said. "That was amazing. I had six months of chemotherapy and had the Whipple in March of 2023. Then I went into remission. Then 15 months later, I had a recurrence in my lymph node near my collarbone."

Stanford went back on chemotherapy for another year; he also underwent radiation. He's currently NED (no evidence of disease) but is still under surveillance. And like most pancreatic cancer patients, he's not resting on any laurels.

"With pancreatic cancer, the hardest thing is the survival odds," he said. "If you look them up, it's like 'I'm done, I'm over.' I had to come to grips with that. When they thought it was inoperable, my wife and I were convinced I might have a year at best. It was difficult."

Gabrieli, too, has had to come to grips with a difficult diagnosis.

"I know the gravity of the cancer I have, it's a pretty bad one," he said. "I guess I've always liked a

challenge. I'm not resigned, I'm fighting it, but I know what the statistics are. So I try to make the best of every day. I still exercise, even on chemo. I still go out and ride as many miles as I can. Part of my therapy is getting my butt into the saddle of my bike."

Devout cyclists both, Gabrieli and Stanford are each training for Fred Hutch's Obliteride in August.

"Since pancreatic cancer has bleak survival rates, my goal every year has been to make it back to Obliteride, even if I'm just walking," Stanford said. "This will be our fourth time."

What does this mean for pancreatic cancer patients?

Now that researchers have found a way to drug the undruggable KRAS mutation, treatment for pancreas cancer may soon experience a sea change. But we're not quite there yet.

"This is just one of a dozen or more drugs that are out there and in development," Sham said. "There are different mutations for KRAS — the G12D, G12V, G12R — and all of them are slightly different so they respond differently. They all have different pluses and minuses, but the bottom line is this is opening a door to a really different class of agent."

KRAS inhibitors are not chemotherapies, or cytotoxic agents; rather they're small molecule drugs that target what he calls "the root cause."

"Chemotherapies kill cells in a very specific way, but RAS inhibitors are targeting the root, the driver mutations," he said. "As a surgeon, I'm super excited because we know that chemo before and after surgery significantly improves outcomes. There's a suspicion that these RAS inhibitors either before or after surgery would also do the same, maybe even to a greater extent."

Coveler, who treats and researches pancreas cancer, called the new oral agent a "huge breakthrough," adding that it "brings a whole new mechanism of action to the disease." He also confirmed the investigational drug had been granted expanded access.

What does that mean for patients?

"It doesn't mean it's available tomorrow, unfortunately," he said. "But we're opening it here and many other institutions are trying to open expanded access protocols. We expect there will be some eligibility that will be defined, similar to what was in this study."

In other words, daraxonrasib will probably first be available to metastatic pancreas cancer patients who've already received — and progressed on — a first-line treatment.

Coveler stressed, however, that if a treatment is working, patients should stick with it.

"If you're on something and it's working, you should stay on it and not be looking to change to this," he said. "It's not really widely available, that's the main thing. But you also don't want to get

off something that's working."

FDA approval will most likely happen by the end of the year, he estimates. And while it will likely be "an expensive drug," he believes insurance companies will cover it.

"A drug doesn't help anyone if you can't get it to people," he said.

When it comes to side effects, Coveler said daraxonrasib "will probably be better tolerated than chemo." Patients may experience nausea, vomiting and diarrhea as well as additional adverse events like rashes and/or blistering. But nothing oncologists haven't dealt with before, he said.

Mainly, he stressed that we are looking at the beginning of a big shift in cancer treatment.

"It's a long road and this is step one," he said. "In other places where you've had targeted therapies, the next ones always work better. We're at the beginning of a paradigm shift; it's a nice place to be."

Holding onto hope

A research breakthrough like this means much to patients Stanford and Gabrieli, too. Most of the studies they've read over the years have provided more hype than hope.

"Your friends and family are trying to save you so whenever they hear stories they send them to you," Gabrieli said. "Even stories about experiments in Spain where rats are cured. I know they do it from their heart, they want to help. They don't understand that it's just frustrating."

This news, however, is something else.

"I don't pay attention to chatter, I go to the trial results," Gabrieli said. "This is not a cure; it's not a panacea. But I've heard several good things, and everybody is extremely excited about it. I think it's going to help a lot of people live much longer than they would otherwise. I think it's real. There is definitely hope when I hear about legitimate things. I'm hoping I can qualify for expanded access because there is nothing else."

Stanford, too, is a study in resilience.

"One thing I would tell every cancer patient is 'It's never over until it's over,'" he said. "A lot of things happen where you think 'This is the end,' but it's not. You have to stay hopeful and do what you can."

SIDEBAR

What else is happening in pancreatic cancer research?

- Fred Hutch's Sita Kugel, PhD, director of Basic and Translational Research in Gastrointestinal (GI) Oncology has identified a biomarker that will help clinicians quickly and cost-effectively distinguish between the "classical" type of PDAC and the more aggressive and lethal "basal" subtype, present in about 20% of cases.

- Fred Hutch immunotherapy expert Philip Greenberg, MD, who holds the Rona Jaffe Foundation Endowed Chair and whose father died from the disease, is exploring a method for boosting the effectiveness of T-cell therapy for treating pancreatic cancer.

- Fred Hutch is currently participating in a national, multi-site clinical trial studying the use of RAS(ON) inhibitors in patients with gastrointestinal solid tumors. Read the full study overview at ClinicalTrials.gov. For more info on this or other pancreatic cancer clinical trials, reach out to clinical trial coordinator Matt Sherman at mfsherman@fredhutch.org.

- Fred Hutch/UW Medicine is also participating in a multisite international surgical clinical trial SWOG 2408, which is investigating whether giving patients a certain drug before surgery will prevent the post-surgery complication pancreas leak or fistula.

- The Vanguard Study is currently recruiting participants for a trial designed to test the efficacy of two multicancer detection tests, or MCDs, which detect cancer by measuring tumor cell biomarkers in blood. Both tests will look for pancreatic cancer signals along with a handful of other cancers. Vanguard is the first study of the NIH-funded Cancer Screening Research Network (CSRN); Fred Hutch serves as the Coordinating and Communications Center and the Statistics and Data Management Center.

- Several companies are developing therapeutic vaccines for pancreatic cancer, as well, including Germany-based BioNTech (in partnership with Genentech) which is creating bespoke mRNA vaccines designed to target individual patients' tumor mutations. Though the patient cohort was small, results were promising.

- Read more about the Expanded Access Program for daraxonrasib on ClinicalTrials.org.

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http://beta.docker.cancerhealth.com/article/pancreatic-cancer-experts-patients-applaud-new-kras-inhibitor-therapy