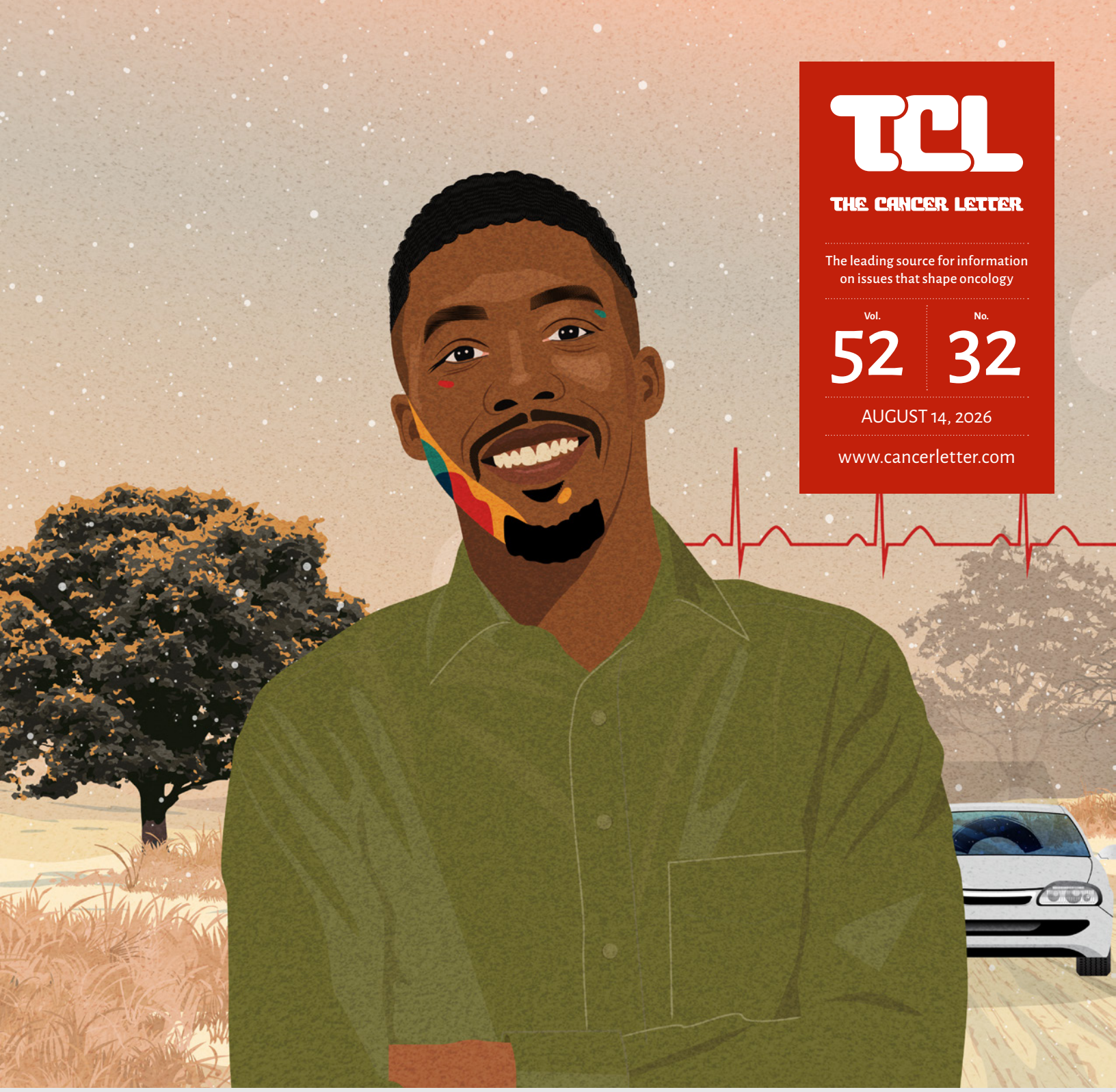

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I GREW UP UNHOUSED. NOW, WITH SUPPORT FROM ACS, I AM AN MD-PHD STUDENT FOCUSED ON ONCOLOGY

My mother instilled in me: "Never become a product of your circumstances."

→ PAGE 6

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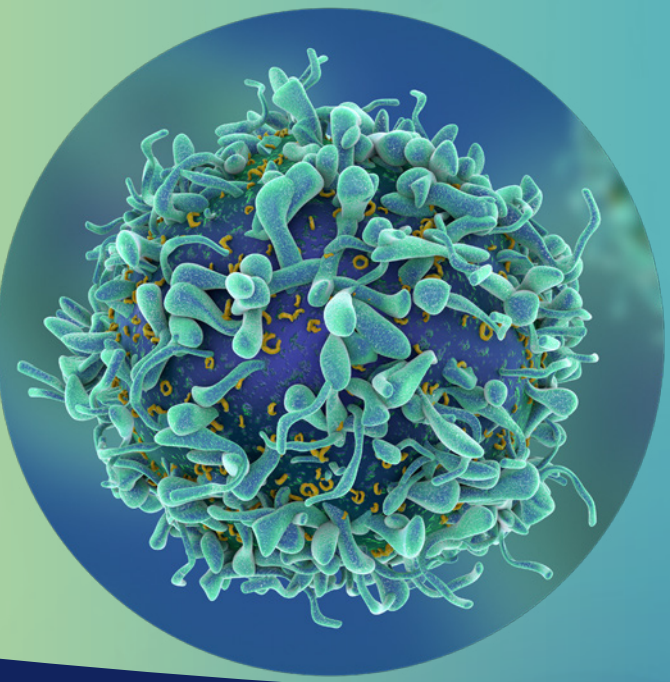

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GUEST EDITORIAL

I grew up unhoused. Now, with support from ACS, I am an MD-PhD student focused on oncology

My mother instilled in me: "Never become a product of your circumstances."

By Lavonté Saunders
Graduate,
American Cancer Society Post-Baccalaureate Fellowship Program,
Case Comprehensive Cancer Center;
MD-PhD candidate, Washington University School of Medicine in St. Louis

My high school experience revolved around constantly worrying about my four younger siblings and mom amidst our normal condition—instability.

Being unhoused meant sleeping in our car.

Our small car provided sleeping quarters for seven people, myself and six others. We slept pressed tightly against each other, our bags of clothes, and the walls of the vehicle.

At nights, in the dark parking lots of closed businesses, my body stayed awake, cautious of who or what may be out there. My upright position and the hot air fueled the anxiety, leading up to all-nighters that began with my waking up with a jolt at, give or take 1 a.m., and looking out the car window.

Often, I gave up my share of meals—combo deals from Wendy's or Little Caesar's—so that the small amount could stretch longer for my siblings. Food or no food, I was going to feel hungry regardless.

I spent some nights outside, with my family's belongings stuffed in garbage bags and suitcases, moving from one part of the city to another after each denial for a room. I stood, frustrated and tired, wondering whether we would ever find a place that would be willing to take in all of us.

On occasion, my family and I stayed with my aunt and uncle who lived an hour away from my school district. Across my siblings and me, our grade levels spanned elementary, middle, and high school.

To make a single round trip, I arrived at my high school extremely early and left extremely late. The school—Berkmar High, in Lilburn, GA—provided what I desperately wanted, the time to focus on my emerging academic passions, plus sturdy shelter against the elements.

Meanwhile, my home life remained chaotic, as each day we had to choose between food, shelter, or gas. Having all three was outside our price range. Even with the large amount of downtime I had before school officially started, these concerns crowded in the forefront of my mind.

I tried my best to maximize my productivity, never knowing what my home life might fling at me later that afternoon. School closed, books opened—day in, day out. Shed some tears, blotch my notes, shake it off, move on. This rhythm became familiar, keeping me pushing ahead, like the rhythm of my heartbeat.

Today, I am an MD-PhD student at Washington University School of Medicine in St. Louis, also known as WashU Medicine, rooted by training at Case Western Reserve University and Vanderbilt University. I've seen these institutions referred to as the "New Ivies." I prefer the image of an "Oak," because that's the role these places played in my life—stable, sturdy, mightily reaching upward. Attending these Oak League universities, I developed my scientific mind and career aspirations, remaining persistent in my goals and persevering with the strength of an oak tree.

My main interest is cancer.

What I just gave you is a rough outline of what happened, how I covered the distance from Point A to Point B, from childhood to the Oak League.

The rest is nuanced, the things that happened backstage. There's always much more happening behind the scenes.

When you grow up the way I did, you never know when and how much to share about your background. Even as I write this, I'm hesitant. Am I telling more than I should? Will this turn around and bite me? But I repeat to myself that if my story can make one person more open-minded or help someone push through adversity, then I'll keep recounting my hardships and my journey.

> "School closed, books opened. Day in, day out. Shed some tears and blotch my notes. Shake it off and move on. That rhythm became familiar, keeping me going much like the rhythm of my heartbeat."

I'm a Black man who struggled with homelessness in the past. My family is still homeless, with secondary effects of homelessness still profoundly impacting our lives. However, the community I developed in each aspect of my life kept pushing me forward, keeping doors open while life was trying to close them.

These good people helped me see beyond that fogged-up car's window from my past. Thanks to them, gradually, I came to see the world as an open place.

My high school struggles culminated in being salutatorian and receiving the Questbridge full-ride scholarship to attend Vanderbilt University.

Undergrad came with luxuries that included three meals a day and certainty that I would be sleeping horizontally, in an actual bed, with sheets, a pillow, and a blanket, night after night.

Meanwhile, my family's situation did not change.

In class, I found my mind drifting off from lecture to images of my family lugging bags, heavy bags, in the sun, with nowhere to go. That's when I took it upon myself to take as many jobs as I could. At one point, I was a host in a sushi restaurant, a tutor, and a math learning assistant.

Before I knew it, in addition to my math and biochemistry double major and time in the lab, I was working near the weekly max of 19 hours for full-time students. This schedule caused sleepless nights and encouraged a monotonous disposition, as my grades suffered and I withdrew from my peers.

I was too tired to do my very best at school and be social. But I was sending home as much as $200 on a good week, and in some cases I would overdraw my bank account by $500 because the amount I made working just wasn't enough.

My mom, noticing with each call how her son's voice was sounding unfamiliar, gave me the most important advice I heard during this period: Never become a product of your circumstances.

At that moment, I brushed it off, moved on.

But over time, I gained an appreciation for those words. Bit by bit, I found myself arriving early to my obligations with newfound energy. I was seating regulars at the restaurant, engaging with them as they talked about their day, or hearing from students I tutored as they shared their test results with me. Their

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emotions were infectious, and they brought meaning to my jobs.

I had only heard my mom's words before. Now, I was listening to them. I would not become a product of my circumstances. Never.

For the first time, I shared the story of my background with my closest college friends. Even though I shook and stuttered getting the words out, they responded with a hug and an invitation to play video games.

All the emotional support I received pushed me to continue striving in my classes while also giving me a fresh burst of energy to keep up with my intense schedule. I was able to immerse myself in my STEM courses, and seeing the intersection of health and science made something click for me.

Sure, my background demonstrates that life is unfair, but illness represents a different type of unfair. Who gets sick and why? Who has limited access to health resources and why?

Sometime during high school, I accepted this unfairness in life, but now I sought to challenge it. I wanted to take the responsibility of both deeply understanding diseases and improving the health of those around me: to give back by helping people recover, to return to the world, to life.

Even with my insane schedule, I managed to spend time in the lab. There, I investigated the proteins of the brain-eating amoeba which causes a rare but deadly brain infection. Throughout my research project, I learned how limited treatment options for this disease were. That's when I realized how the laboratory work was aimed to address this issue, and how I could join the fight to combat poorly characterized diseases, to fill in critical gaps in healthcare through rigorous, reproducible research.

Saunders was the featured post-baccalaureate speaker at the 2026 American Cancer Society Medal of Honor ceremony.

I shifted career ambitions to see if there was a job that involved both basic research and clinical medicine. Not just a role that allowed me to do both, but something that fully integrated the two on a daily basis and that's when I discovered it; my true career aspiration.

By graduation from Vanderbilt, I was clear that I wanted to become a physician-scientist and train in a dual MD and PhD degree-granting program. However, I lacked the lab experience and skills required to achieve that goal compared to my peers who didn't need to work to provide for their families.

With my efforts devoted to making money and sending it to my family, I missed out on learning how to communicate through speech and writing, and how to drive a research project independently. I realized that these were not things you pick up through perseverance, natural smarts, and resourcefulness.

I knew that I could do better if I just had more time, support, instruction, and mentorship.

Fortunately, the American Cancer Society-funded postbaccalaureate program at the Case Comprehensive Cancer Center provided the perfect opportunity to catch up.

The Center for Innovation in Cancer Research Training at ACS, led by Dr. Ellie Daniels, strives to create a pool of talented trainees with skills needed to

excel in cancer research and—yes—revolutionize the field.

ACS funds 31 post-baccalaureate programs across the U.S., providing mentored research training, career development, and social support to facilitate the successful transition to graduate or professional school.

The basis of my research project in the program at Case aimed to investigate lung cancer cell interactions under different environmental conditions through a mathematical and ecological lens.

I loved it!

I spent time troubleshooting experiments, presenting my research at conferences, and engaging with researchers at other institutions. Most importantly, I received incredible mentorship from my PI, Dr. Jacob Scott, a radiation oncologist at the Cleveland Clinic, who served as my role model for the physician-scientist path.

While making clinical rounds with him, I experienced how appreciative patients with a recent cancer diagnosis were with his bedside manner. Their facial expressions conveyed a sense of relief as he listened to their concerns and explained treatment options.

Afterwards, he brought me to another section of the hospital, where I witnessed his collaboration with colleagues to develop a radiation treatment plan. The procedure was only possible with the input he received from the dosimetrists, who direct where the radiation goes, and medical physicists, who ensured the accuracy of the radiation machine.

In the lab, I saw students go into his office and come out eager to work on the next steps for their project.

One day, a patient stopped by and toured the facility.

As he spoke about his experience with cancer, he showed us a scar on his leg where a tumor was resected, tearing up in the process. He looked around the lab, inquiring about our cell culture work and math theories on the whiteboard, and thanked us for the work we perform.

Seeing the patient connect benchwork to real human stakes, I understood the significance of the research my peers and I conducted under Dr. Scott's guidance. Moreover, the physician-scientist role became clear.

When a patient presents with an illness with no treatment in the clinic, research can push against that, leading to a discovery that improves that patient's life and the lives of others with a similar condition. That core purpose is what I strive to achieve.

I knew I was on the right path.

Along with my experience in Dr. Scott's lab, the ACS Case CCC postbaccalaureate program director and assistant director, Drs. Ruth Keri and Damian Junk, have dedicated themselves to making the program rigorous and impactful.

At Case, I took graduate cancer biology courses, engaged in oncology shadowing, and attended workshops to obtain new skills. The final requirement was a research manuscript and presentation, after which I was awarded with my Case Western Reserve University graduate certificate in cancer studies.

Throughout the whole program, Drs. Keri and Junk were available to guide all the fellows and answer questions about our future career pathway. No matter what topic I had in mind, I could simply walk into their office and sit down to talk about it. Because of them, I became familiar with techniques to make grant applications concise and compelling, common difficulties that faculty researchers experience, and factors in scientific literature that strengthen or weaken its claims.

Next, I had to overcome my weakness with oral presentation.

My first time speaking before my peers and the directors, I stumbled over my words and failed to convey my presentation's key points.

Public speaking is a talent, of course, but it's also a skill that can be developed.

I lacked public speaking experience, and I grew scared of all the eyes focused upon me, never quite sure if what I had to say was being heard, or judged. I spoke with so little confidence that if my sentences were transcribed, most of them would end in question marks as opposed to periods.

Since then, I've worked toward distilling the "why" and "how" of my research with feedback from Drs. Keri and Junk, ensuring the audience understands the takeaway from my presentations: Not a fact, figure, or workflow, but rather the image of a person now with the opportunity to improve their disease course. As I continued honing this skill, my confidence naturally increased as well and I could say my words with conviction. I could now give a compelling talk.

This growth led to ACS inviting me to be the featured post-baccalaureate who spoke at their Medal of Honor ceremony in honor of the award recipient Dr. Tyler Jacks. Speaking beneath a crystal-dripping chandelier at the Willard Hotel, with Dr. Jacks as well as NCI Director Anthony Letai and former NCI Directors Ned Sharpless and Kimryn Rathmell in attendance was terrifying.

My goal was to survive. The applause from national leaders in cancer research and policy was a bonus. Being able to talk about the struggles of my family—and to thank the many friends and mentors—was the greatest reward I could imagine.

I also realized the importance of postbacc programs from this experience. Just like me, there are people from different but also challenging backgrounds who need to be lifted up so that their perspectives can be incorporated into science and medicine.

My friends who were also in the ACS Case CCC postbacc program showed me this firsthand and I know that this trend will enrich patient care and research innovation.

Because of the support from ACS and the training at Case CCC, I'm more aware of what my career training pathway will entail, and I am determined to succeed.

I'm incredibly grateful to have that opportunity combined with a network of individuals across different career stages who will continue to support me.

My next steps?

I applied to multiple MD-PhD programs, received five acceptances, and ultimately chose WashU Medicine. The program is one of the largest and most respected in the country with friendly, down-to-earth faculty supporting the trainees and a curriculum that integrates three-week-long immersive clinical experiences throughout the classroom learning phase of medical school.

The main draw for me was everything I saw about the institution at each stage of the application process from interviewing to visiting the campus at their second-look weekend.

All my time spent with WashU Medicine assured me that the guidance, support, and training Vanderbilt and Case Western gave me to thrive despite adversity were also available there.

I humbly acknowledge the enormity of challenges in this next stage of my journey, and, of course, I know that victory is never a sure thing, but as my mentor Dr. Scott reminds me, "things never get easier, you become better at handling harder tasks."

With that bit of wisdom in mind, I'm incredibly excited for my journey through medical and graduate school with my peers and the support of the WashU Medicine faculty. At each step in my life, the community around me was crucial in helping me stay on track to reach my career goals.

I will invest back in the community through robust research and clinical care to find cures for some of the most complex diseases. I will also pay it forward to help the next generation of students who also face adversity but have so much to give to medicine and research.

Recently, I found something Dr. Robert Winn, director of Fox Chase Cancer Center who years ago made a journey that was in many ways similar to mine, said in a podcast about the importance of diversity being that, "you are bringing different life experiences, which then can ultimately lead to a richer conversation and a more robust way of moving forward."

This is especially important when insight travels from the lab to the clinic and back to the lab, and then again to the clinic.

Each background comes with a perspective that can uncover what may be invisible to others. As a physician, I'll draw on the lessons from my past to find trends or answers that otherwise would go unnoticed to improve patient outcomes and trust in medicine.

I want to engage with colleagues who can leverage their own life events to reveal what I may miss when treating patients. By working together like this, we can make healthcare more robust for everyone.

All of us have our worries. I still lose sleep, worrying about my family. When I can, I send money to support them.

From sleeping in the car to failing an assay in the lab to overcoming the impostor syndrome, everything in my life has built me up to this point.

Today, I can finally reassure myself with one phrase, "I've got this!"

> "Sure, my background demonstrates that life is unfair, but illness represents a different type of unfair. Who gets sick and why? Who has limited access to health resources and why?"

GUEST EDITORIAL

From "default dead" to living the future of cancer care

As founding CEO of GitLab, I went "founder mode" on my osteosarcoma

By Sid Sijbrandij
Co-founder and executive chair, GitLab Inc.
Co-founder, Sijbrandij Foundation

In November 2022, I was 43 years old, healthy, active, and the founding CEO of the publicly traded tech company GitLab.

I was doing a bench press when I felt a strange pain near my chest. I'd felt something like it before and it had passed. This time it didn't. Two weeks later, unable to sleep at 4 a.m., I drove to the emergency room. The doctors found nothing on the X-ray and sent me home.

A few hours later, my GP called and asked if I knew how to meditate. I said yes. He told me to start immediately, because I might be having an aortic aneurysm and the pain could be my aorta starting to burst. I went back to the ER. My aorta was fine, but the scan found something else: a six-centimeter tumor growing out of my vertebrae.

The diagnosis was high-grade osteosarcoma of the thoracic spine.

What follows is my story through treatment, remission, recurrence, and into the fight for survival once the standard of care had been depleted. That fight required developing a new, fully personalized paradigm for my own treatment, one that I'm proud to say has resulted in me being measurably disease-free for over a year.

Mine is an n=1 case, but I believe it points to a possible future that can and should be more broadly accessible.

In the beginning

After my diagnosis, my team treated the cancer aggressively. I had surgery to remove the mass, a spinal fusion, radiation, and multiple rounds of chemotherapy so intensive that I required four blood transfusions.

During that same stretch of treatment, I got my first glimpse of what exists beyond standard of care. Years earlier,

through Y Combinator, the famed start-up accelerator, I'd become friends with Jose Mejía Oneto, MD, PhD, the CEO and founder of Shasqi. He was working on applying click chemistry to medicine. The vision was and continues to be to enable drugs to be active at the right location in the body, in order to limit off-target toxicity and maximize efficacy of drugs. Biotech investors were skeptical of the approach, but I believed, and became its largest investor.

When I was diagnosed, Jose and my oncologist determined that the targeted chemotherapy his company was developing was a viable treatment option for me, but access looked nearly impossible. The clinical trial had already closed, and everyone told us the FDA route would be too slow. It wasn't. We filed a single-patient IND, and it moved quickly.

Our roles quietly reversed. I had spent years helping keep Jose's company alive. Now he was helping keep me alive. The combination of standard of care and the Shasqi therapy put my cancer into a remission that lasted about a year.

Then the cancer came back. It progressed locally, and there were no more standard of care therapies with extensive evidence behind them. My oncologist, whom I respect tremendously, told me he had nothing left he could recommend.

He suggested I look for a clinical trial. Osteosarcoma is rare, particularly in adults, and there were none that fit. Standard of care had run its course.

Sijbrandij and Dr. Jose Mejía Oneto together as Sijbrandij receives a Shasqi drug under single-patient IND.

Going "founder mode" on my cancer

Paul Graham, who founded Y Combinator and who has spent decades thinking about what separates startups that survive from those that don't, coined the term "default dead" to describe a startup that, at its current rate of spending and growth, will run out of money before it reaches a point where it can sustain itself.

When I ran out of standard of care, I was "default dead" in the most literal sense there is. My runway of options was at an end, and if nothing else changed, I was going to die.

But Graham has another essay, detailing a set of behaviors he calls "found-

> Mine is an n=1 case, but I believe it points to a possible future that can and should be more broadly accessible.

Sijbrandij receives the first dose of a personalized mRNA vaccine at Houston Methodist Hospital.

er mode." While a person operating in "manager mode" will delegate decisions to their team and trust in established processes to surface the right answers, "founder mode" requires diving in directly, getting into the details, staying close to the information, and making decisions at the pace the situation requires.

In a piece published earlier this year, the writer and investor Elliot Hershberg aptly connected this idea to what I did next: I quit my job and went "founder mode" on my cancer.

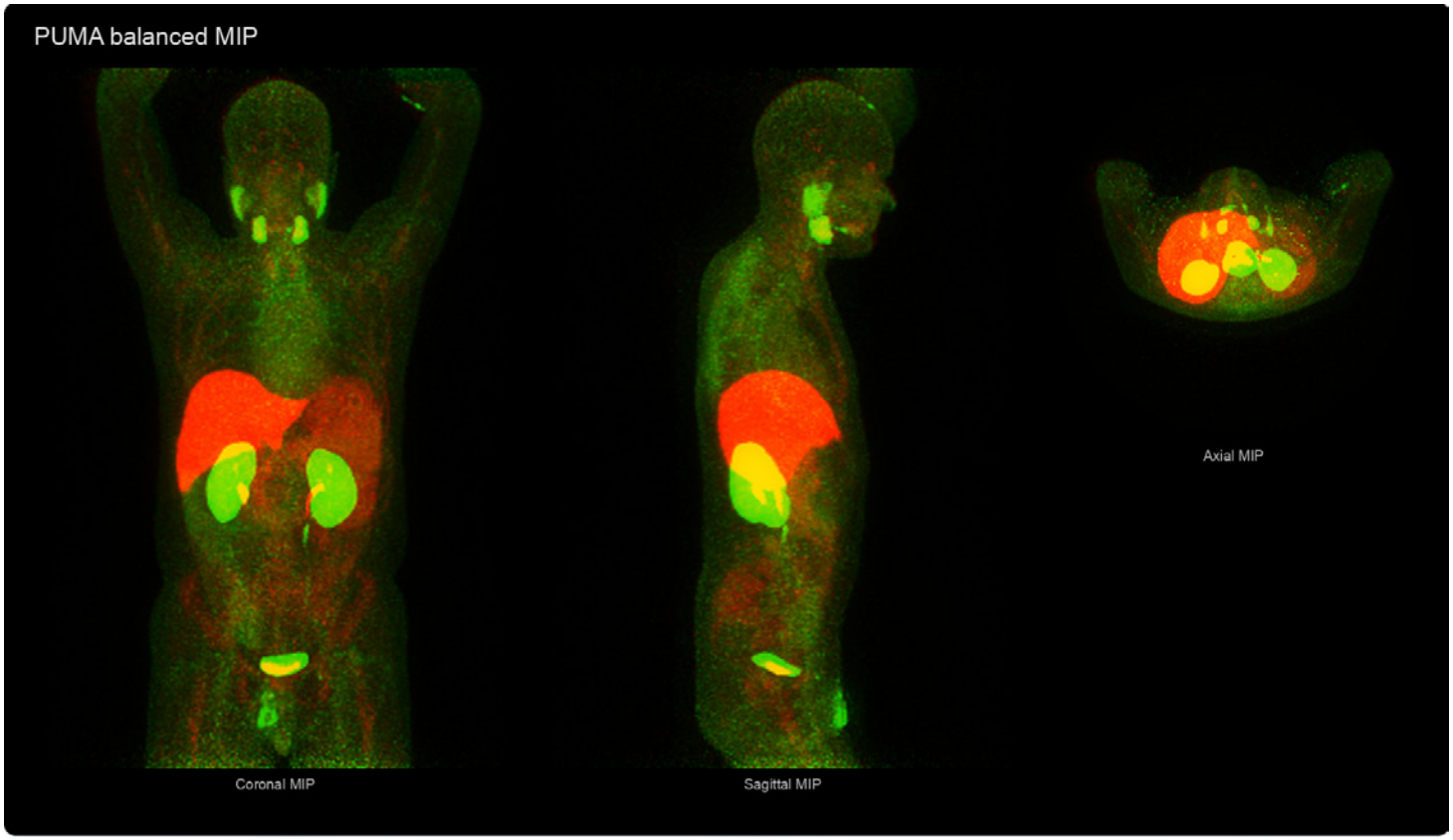
I said, "I'll talk to anyone, I'll go anywhere, and I can be there anytime."

I took calls at odd hours and flew to wherever the right person was. With the help and prodding of Jose, as time was of the essence, even before standard of care ran out we looked for every potential support and alternative available.

As we found like minded individuals willing to explore beyond the obvious, I formed my own "ODAC" (FDA's Oncologic Drug Advisory Committee), with members including Sant P. Chawla, MD, Santosh Kesari MD, PhD, Jeremiah Wala, MD, PhD, and Nima Afshar, MD.

To complement their expertise, I also assembled a separate scientific advisory board made up of informatically-savvy scientists, navigation specialists, and even a "CEO of my health," Jacob Stern, to help me expand and triage my range of options.

I learned that a willingness to engage with a specific, messy, real case is a different trait than reputation. Some of the most useful input I got came from mid-career researchers with expertise in a pathway relevant to my tumor. When two experts disagreed with each other, that disagreement was often where the most useful information emerged.



Two PET scans of Sijbrandij taken on consecutive days—an EphA2-targeted tracer on Feb. 2 and a B7-H3-targeted tracer on Feb. 3—warped onto the same anatomy and combined into one color-coded image. EphA2 is green and B7-H3 is red, so yellow marks where both signals appear in the displayed image.
Source: osteosarc.com

Underneath all of it sat logistics nobody warns you about. One of the most challenging was getting access to my own tumor tissue. Not only was it difficult to get the institution to release the biopsy sample, it was difficult to get the surgery teams to handle it in a way where it could be preserved for maximal reuse.

In many ways, managing these logistics and clinical coordination mattered as much as anything else we did.

Building more runway

In the two years since going "founder mode" on my cancer, our approach has evolved into a four-part structure: Maximal diagnostics, creating new treatments, taking treatments in parallel, and scaling this for others. For me, it has worked so far. I'll get into more detail below, but to summarize briefly the course of treatment after standard of care:

I first took an intensive course of immunotherapies, including select checkpoint inhibitors, a personalized peptide neoantigen vaccine, and an oncolytic virus, followed by a radioligand therapy, followed by a surgical procedure to remove what was left of the tumor once the radiotherapy had shrunk it sufficiently.

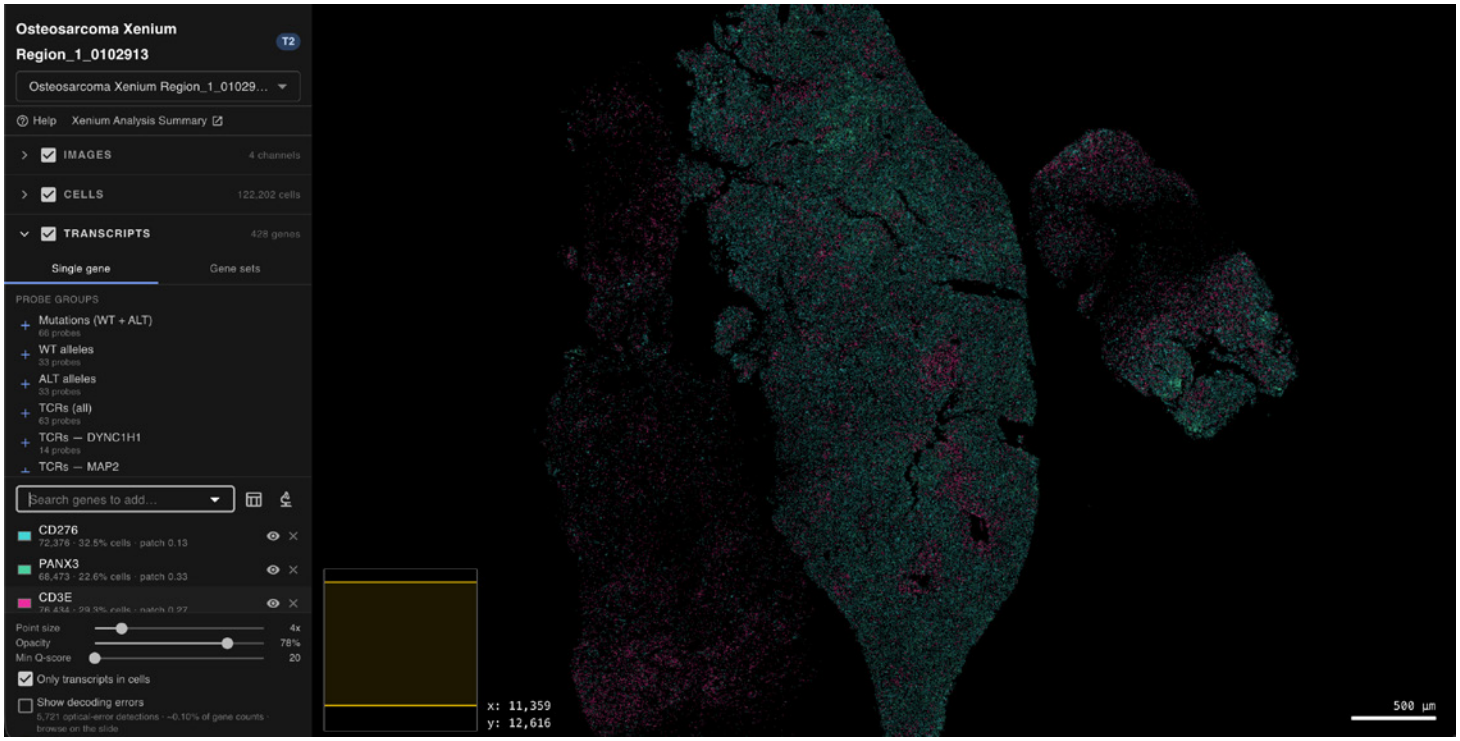
I've gone from "default dead" to having no evidence of disease for over a year, meaning that my monthly blood-based MRD tests come back negative, as well as my regular CT and biomarker scans.

I recognize that my access to incredible resources and a good deal of luck played into this result, but I also believe that for patients who have reached the end of their standard of care runway, there is much to learn from what worked for me.

Maximal diagnostics

As I've learned from my doctors, the standard practice is to only run a test if you know how you'll act on the result. Once in "founder mode," we collected data first and figured out what to do with it after, and ended up with >30 terabytes of it, publicly available at osteosarc.com.

We've endeavored to measure as many aspects of my tumor as possible, including bulk DNA and RNA sequencing, sin-



Visualization of spatial transcriptomics data generated using the 10x Genomics Xenium platform with sample taken prior to radioligand therapy. Tumor cells marked in turquoise by B7-H3 (CD276), MDM2 and PANX3. T cells marked in magenta by CD3E. *Source: osteosarc.com*

gle cell and spatial RNA sequencing, pathology staining, drug response testing on personalized organoids made from my tumor's cells, multiple MRD tests, and radioligand imaging.

Through this approach, we found something specific and consequential. Bulk RNA sequencing of the recurrent tumor tissue first flagged unusually high expression of FAP, fibroblast activation protein. Single-cell sequencing confirmed expression not just in the fibroblasts in the microenvironment, but also in my tumor.

That mattered, because my team had identified an experimental treatment in Germany that could be administered by Richard Baum at CURANOSTICUM in Wiesbaden-Frankfurt, a pioneer in nuclear medicine who has successfully treated patients with a radioligand therapy targeting FAP. The drug pairs a FAP-targeting molecule with a radioactive isotope, delivering radiation directly to FAP-expressing cells. I traveled to Germany and went through the treatment twice. It worked better than expected: 60% necrosis, 20% shrinkage, and the effect was that surgeons were able to remove the bulk of the tumor.

The maximal diagnostics approach has also nominated other therapeutic targets we're tracking closely, including B7-H3. There's no approved B7-H3 therapy for osteosarcoma, but multiple antibody-drug conjugates targeting B7-H3 are in active development for other cancers, and if my disease were to recur, we could potentially rationally repurpose one of them.

Creating new treatments

Most of the drugs I've taken, as well as nearly all of the 25 drugs in my current therapeutic ladder, are off-the-shelf or traditional investigational therapies. But I've also had a chance to work at the leading edge of what's possible in personalized medicine, and the pace of progress there surprised me.

Technical advances and a growing ecosystem around them are making truly bespoke treatments possible.

One example: a personalized mRNA cancer vaccine, developed by a world-class team at Houston Methodist led by Dr. John Cooke and Dr. Jimmy Gollihar, tailored to neoantigens from my tumor. I was the first patient in an investiga-

tor-initiated trial for this vaccine, and the whole process, from initial discussion to injection, took six months.

This anecdote exemplifies how my team and I make decisions about my care. We engage deeply with specialists, complementing their expertise in the evidence base with the in-depth knowledge of my tumor that we've derived from the maximal diagnostics. Together, we map out risks (side effects) and rewards (likely response / recurrence prevention). In this case, we leveraged the preponderance of data from cancer vaccine trials and the COVID vaccine rollout to determine that the risk profile was low. Even though the evidence base on response was thin, the approach was mechanistically reasonable, making the risk versus reward favorable. The final decision always rests with me and my oncologist.

The breadth of what is possible in personalized medicine today struck me as much as the speed. We are running a custom binder discovery campaign against PANX3, a channel protein specifically expressed on my tumor cells. This is a relevant target for me but rare enough that it has not warranted an approach from biopharma that we know of.

We are building new radiodiagnostic agents to confirm where a candidate drug target would and wouldn't bind in my body before committing to a treatment built for that target. We have a personalized TCR T-cell therapy manufactured, and a CAR T-cell therapy in development, to be deployed if needed.

In many ways, these are treatments of the future: built around the patient's biology instead of a population average. There is still an enormous amount of work needed to bring bespoke therapies to patients who don't have my resources or access. But an n=1 case like mine can still benefit the whole ecosystem, in two ways. It's a tangible demonstration of what's possible at the leading edge. And for much of what has been built for me, the manufacturing know-how, the regulatory groundwork, and in some cases the molecules themselves can inform or be reused for other patients. I see this as a foundation for getting more patients access to bespoke therapies when they need them most.

> “In the two years since going ‘founder mode’ on my cancer, our approach has evolved into a four part structure: maximal diagnostics, creating new treatments, taking treatments in parallel, and scaling this for others.”

Running treatments in parallel

One of the core principles of my approach was taking many treatments in parallel instead of one after another. While pursuing the FAP-targeted therapy in Germany, I was also going through dual checkpoint blockade, NK cell therapy, an IL-15 superagonist, and an oncolytic virus, all in parallel. Combination chemotherapies are not controversial, nor are combinations between different modalities such as chemotherapy and radiation.

The concern I have encountered around combinations seems to arise from the fact that it is not possible to run a clinical trial to test every possible combination that may be beneficial to a particular patient or to identify the contributions of each treatment. This is especially true when dealing with investigational or personalized therapies, like I was.

The main source of risk with the parallel treatment approach is interactions between drugs, particularly overlapping toxicities that could be problematic. Our approach has been to work through these decisions with our scientific and medical teams based on known mechanisms of action, available pharmacological data, and biological first principles, even when we don't have formal evidence for every combination. What we've learned is that the key to working with this uncertainty is accelerating our feedback loops. Instead of waiting months between tests, we tightened the cycle of diagnostics, imaging and biopsies to gather information more quickly and change course when needed.

People sometimes ask what I think actually worked.

Because I was running several treatments in parallel and because this is an n=1 case, it is impossible to determine causation or attribution with certainty. Because we have deep longitudinal profiling, we can develop reasonable mechanistic hypotheses. Darya Orlova and Hareem Maune analyzed longitudinal single-cell data from my tumor microenvironment, mapping cell-to-cell signaling across treatment. Their analysis points to a shift in neutrophil behavior, from largely inert to actively sending pro-tumor signals, a pattern that held through intensive immunotherapy and partially reversed after the FAP-targeted radiotherapy, suggesting the treatment may have disrupted a suppressive signaling network the immune system alone couldn't overcome.

We see clonal expansion of tumor-reactive T-cell clones in the tumor microenvironment after the radioligand therapy, further pointing to a favorable remodeling of the immune milieu. Working with Will Hudson at Baylor, we've used monthly flow cytometry and single-cell TCR sequencing to track how my immune system has responded over time. That data shows sustained T cell activation well above healthy donors, along with a population of CD39+ CD8+ T cells that has persisted at elevated levels throughout, cells that show signs of prior antigen exposure and preferentially bind the anti-PD-1 antibody I was on, consistent with ongoing tumor surveillance.

While speculative, these data points highlight that it is possible to learn from longitudinal sampling and exploratory analyses.

I've said publicly that I'd rather die from a treatment than from my disease. I am aware this is an extreme position, and that I have made choices that would not be appropriate for every patient. I am still relatively young and generally healthy; the calculus would be different if I was elderly and frail. But I do believe that once the standard of care has been exhausted, patients deserve to have agency in their care and health systems should work to support their wishes.

The future is already here

While my cancer has been undetectable for more than a year, our work is far from over.

On the personal side, our ethos is "stay paranoid." We continue to run maximal diagnostics, identify new biomarkers,

We continue to create new therapies, arm my immune system and update my therapeutic ladder as new information comes online.

But more broadly, we're focused on scaling this approach to serve other patients who are facing the end of their standard of care runway.

What I did won't scale in its current form. Saving my life has been a very expensive endeavor. But even beyond the financial aspect, I had numerous advantages, including a friend who was working in sarcomas, multiple avenues of access to care and a familiarity with the "founder mode" mindset. I'm not holding this up as a model. I'm holding it up as a proof of concept.

> "I'm not holding this up as a model. I'm holding it up as a proof of concept."

Another quote that stuck out to me from Elliot Hershberg's piece was from the science fiction writer William Gibson, who said "The future is already here, it's just not evenly distributed." The diagnostic tools and treatments I leveraged are the future, and fortunately for all of us, they are getting better, cheaper and more accessible every year.

Sequencing a tumor down to the single cell is no longer exotic or impossibly expensive. Analyzing and interpreting the resulting data, which used to require significant time from multiple specialists that almost no patient could access, is becoming something AI tools can meaningfully democratize. This means that the kind of individualized reasoning that uncovered the FAP connection for me could reach far more patients.

Computational modeling can now predict how a protein folds or how a molecule might bind, work that used to take years at the bench. And manufacturing a personalized therapy, a vaccine or a cell therapy built for one person's biology, is possible, though challenges still remain.

None of this replaces the evidence base standard of care is built on. What I'm describing is what becomes necessary at the edge, where that evidence does not exist and a patient is otherwise "default dead." This is a growing movement, and I see the work that Laura Esserman and her colleagues are doing with I-SPY 2, a breast cancer trial designed to learn and match patients to therapies as evidence accumulates, instead of waiting years for a single fixed endpoint, as stemming from the same point of possibility. I think what's coming next takes this even further, down to one patient at a time.

Through Future of Cancer Care Today, part of the Sijbrandij Foundation, we're working to build the infrastructure to help other patients look beyond the standard of care. We're beginning by connecting patients with resources, information and support, but our goals are to develop programs that move the needle across sequencing, interpretation, modeling and manufacturing.

It is often said, the future is not guaranteed. While I am currently in remission, I do not say I am cured. Science is advancing, but much that is possible hasn't made it to patients yet. To bring the future of medicine that I experienced to the wider population will require continued, determined effort.

I want to help that future arrive faster, and if that's work you want to be part of, I'd like to hear from you—please reach out at cancer@sytse.com.

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BOOK REVIEW

What are The CheckPoints movin' and groovin' to this summer?

Join the journal club with the best bops: We asked SITC's 13-piece band of medical musicians for the top papers and songs of the summer

By Sara Willa Ernst

Physician-scientists by day, a funk-loving musical troupe by night. You may have seen The CheckPoints—a 13 member cover band with a three-piece brass section and Jim Allison on harmonica—movin', groovin', and gettin' down as a mainstay closing act at ASCO, AACR, or the Society for Immunotherapy of Cancer annual meetings.

During past performances, the band has put their own spin on motown classics like Brick House by the Commodores, as well as pop staples like Adele's Rolling in the Deep and Walking on Sunshine by Katrina And The Waves.

The ensemble, by design, straddles between two worlds: Cancer research and artistic expression.

All in the same day, you might witness the band's members at an annual meeting, all buttoned up, presenting something or other on the sustained clinical benefit of a phase III trial of checkpoint inhibitors. But come nightfall, the top buttons come undone and you'll find them on stage belting out lyrics to "Sweet Home Chicago" or an immunotherapy-inspired cover song (*The Cancer Letter*, Oct. 5, 2018).

In our annual roundup of what people in oncology are reading (or watching, or listening to), *The Cancer Letter* asked the SITC house band to craft a recommendation list that similarly blends these two worlds. The bandmates are keeping rhythm with the latest journal articles published in the academic literature, as well as songs, albums, and playlists that may have healing properties of their own.

Their recommendations, which span many genres, can be found on this Spotify playlist. So, pop on some music, crack open a journal, and enjoy the vibes.

Here is our check-in with The CheckPoints:

Rachel Humphrey, MD

Lead vocalist, The CheckPoints;
President,
Founding CEO,
Normunity

Articles:

- "Daraxonrasib or Chemotherapy in Previously Treated Metastatic Pancreatic Cancer," published in *The New England Journal of Medicine*

Music:

- Hello, Mr. Jambo, by Kyle Gordon

- Planet of the Bass, by Kyle Gordon

- Jaxen James

Books:

- "Project Hail Mary," by Andy Weir

- "Sex on Murder Island," by Jo Firestone
- "A Murder in Springtime," by Martin Walker
- "Heather," by Caitlin Mullen
- "ReInception," by Sarena Straus
- "DeInception," by Sarena Straus

What do you think was the most impactful paper of the year?

The results in pancreatic cancer of the Revolution Medicines daraxonrasib (Pan RAS inhibitor) is inspiring. Pancreatic cancer is a particularly difficult tumor to treat, and any progress is a blessing. I lost my grandfather to pancreatic cancer, and it's wonderful to see the progress.

What are you listening to (albums, EPs, songs) this summer?

Kyle Gordon's musical comedy is fantastic. He has multiple albums and is currently touring in the US and Europe. His song, "Hello, Mr. Jambo," is awesome. His brother, Sam, does the videos, which are also fantastic. A few summers ago, Kyle's song, Planet of the Bass, was the "song of the summer."

He's a modern Weird Al Yankovitch, only better (I'm not biased, or anything!! Kyle and Sam are my nephews).

Jaxen James— is a new artist whose music is also lovely. Easy listening country and a young man who grew up with the daughter of Normunity's head of Clinical Operations. I love getting close to the work of people I care about.

What are you reading?

My favorite book of all time on Audible is Project Hail Mary (Andy Weir). The movie was wonderful, but the book is filled with a great story of redemption and loaded with wonderful science. I love listening to books on Audible (instead of reading them) because it enhances the experience. The narrator, Ray Porter, does an amazing job of bringing the book to life. I've also been binging murder mysteries, after the NY Times released a list of their favorites. (I love solving the murders ahead of the book…Whodunits are so fun!!).

My latest list includes "Sex on Murder Island" (Jo Firestone), "A Murder in Springtime" (Martin Walker), and "Heather" (Caitlin Mullen). Finally, my cousin, Sarena Straus, has released the first two books in her Sci Fi trilogy. "Reinception" and "Deinception" are great reads!

Thomas Gajewski, MD, PhD, FAIO

Lead guitarist, The CheckPoints;
AbbVie Foundation Professor of Cancer Immunotherapy
Professor of Ben May Department of Cancer Research,
Leader,
UCCCC Immunology and Cancer Program
UChicago Medicine

Articles:

- "Dual tumour-myeloid targeting of glioblastoma with GPNMB CAR-T cells," published in *Nature*

Music:

- The Door, by Teddy Swims

- Best of Vivaldi, a Spotify playlist by Deutsche Grammophon

Books:

"Devil in the White City," by Erik Larson

What do you think was the most impactful paper of the year?

I really liked the following paper: 'Dual tumour-myeloid targeting of glioblastoma with GPNMB CAR-T cells," by Savage N., et al.

It was an advance in glioblastoma, but more importantly validated GPNMB on tumor-associated myeloid cells as a therapeutic target. This pathway will be valid in a wide range of difficult to treat cancers.

What are you listening to (albums, EPs, songs) this summer?

In terms of music, I discovered a song from Teddy Swims called "The Door." It's a great danceable song. But most importantly, it was therapeutic because of a recent relationship breakup in which I had to show someone the door. I felt validated.

And in the mornings, when I am sipping Earl Grey tea and doing the NYT puzzles, I've been listening to a Spotify playlist called the Best of Vivaldi from Deutsche Grammophon. It's actually amazing and varied music, and calms my mind before the intensity of the day.

What are you reading?

In terms of reading, I'm currently working on the "Devil in the White City," by Erik Larson. I'm from Chicago, and this is a historical fiction-style story centered on the Chicago Worlds Fair in 1893. This is around the same time as the founding of The University of Chicago, so it really connects to me.

Patrick Hwu, MD

Keyboard player, The CheckPoints;
President and CEO,
Moffitt Cancer Center

Articles:

- "Postprandial lipid metabolism durably enhances T cell immunity," published in *Nature*
- "Diet–microbiome synergy underlies obesity-associated immunotherapy efficacy," published in *Nature*

Music:

- Laufey

- Counting Crows

- Noctures, by Frédéric Chopin

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- Stella Cole

Books:

- "Project Hail Mary" by Andy Weir
- "Watchmen," by Alan Moore and Dave Gibbons

What do you think was the most impactful paper of the year?

The paper that stopped me in my tracks this year was Kumar et al., "Postprandial lipid metabolism durably enhances T cell immunity," published in *Nature* this April from Greg Delgoffe's lab at Pitt. Their finding is disarmingly simple: a single meal, acting through triglyceride-rich chylomicrons, durably reprograms T cell metabolism via mTORC1.

And in a result that hit close to home for those of us in cell therapy, CAR-T cells manufactured from the same donor in the fed state outperformed those collected while fasted. After a career spent trying to engineer T cells to fight harder, the idea that we might tune potency by asking a donor when they last ate is both humbling and thrilling. It is a lovely reminder that biology often keeps its best secrets in plain sight.

Honorable mention to Desharnais, Elkrief and Routy et al. in Nature, showing that diet, more than body weight, shapes the gut microbiome and response to anti-PD-1. Together these papers make a strong case that diet is the immunotherapy adjuvant hiding on our plate.

What are you listening to (albums, EPs, songs) this summer?

A wide arc. Laufey, for her lush jazz-classical songwriting. Counting Crows, revisited after watching a terrific documentary about the band. Chopin nocturnes for late-night decompression, which I will admit is a pianist's confession, since I play keys in the CheckPoints. And a new discovery, Stella Cole, whose full, jazzy voice makes the American songbook feel newly minted.

What are you reading?

"Project Hail Mary," by Andy Weir, which is riveting and one of the most scientifically imaginative novels I have read in years. The interspecies problem-solving is pure joy. Alongside it, the original "Watchmen" graphic novel by Alan Moore and Dave Gibbons. Beautifully written, and its meditation on nonlinear time and moral responsibility has been sitting with me long after I put it down.

John Timmerman, MD
Guitarist, The CheckPoints;
Professor,
Department of Medicine,
Hematology/oncology,
Ronald Reagan UCLA Medical Center

Articles:

- "Daraxonrasib or Chemotherapy in Previously Treated Metastatic Pancreatic Cancer," published in *The New England Journal of Medicine*

Music:

- So Easy (To Fall in Love), by Olivia Dean

- Man I Need, by Olivia Dean

- WHERE IS MY HUSBAND! by RAYE

Books:

- "Sounds Like Me: My Life (So Far) in Song," by Sara Bareilles
- "Making Rumours: The Inside Story of the Classic Fleetwood Mac Album," by Ken Caillat and Steve Stiefel
- *Looking forward to:* "Brothers: An Intimate Account of Brotherhood and Rock Music," by Alex Van Halen

What do you think was the most impactful paper of the year?

Without hesitation, I cite the RASolute 302 trial, published in NEJM on the day of the historic presentation at the ASCO Plenary Session on May 31, where lead author Brian Wolpin received a standing ovation when revealing the doubling of survival in metastatic pancreatic cancer by the new KRAS inhibitor daraxonrasib.

Even though I knew about the data from previous presentations, the moment this unprecedented advance in the treatment of this most-feared cancer diagnosis really sunk in was thrilling to all in the room, including myself.

While the treatment is far from a cure, it is a huge first step in cracking this nasty malignancy, and I'm most excited about what is to come next scientifically.

We already know now that disarming pancreatic cancers of RAS signaling not only slows cell growth but alters the tumor immune microenvironment, possibly paving the way for effective immunological interventions, which alone have proven ineffective in pancreatic cancer.

With a foot in the door, investigators will now begin to further pry the disease open, and learn what strategies work best once an oncogene-addicted cell's major driver has been crippled.

What are you listening to (albums, EPs, songs) this summer?

Lately I've been drawn to several new female artists from across the pond, both offering fresh R&B flavorings to growing audiences. From last year's Grammy-winning best new artist Olivia Dean ("Man I Need", and "So Easy (to Fall in Love"), to RAYE ("Where is my husband?"), their upbeat music is a welcome antidote to the geopolitical chaos of today's world.

What are you reading?

The musician in me never gets tired of understanding the creative process and the talented people behind our favorite recordings. So I've been exploring this in several books including Sara Bareilles' autobiographical memoir "Sounds Like Me: My Life (So Far) in Song."

For any Fleetwood Mac fan, I'd recommend producer Ken Caillat's "Making Rumours: The Inside Story of the Classic Fleetwood Mac Album," that chronicles the process behind each of the album's amazing songs. As a forever fan of unique guitar talent Edward Van Halen, I'm looking forward to reading the instant *New York Times* bestseller "Brothers: An Intimate Account of Brotherhood and Rock Music," drummer Alex Van Halen's poignant memoir and tribute to his brother, who died of head and neck cancer in 2020.

> The moment this unprecedented advance in the treatment of this most-feared cancer diagnosis really sunk in was thrilling to all in the room, including myself.
>
> – *John Timmerman*

Brad Reinfeld, MD, PhD

Bass guitarist, The CheckPoints;
Clinical oncology fellow,
Memorial Sloan Kettering Cancer Center

> How could the bass player of The CheckPoints leave out Vulfpeck?! Joe Dart is a personal hero of mine. He is able to play the bass to heights never before seen. This album has a great mix of what's made Vulfpeck a staple of festivals this summer. Catchy lyrics, wicked instrumentals, and a wacky sensibility like no other.
>
> *– Brad Reinfeld*

Articles:

- "Postprandial lipid metabolism durably enhances T cell immunity," published in *Nature*
- "Ketogenic diet mediates intestinal tumorigenesis through lipids not ketones," published in *Nature*

Music:

- Lover's Game, by The War and Treaty

- The Bywater Sessions, by Jon Cleary

- The Beautiful Game, by Vulfpeck

What do you think was the most impactful paper of the year?

On almost every cancer patient's journey, they ask their provider, "What food should I eat to help control the cancer?"

In this time of instability, patients and their families often seek control. Their perspectives are typically informed more by layman's articles, friends' hearsay, YouTube videos, and TikToks than the latest oncology literature. I often hear patients wonder," Doc doesn't sugar feed cancers."

Unfortunately, this is a vast oversimplification of the relationship between diet and tumorigenesis that we, as a field, need to clarify for our patients.

These two studies, published in *Nature*, uncover new relationships between diet and cancer biology that are important for patients, their loved ones, and many facets of clinical oncology. The paper from Greg Delgoffe's group at the University of Pittsburgh suggests that CAR T cells taken from patients AFTER they eat a meal work better than CAR T cells made from fasted patients. The referenced adage "sugar feeds cancer" ignores the importance of nutrient uptake and utilization in anti-tumor immune cells.

The second paper comes from MIT and shows that ketogenic diets paradoxically accelerate the development of small bowel cancer. How can this healthful diet do so much harm? Switching mice from a balanced diet to a keto diet increased dietary lipids, which, in turn, the cancer cells use as fuel to proliferate.

Therefore, ketogenic diets may be reasonable to trial in healthy, fit patients looking to gain an edge in the gym, but they may provide malignant cells with more fuel for their growth.

I hope that, as a field, we embrace nuance to provide patients with the current state of dietary interventions for cancer treatment. Unfortunately, this field is still in its infancy. I often tell my patients that, if possible, they should follow a heart-healthy diet rich in fiber, fruits, and vegetables, with a preponderance of lean meats (no different from what our fellow cardiologists endorse).

Given the equipoise in the field, I do tell my patients they can have donuts or cookies, just not a dozen of them in one sitting. Many of our patients have life-limiting diagnoses, and without compelling improved overall survival data, I find it hard to say eliminating certain foods completely from their diet is an itch worth scratching in this time of uncertainty.

What are you listening to (albums, EPs, songs) this summer?

"Lover's Game," – The War and Treaty is a band I fell in love with as a graduate student living and playing music in Nashville. A genre-bending country/blue/R&B group that brings love in our uncertain times.

"The Bywater Sessions" – Mr. Cleary is an interesting fellow to say the least. UK-born but New Orleans-raised, his piano playing has all the flair of Professor Longhair. His songs travel from irreverent to playful while keeping that NOLA beat on the 2 and 4. Dial Jon up on your Spotify, and it feels like you are celebrating Mardi Gras, whether it's a hot, steamy summer day or snowing in the dead of winter!

"The Beautiful Game" – How could the bass player of the checkpoints leave out Vulfpeck?!? Joe Dart is a personal hero of mine, able to play the bass to heights never before seen. This album has a great mix of what's made Vulfpeck a staple of festivals this summer. Catchy lyrics, wicked instrumentals, and a wacky sensibility like no other.

What are you reading?

Honestly, between clinical duties, research, I listen to more podcasts than read.... I don't know if this is a good or bad thing, but it's the truth.

Jedd D. Wolchok, MD, PhD

Sousaphone and tuba player,
The CheckPoints;
Meyer Director,
Sandra and Edward Meyer Cancer Center;
Professor of medicine
NewYork-Presbyterian/Weill
Cornell Medical Center

Music:

- Tedeschi Trucks Band

Books:

- "The John McPhee Reader," by John McPhee, edited by William L. Howarth

What do you think was the most impactful paper of the year?

"I read too many papers each week to pick one," Wolchok said to *The Cancer Letter*. "I'm an editor for the *Journal of Experimental Medicine*, so there are just too many to pick from!"

What are you listening to (albums, EPs, songs) this summer?

Listening to Tedeschi Trucks Band! Going to hear them with Rachel in a few weeks.

What are you reading?

I started a compilation of stories by John McPhee and am enjoying that!

> I read too many papers each week to pick one. I'm an editor for the Journal of Experimental Medicine so there are just too many to pick from!
>
> *– Jedd D. Wolchok*

Ferran Prat, PhD

Saxophonist, The CheckPoints;
Chief commercial officer
BostonGene

Music:

- Sun Bear Concerts, by Keith Jarrett

Books:

- "The Power Broker: Robert Moses and the Fall of New York," by Robert Caro

What are you listening to (albums, EPs, songs) this summer?

This summer I've been re-listening to the "Sun Bear Concerts" by Keith Jarrett. I don't think saying that "Jarrett is the Mozart of the 20th century" is far off. Whereas the Köln Concert is Jarrett's most famous record, the "Sun Bear Concerts" in Japan may be his most "complete" and deep work. It's music that, although improvised on the spot, can be re-listened to dozens of times. It can, and I have. It's an utter pleasure every single time.

What are you reading?

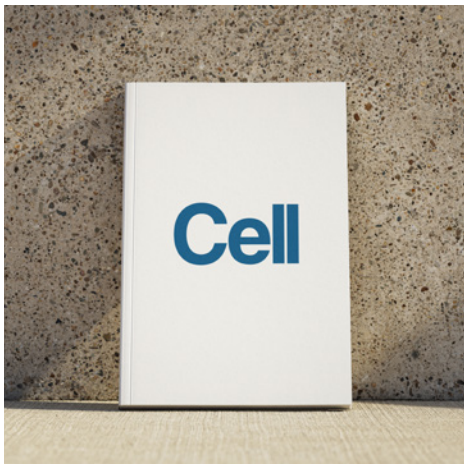
As for reading, I was dragged kicking and screaming towards "The Power Broker" by Robert Caro. I don't read non-fiction, so 1,300 pages on the biography of a bureaucrat was rather unappealing. How wrong I was. It truly is the Machiavelli's Prince of modern times. You just have to read it to understand.

> It's music that, although improvised on the spot, can be re-listened to dozens of times. It can—and I have. It's an utter pleasure every single time.
>
> *– Ferran Prat*

Jason Luke, MD

Trumpeter, The CheckPoints;
Chief medical officer,
Strand Therapeutics

Articles:



- "LUMI-lab: A foundation model-driven autonomous platform enabling discovery of ionizable lipid designs for mRNA delivery," published in *Cell*

- "A multiobjective AI model for LNP engineering enhances tissue-selective mRNA delivery," published in *Nature Biotechnology*

- "Engineering drug-responsive replication machinery for precise control of self-amplifying RNA," published in *Nature Biomedical Engineering*

Music:

- Jazz House 2026 by Brass House Collective

Books:

- "Why Nothing Works: Who Killed Progress—And How to Bring It Back," by Marc J. Dunkelman

What do you think was the most impactful paper of the year?

For those of us in the RNA therapeutics and synthetic biology space, there have been a series of extremely useful papers in LNP discovery/design as well as further iteration of in vivo "programming" of genetic medicine.

What are you listening to (albums, EPs, songs) this summer?

Jazz House 2026 by Brass House Collective – perfect music to just chill on a summer evening.

What are you reading?

Why Nothing Works by Marc Dunkelman – trying to imagine a future world where rational and long-term decision-making might get us out of this cyclical political and economic stalemate we seem to be in.

Russell K. Pachynski, MD

Trombone player, The CheckPoints
Associate professor
Director of Genitourinary Oncology Research
Division of Oncology
Washington University School of Medicine

Articles:

- "Evolution of myeloid-mediated immunotherapy resistance in prostate cancer," published in *Nature*

Music:

- In the End, by Animal Liberation Orchestra

- Hot Damn, by Animal Liberation Orchestra

What do you think was the most impactful paper of the year?

Very elegant work from Larry Fong's group showing critical regulators of immunotherapy resistance in prostate cancer and a mechanism to reverse it. Nice preclinical and clinical/translational confirmatory data.

Prostate cancer has been one of the tumor types that has been particularly under-responsive to many flavors of immunotherapy and identifying key mediators of resistance has wide-ranging implications. We have now also been focusing on these SPP1+ myeloid population in many of our datasets, including some ongoing single cell RNA-seq analysis of Sipuleucel-T, the only FDA-approved cellular therapeutic for prostate cancer.

“Prostate cancer has been one of the tumor types that has been particularly under-responsive to many flavors of immunotherapy and identifying key mediators of resistance has wide-ranging implications.”

– *Russell K. Pachynski*

What are you listening to (albums, EPs, songs) this summer?

ALO (Animal Liberation Orchestra)—a fantastic Bay Area band in the Phish/jam-band vein… so many great songs but from their last couple albums my favs are “In the End” off of their 2025 Frames album, and “Hot Damn” off their 2023 Silver Saturdays album—check them out!

What are you reading?

Unfortunately nothing for leisure, but a LOT of grants for both ACS and NCI.

Lisa Butterfield, PhD

Vocalist, The CheckPoints; Consultant

Articles:

- “Whole-protein screening and multi-modal profiling of antigen-specific CD4+ T cells at single-cell resolution,” published in *Nature Communications*
- “Immune modulatory vaccines targeting tumor microenvironment antigens: recent advances in oncology and beyond,” published in *Signal Transduction and Targeted Therapy*

Books:

- "The Leopard," by Jo Nesbo
- "A River Red with Blood," by John Connolly

What do you think was the most impactful paper of the year?

I think everyone's idea of the most impactful paper in the first half of 2026 will vary a lot. I enjoyed a paper from Jim Health's lab, with Connie Trimble: Zhang et al, *Nature Communications*, "Whole-protein screening and multi-modal profiling of antigen-specific CD4+ T cells at single-cell resolution" about development of technology that allows identification of antigen-specific CD4+ T cells.

I also enjoyed the review earlier this year from Mads Hald Andersen: "Immune modulatory vaccines targeting tumor microenvironment antigens: recent advances in oncology and beyond", which summarizes the years of effort of developing cancer vaccines directed against tumor microenvironment inhibitory molecules.

What are you listening to (albums, EPs, songs) this summer?

I am, as usual, rotating between '70's rock and funk, '80's hair band rock, and '90's grunge. The evolving CheckPoints set list in 2026 is the only reason I'm expanding my musical horizons at all.

What are you reading?

I'm reading and re-reading my team's latest revised manuscript about autoantibodies in cancer patients as it gets closer to the final submission (with Paul Munson, Juraj Adamik and collaborators). When I can't read it any more, I switch to reading Scandinavian thrillers, like Jo Nesbo's "The Leopard" or anything and everything by John Connolly (his 2026 latest: "A River Red with Blood").

Anna Crosetti, MD

Vocalist, The CheckPoints;
Internal medicine resident,
Massachusetts General Hospital

Articles:

- "Cytokine-mediated CAR T therapy resistance in AML," published in *Nature Medicine*

Music:

- WHERE IS MY HUSBAND! by RAYE

- So Easy (To Fall in Love), by Olivia Dean

- Oscar Winning Tears., by RAYE

- Click Clack Symphony., by Hans Zimmer and RAYE

What do you think was the most impactful paper of the year?

As a budding oncologist, my interests have focused on cellular therapies in acute leukemias, particularly the challenge of the highly immunosuppressive and complex tumor microenvironment in high-risk myeloid malignancies. An interesting read I came across this year was by Baghwat and colleagues, published in *Nature* in 2024.

Their team looked at anti-CD123 CAR T cells in a small group of AML patients who ultimately relapsed despite therapy. They explored the role of cytokine mediated resistance of AML, particularly driven by the JAK/STAT pathways that are inherently activated by cytokine release syndrome in CAR T cells activation.

It highlights the complex interplay of cytokines in the healthy bone marrow response and the same pathways highjacked by acute leukemias to maintain survival and proliferation.

What are you listening to (albums, EPs, songs) this summer?

For the last three years, 99% of my days are spent in the hospital as a medical resident at MGH. I often make a joke to my patients saying that I "live" upstairs as we admit them from the emergency department to our medicine floors.

Last year, I would say my most listened to song is the melody of the telemetry monitor in the cardiac intensive care unit alarming arrhythmias, or the lullaby of bed alarms on the floors overnight. The last year has been particularly full of work and research; I'm currently applying for oncology fellowship and starting the interview process this fall. In those few moments where I can explore new music, I've become quite enamored with RAYE, the artist who wrote the very popular song "Where is My Husband."

> "I'm reading and re-reading my team's latest revised manuscript about autoantibodies in cancer patients as it gets closer to the final submission (with Paul Munson, Juraj Adamik and collaborators). When I can't read it any more, I switch to reading Scandinavian thrillers"
>
> *– Lisa Butterfield*

My original career plan was musical theater, for which I have clearly changed course. Her music touches that inherent love for dramatic, dynamic vocal and instrumental pieces with musical breaks that mirror the overture one might hear in the beginning of a Broadway show.

A couple other interesting songs of hers include "Oscar Winning Tears" and "Click Clack Symphony." They are great songs for running along the Boston Charles River Esplanade. When I'm looking for a more relaxing sound, I listen to Olivia Dean. My current favorite is "So Easy (To Fall in Love)."

What are you reading?

I can't say I've read much outside of the world of academics lately. I keep my peace with long-distance running outside, short overnight backpacking trips to the Sierra Nevada when I visit family in California, and fiddling with my own guitar at home to learn new songs when I'm not singing with the CheckPoints.

Dirk Spitzer, PhD

Drummer, The CheckPoints;
Scientific project manager,
HUMAN project
HZI Braunschweig, Germany

Music:

- Tool

- Porcupine Tree

- Saliva
- Linkin Park, Eminem, and Slipknot mashups

Books:

- "The Swarm," by Frank Schätzing

Here are my hobbies:

If I don't play the drums, I like ice skating, model RC planes (electric aerobatic and sail planes), soccer, table tennis, swimming, and basketball, among other things.

I like to listen to Tool, Porcupine Tree, Saliva, and the mashups with Linkin Park, Eminem, and Slipknot, among many other genres. Best drummers: Vinnie Colaiuta, Tony Royster Jr.

What are you reading?

I like to read travel books and science fiction such as "The Swarm" (Frank Schätzing).

Karen Popkin, MA, LCAT

Percussionist, The CheckPoints;
Music therapist,
Memorial Sloan Kettering Cancer Center

Articles:

- "Beyond Distraction: Music Therapy for Chronic Pain Management in People with Advanced Cancer," published in *Integrative Cancer Therapies*

Music:

- Beethoven Blues, by Jon Batiste

- Everybody Scream, by Florence + The Machine

- At Peace, by Ballake Sissoko

Books:

- "In the Distance," by Hernan Diaz
- "Summer Husband," by Amy Lorowitz
- Currently reading: "The Bold World: A Memoir of Family and Transformation," Jodie Patterson

> There's something about his Batiste's turn of phrase that makes me breathe a little deeper and relax into this genius blend of genre and time periods.
>
> *– Karen Popkin*

What do you think was the most impactful paper of the year?

As a long-time music therapist who has experienced meaningful shifts in best practice that are growing the field, I found this study not only informative but also affirming: Bradt J, Gumert L, Cottone C, et al. Beyond Distraction: Music therapy for chronic pain management in people with advanced cancer.

What are you listening to (albums, EPs, songs) this summer?

I've been listening to Jon Batiste's "Beethoven Blues." There's something about his turn of phrase that makes me breathe a little deeper and relax into this genius blend of genre and time periods. I also have great appreciation for Florence + Machine's 2025 release, "Everybody Scream," for its pure emotional energy. And lastly, I keep coming back to Ballake Sissoko, master kora player, whose aptly named album, "At Peace" is just bliss.

What are you reading?

I'm still contemplating the gorgeous and devastating novel, "In the Distance" by Hernan Diaz. After that, I needed and found a delightful read, "Summer Husband," a break-out novel by a friend of mine, Amy Lorowitz, and am now wrapping up Jodie Patterson's memoir, "The Bold World."

GUEST EDITORIAL

BOOK REVIEW

From the desk of Kimryn Rathmell: What to read before these beautiful days slip away

My summer reading challenged me to see people, purpose, and complexity in a new way

W. Kimryn Rathmell, MD, PhD, MMHC
CEO, The James Cancer Hospital and Solove Research Institute, Director, The Ohio State University Comprehensive Cancer Center; Former director, National Cancer Institute

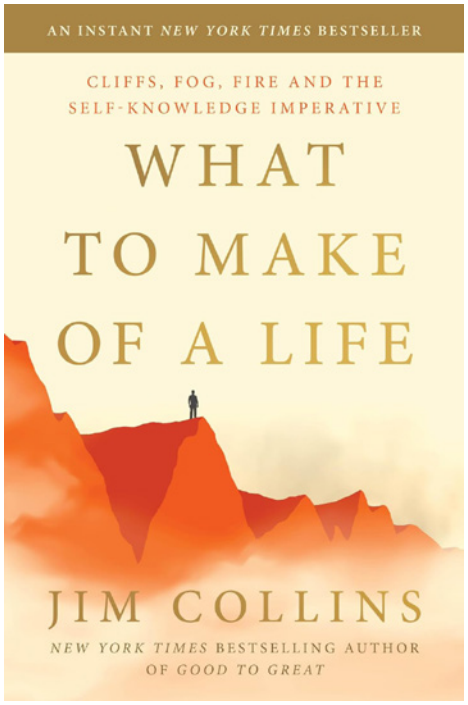
> I know I'm writing for a cancer audience, and I think reading that we do outside of the cancer literature also expands our horizons and makes us more effective at our missions in cancer, at the bedside, in the lab, or behind a desk.

One of the great pleasures of summer is having more time to read.

Whether on vacation, at the beach, or listening to an audiobook during a cross-country drive or evening walk, summers offer an opportunity to read more broadly and reflect more deeply.

I know I'm writing for a cancer audience, and I think reading that we do outside of the cancer literature also expands our horizons and makes us more effective at our missions in cancer, at the bedside, in the lab, or behind a desk.

I tend to read one print book alongside an audiobook, which I enjoy while walking or traveling. I thought I'd share a few of my picks from this summer in case anyone is looking for one more book before these beautiful days slip away.



What to Make of a Life: Cliffs, Fog, Fire and the Self-Knowledge Imperative
By Jim Collins

This was an audiobook that caught my attention this summer.

This book analyzed pairs of people for traits and experiences that shaped a life that was meaningful and fulfilling. All of us in the cancer field can be comforted in knowing that in finding our way here, we have likely aligned our encodings, one of the keys he identifies to finding satisfaction. During periods of non-alignment, he observes there can be discord or the sense of being in a fog, a sensation I could recognize, of going forward, but with unease and without a clear sense of direction.

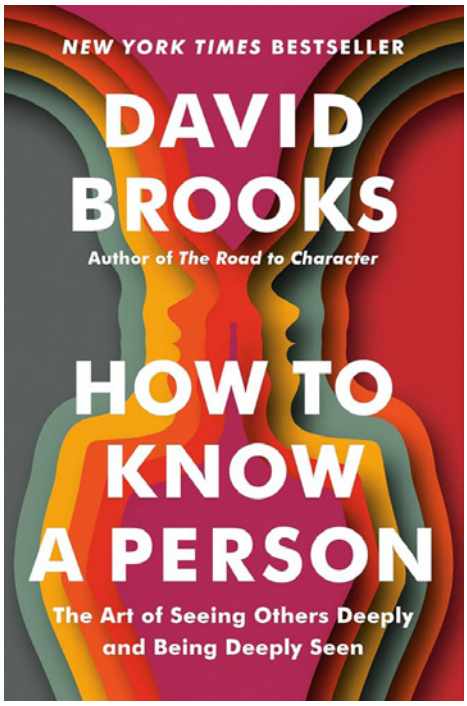
He also argues that cliff experiences (episodes of trauma from which one experiences recovery) are a necessary part of the journey. We see our patients facing those experiences every day, and we are not immune from the trauma of loss, injury, or disruption.

Ultimately, igniting a fire in an area of deep passion can lead to focused activity, which he refers to as "hedgehog mode" (making reference to the allegory of the cunning fox and the persistent hedgehog—acknowledging that people may experience many distinct hedgehog phases over the course of a life).

One of the book's most important ideas is that a meaningful life unfolds through distinct phases rather than a single continuous mission.

This idea resonated with me as I looked back at phases in my own life, with defined periods focused on scientific exploration, kidney cancer, physician-scientist development, and collaborative networks, all of which have helped shape my focus on community connectedness, while overlapping with equally important phases centered on personal growth, family, talent development, and community engagement.

The cliffs in my life played a role in focusing my attention, driving new alignments, and forcing phase shifts. Fundamentally, we can all find meaning and fulfillment, and the analysis of the lives of his prototypes: Barbara McClintock, Roger Sherman, and John Glenn are among my favorites.



How to Know a Person: The Art of Seeing Others Deeply and Being Deeply Seen
By David Brooks

This one was another audiobook that I profoundly enjoyed and will probably listen to again.

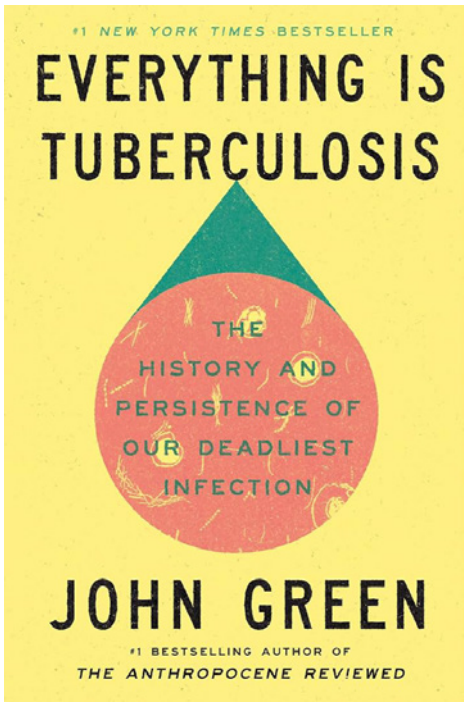
This book is full of practical concepts that our palliative care colleagues will recognize instantly. The premise is simple: we can form deeper, more meaningful relationships by being curious about what truly drives the motivations and feelings of people.

The book probes more deeply into the meaning of connection and being seen as a unique individual. In this era of personalization in health care, with all the tools we have to create a personal plan of care—based on genetics and immune status, as well as social factors—this book is a wonderful reminder of the key ingredient of personalizing care: listening to the patient and seeing them as a whole person.

This practice extends to our interactions with each other, even in professional settings.

I've also seen this principle play out during Cancer Center site visits. The most valuable insights often emerge not from presentations, but from genuine conversation, curiosity, and the opportunity to understand how others see their work and mission.

There is a richness in conversation, in listening and digesting inputs, and in allowing oneself to see briefly through another's eyes. This process also does a fantastic job of revealing both the uniqueness of each Cancer Center and the contributions that each Cancer Center makes to the overall impact of the Cancer Center Program.



Everything Is Tuberculosis
By John Green

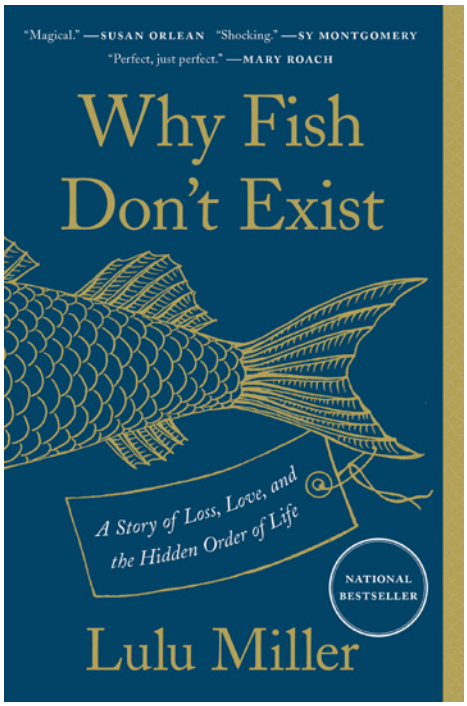
This was probably my favorite book of the summer.

My print reading usually takes a slightly different course than audio. I tend to switch between fiction and nonfiction, but this summer I leaned more toward science topics.

This book uses a simple premise and, through the action of storytelling, reveals the massive impact this single disease has had on our culture, language, social fabric, and global economics, as well as driving models of health care, of course. Told through the lens of tuberculosis patient Henry Reider, the book also unleashes a thoughtful and deep analysis of the impact of poverty, health discrimination, and generational loss that is intricately tied to the disease.

It is easy to see the parallels with cancer. Many of the inequalities of prevention, screening, treatment, and outcomes for cancer are not intrinsically different from that of tuberculosis.

This book shares the story in a poignant and tractable way and reflects the ways we can and should see people who experience cancer, so that we can ultimately make larger advances for all people.



Why Fish Don't Exist
By Lulu Miller

Finally, this book was loaned to me by our head of communications. It is a wonderful read for a summer week at the beach, and is a personal memoir woven into a biography of fish taxonomist David Starr Jordan.

Jordan was a hedgehog, who at the peak of his scientific career was responsible for cataloging and classifying his passion class (remember kingdom, phylum, class, order, family, genus, species?)—fish, before going on to be the President of Indiana University and the founding President of Stanford University.

He experiences thrilling discoveries, as well as his own share of cliffs, including facing involvement as a possible suspect in the strychnine murder of Jane Stanford (of Stanford University fame). I will confess, as a 2x graduate of that great university, I was unaware of the drama behind her death!

Interwoven with the memoir of the author, the book challenges the reader to realize that rigid classifications are in fact transient constructs, as well as artificial.

Life is complex and messy, and those classifications can both enable us to define the world but do so in a way that creates blinders to the true complexity of the universe. I won't spoil the dark turn this rigid classification mentality takes in history, but this book illustrates how neglecting to be truly curious, to dig in and really know a person or an issue, can allow the structure to prevent seeing some beauty or truth that has been there all along.

In cancer, we are at an extraordinary moment. As we move beyond traditional classifications and uncover deeper layers of biology, we are learning that complexity is not a barrier to progress but a pathway to it. The same curiosity that helps us better understand cancer can also help us better understand our patients, colleagues, and communities.

Thanks for joining me on this summer reading tour. Each of these books offered more than a compelling story; each challenged me to see people, purpose, and complexity in a new way. Those are perspectives worth carrying into every season, including our work in cancer.

“In cancer, we are at an extraordinary moment. As we move beyond traditional classifications and uncover deeper layers of biology, we are learning that complexity is not a barrier to progress but a pathway to it. The same curiosity that helps us better understand cancer can also help us better understand our patients, colleagues, and communities.”

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GUEST EDITORIAL

The defining question of the next decade is not how many drug candidates can be generated, but who decides which ones move forward, and why

Drug development must convene a forum for candid, cross-sector discussion

Richard L. Schilsky, MD
Chair, Board of directors, Accelerating Anticancer Agent Development and Validation Workshop Foundation; Professor emeritus, University of Chicago; Former executive vice president, Former chief medical officer, American Society of Clinical Oncology

H. Kim Lyerly, MD
Member, Board of directors, Accelerating Anticancer Agent Development and Validation Workshop Foundation; George Barth Geller Professor of Cancer Research, Professor of surgery, Duke University School of Medicine

Thomas R. Fleming, PhD
Member, Board of directors, Accelerating Anticancer Agent Development and Validation Workshop Foundation; Professor and former chair of biostatistics, University of Washington

Renzo Canetta, MD
Member, Board of directors, Accelerating Anticancer Agent Development and Validation Workshop Foundation, Chair, AAADV Workshop Program Committee; Former vice president of oncology global clinical research, Bristol Myers Squibb

At the 2026 Annual Meeting of the American Society of Clinical Oncology in Chicago, results from the phase III HARMONi-6 trial were presented at the plenary session and published simultaneously in *The Lancet*.[1] The HARMONi-6 trial tested a novel bispecific antibody that engages PD-1 and VEGF (ivonescimab), given with platinum-doublet chemotherapy to patients with previously untreated advanced squamous non-small cell lung cancer.

The comparator was an antibody that engaged PD-1, but not VEGF (tislelizumab) plus the same chemotherapy, and ivonescimab appeared to be superior, with a median overall survival of 27.9 months compared to 23.7 months (hazard ratio for death 0.66, suggesting the average improvement in OS is considerably larger than 4.2 months).

Results from the HARMONi-6 trial were widely reported, as this was the first regimen that improved OS compared to an anti-PD-(L)1 antibody plus chemotherapy in a randomized trial for first-line treatment of advanced squamous non-small cell lung cancer. In previous years, the presentation and subsequent publication would typically be associated with the sponsor's submission of a marketing application to the US Food and Drug Administration and to other international agencies such as the European Medicines Agency. While ivonescimab is approved for use in China,[2] it is not yet available to lung cancer patients in the United States or Europe.

Why not?

The HARMONi-6 trial was conducted entirely in China, at 50 hospitals; 93% of the 532 randomized patients were men, and all had squamous cell carcinoma, a histology strongly associated with tobacco exposure.[1] This calls into question the applicability of the results to lung cancer patients in other parts of the world, particularly the U.S. where non-smoking related adenocarcinoma is the predominant lung cancer type. Another challenge to interpreting the HARMONi-6 results is the choice of control arm. Tislelizumab plus chemotherapy is considered standard of care in China, and tislelizumab is approved in Europe and Australia for first-line squamous cell lung cancer. In the United States, however, while tislelizumab is approved for several other tumor types, it is not approved for this indication, either as a single agent or in combination.[3]

Further complicating the interpretation of this study, results were reported earlier this year from the HARMONi-3 trial, a multiregional phase III trial comparing ivonescimab plus chemotherapy against pembrolizumab plus chemotherapy—a control arm that would be considered acceptable by the U.S. FDA.[4] In contrast to the HARMONi-6

trial, the separately powered cohort of patients with squamous cell carcinoma in HARMONi-3 did not cross the efficacy threshold at an interim analysis of progression-free survival conducted on a minimal alpha allocation. The independent data monitoring committee recommended that the trial continue as designed and remain blinded.

Collectively, the clinical benefit of ivonescimab remains promising, but it is not completely clear that these benefits will extend to patients in the United States, or other Western economies, compared to their current standards of care. Indeed, the clinical development of ivonescimab is illustrative of both the opportunities and the pitfalls of cancer drug development in a global market.

More medicines but more complexity

More new cancer drugs are reaching more patients than at any point in the history of oncology. At the same time, the path from a promising molecule to a patient who actually receives it has never had more moving parts.

The scale of the cancer drug development enterprise is now well documented. Kang and Ji recently examined early-stage drug development programs worldwide—each defined as the development of a specific drug for a specific indication, at the discovery, preclinical, or phase 0–2 stage, catalogued in a commercial development database and attributed to the headquarters country of the originating company.[5] Across all diseases, the number of such programs nearly doubled between 2015 and 2024, from roughly 10,400 to about 19,000, and the U.S. share fell from 48.2% to 37.4%.

The shift is even more dramatic for cancer drugs. Early-stage cancer programs rose from 3,720 to 11,115 over the same period; although U.S.-origin programs substantially grew (from 1,811 to 4,051) during this time, they fell as a share of the global total from 48.7% to 36.5%, largely driven by the major increase in China-origin programs from 381 to 4,152, in turn increasing China's portion from 10.2% to 37.4%. China now originates more early-stage development programs for cancer drugs than the United States. In an accompanying editorial, Richard Pazdur and Steven Usdin observed that in development of antibody-drug conjugates, bispecific antibodies, and cell therapies, China now rivals or surpasses the United States in scale and, in some areas, in innovation.[6]

A cross-national analysis by Friends of Cancer Research reported that from 2020 through 2025, FDA approved 87 novel oncology drugs and China's National Medical Products Administration approved 94.[7] From 2023 onward, NMPA's annual volume exceeded FDA's. FDA remained faster—review times a median of 182 days shorter, approvals a median of 164 days sooner—and first-in-class approvals remained predominantly at FDA. Of those 181 approvals across six years, only 14 drugs were approved by both agencies. Some of that divergence reflects differences in epidemiology, in unmet need, and in the standards of care against which a new agent must be judged, while some of it reflects where a sponsor chose to run the trial.

The coming challenges in cancer drug development

The use of artificial intelligence is generating candidate drug targets and molecules faster than any prior method, and in greater volumes than the downstream system can absorb. A generation ago, a well-equipped screening operation might evaluate a few hundred compounds against a target in a week. The constraint today is not the number of plausible structures. It is the number of chemists who can synthesize them, the number of pre-clinical models that can reliably triage them, and, perhaps most importantly, the number of patients and clinical trial sites available to test them.

This means that the defining question of the next decade is not how many drug candidates can be generated, but who decides which ones move forward, and on what basis. In practice, that decision is made company by company, and it is driven substantially by commercial opportunity: novelty of the target, size of the population, unmet medical need, competitive density, likelihood of reimbursement. But this calculus reliably rewards risk reduction—the third or fourth agent against a validated target in a more narrow indication—over the novel, unvalidated mechanism of action that might have greater impact.

The current environment sustains this paradigm. When a highly innovative small company spins out of an academic laboratory, the principals quickly learn what they must demonstrate to justify the next round of investment. Unfortunately, the direction chosen is not typically "prove the new biology." It is more often "find a niche indication where the regulatory path is proven and predictably short." If one can imagine these conversations occurring among boardrooms across the biotechnology ecosystem, the result is cancer therapy opportunities that look enormous, but can be remarkably narrow in some instances.

Patients will bear the cost if we are not efficient

Patients will ultimately bear the cost when the same scientific question is asked and answered multiple times in multiple jurisdictions because drug sponsors and regulators are not aligned on the trial designs. They bear it when a dose that was never optimized produces toxicity that limits treatment tolerance and duration of therapy. They bear

it when a development program for a novel agent is abandoned not because the biology failed but because the commercial case was not compelling or the large-scale manufacturing challenges could not be overcome.

Intrinsic and extrinsic factors affecting the acceptability of foreign clinical data—differences in patient populations, in medical practice, and in health systems—are a real scientific issue, addressed in ICH E5(R1) and revisited regularly since.[8] Nonetheless, fragmentation has a cost, and that cost is paid in patient-years.

That cost is not hypothetical, and the same molecule we used to introduce this story illustrates both the cost and the remedy. Ivonescimab was first tested in patients with EGFR-variant nonsquamous NSCLC whose disease had progressed on a tyrosine kinase inhibitor in HARMONi-A, a randomized, double-blind phase III trial conducted at 55 centers, all of them in China. An interim progression-free survival analysis supported NMPA approval in May 2024.[9] The final overall survival results, published in JAMA in June, showed a median of 16.8 months with ivonescimab plus chemotherapy versus 14.1 months with chemotherapy alone (hazard ratio 0.74).[10]

The investigators were candid about the constraint: because the trial was conducted exclusively in China, generalizability to non-Asian populations remains unproven, and they pointed to the ongoing global HARMONi study as the trial that may resolve it. They also noted that clinical practice in this patient population had changed during the study's conduct, so the population in which the question is now clinically relevant is not quite the population that was enrolled.

That global study—HARMONi, sponsored by Summit Therapeutics, which licensed ivonescimab outside China—asks essentially the same question in a multiregional population, and Summit has expanded the study from a single-region design. An updated analysis reported consistent overall survival benefits in Western and Asian patients, and the resulting Biologics License Application was accepted for filing in January 2026, with an action date of November 14, 2026.[11]

> “A field with that many degrees of freedom and no forum for candid, cross-sector discussion becomes more expensive, slower, and less equitable and accessible to patients.”

Whether that sequence represents appropriate regulatory caution or avoidable duplication is a question worth discussing, and reasonable people in this field might answer it differently. Nonetheless, roughly 30 months separate the Chinese approval from the U.S. action date, and patients outside China have been waiting.

One opportunity to convene, debate, and learn: the AAADV Workshop

Guidance documents, advisory committees, and consensus papers each provide valuable information and perspectives. What none of them does is to enable direct dialogue—a biostatistician asking a regulator a question about trial design; a company medical director describing, candidly, a dose-optimization decision that turned out to be wrong; the sponsors of drugs from the same class sharing and highlighting common problems; an investigator hearing how an identical data package was received in Silver Spring, Amsterdam, and Beijing; or a patient advocate saying out loud that a multi-year gap between approval in one country and approval in her own is not acceptable to the people she represents.

The unscripted exchange—the questions that arise on the fly during discussion, and the recognition that a common problem may exist while individuals in the room each grappled with it individually—is what the AAADV (Accelerating Anticancer Agent Development and Validation) Workshop has enabled since 2004. The workshop, held in collaboration over the years with the National Cancer Institute, FDA, AACR, ASCO, and multiple stakeholders, has supported and enabled these conversations. In 2025 the AAADV Workshop reorganized as an independent 501(c)(3) foundation in order to broaden access, expand virtual participation, and support year-round educational programming.

Twenty years ago the key features of a registration program where the trial runs, what the control arm is, which primary endpoint, which agency sees it first—were largely settled questions. Today the selection of drug, target, biomarker assay, patient population, control treatment, clinical endpoint, and region of the world is more complex than ever. A field with that many degrees of freedom and no forum for candid, cross-sector discussion becomes more expensive, slower, and less equitable and accessible to patients.

The 2026 AAADV Workshop will convene November 5–6, 2026, at the North

Bethesda Marriott Hotel & Conference Center, in person and virtually. The program takes up exactly the questions this article raises: multiregional clinical trials and global development strategy; benefit-risk assessment in regulatory decision-making, including the sufficiency of a single pivotal trial and the role of post-market evidence; dose optimization for novel agents, combinations, radiopharmaceuticals, and cell therapies; "me too or not me too," discussion on follow-on agents, biosimilars, and novel formulations; failure to launch, a case-based examination of what FDA complete response letters reveal and teach us; and immune-related adverse events and their implications for treatment tolerance and acceptability. Because of its increasing importance to the field, an evening session is devoted specifically to cancer drug development in China.

Keynote addresses will be delivered by Monica Bertagnolli, president of the National Academy of Medicine; Robert Califf, former FDA Commissioner; Peter Marks, former director of FDA's Center for Biologics Evaluation and Research; and Thomas G. Roberts, Jr., of Farallon Capital Management. Richard Pazdur, former director of FDA's Oncology Center of Excellence, will join one of us (RLS) for a fireside chat on the globalization of cancer drug development. Registration and the full program are available at www.AAADV.org.

The question for the cancer care community today is not whether the scientific opportunities remain. It is whether the global development system can convert innovative science into benefit for patients everywhere, within a reasonable time, without requiring each region to relearn what another has already established.

Many of these questions will get worked out in rooms where the people who design, conduct, review, and fund these trials talk to one another, and to patients and their advocates directly—including about the things that did not work.

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IN THE HEADLINES

What happened at FDA? Replimune approval raises questions

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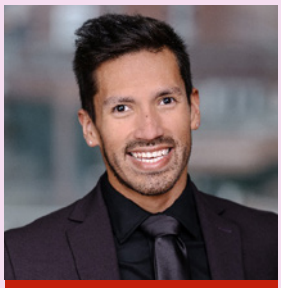
GUEST EDITORIAL CLINICAL

Like it or not, AI psycho-oncology care is already happening. Urgently needed: An ethical framework

Developers and mental health providers must share the same goal: Safe, equitable, trustworthy, and patient-centered care



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In 2026, more than 900 million people are estimated to be regularly using generative artificial intelligence—computer systems capable of creating human-like text, images, audio, video, and other original content.[1] AI is becoming integrated into nearly every aspect of daily life. Health care is no exception.

Across mental health care, cancer care, and the intersection of these disciplines, psycho-oncology, AI is rapidly emerging as a tool to support patient education, clinical decision-making, communication, symptom management, and psychosocial care.

As these technologies continue to evolve, they present unprecedented opportunities to improve access to comprehensive, personalized care while simultaneously introducing important ethical challenges surrounding fairness, accountability, transparency, privacy, and patient safety.[2-7]

Among the populations most likely to engage with emerging AI technologies are the more than 2.1 million adolescent and young adult, or AYA, survivors of cancer in the United States. AYAs face unique psychological, social, and treatment-related challenges that often require personalized, long-term support. As adolescent and young adults are some of the earliest adopters of emerging digital technologies, ensuring that AI-based tools are developed, recommended, and implemented ethically is essential to providing safe and equitable psycho-oncological care for this specific population.[8-17]

Ethical AI and mental health ethics have often developed along separate paths, but with new integrations come the new challenge of sharing the same goal: Providing safe, equitable, trustworthy, and patient-centered care.

The purpose of this editorial is to present a collaborative ethical framework that combines principles of ethical AI development with professional mental health ethics to guide the design, implementation, and use of AI technologies in psycho-oncology.

Although our framework *(Figure 1)*, is presented in the context of adolescent

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and young adult survivors of cancer, within psycho-oncology, its guiding principles may serve as a foundation for the ethical development and implementation of AI technologies across other patient populations and healthcare settings as AI continues to transform clinical care.

AI developers are guided by principles such as fairness, transparency, accountability, privacy, and security, while mental health professionals follow ethical standards including justice, integrity, fidelity and responsibility, respect for people's rights and dignity, and beneficence and nonmaleficence.

Together, these complementary principles provide a strong ethical foundation for integrating AI into psycho-oncological care.[18,19] *(Figure 1)*

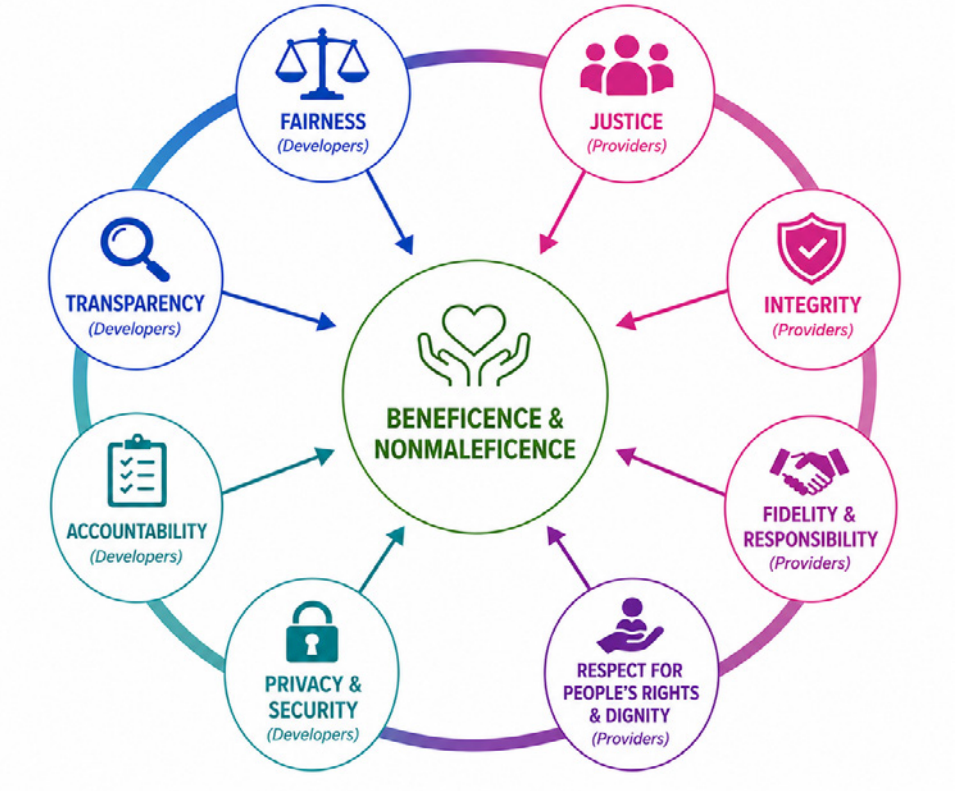
Achieving this goal requires collaboration between the individuals who build AI technologies and the mental health providers who recommend and use them. Ethical guidance is therefore needed for both developers and mental health providers.

Fairness & justice

Fairness in AI and the mental health principle of justice share a common goal: Ensuring that every patient has an equitable opportunity to benefit from AI-enabled care. Ethical AI should perform consistently across the diverse populations it is intended to serve, while mental health providers have an ethical obligation to ensure that all patients receive fair, inclusive, and appropriate care.

Together, these complementary principles help reduce disparities and promote equitable psycho-oncological care for adolescent and young adult survivors of cancer.[8-17]

Figure 1: A Collaborative Ethical Framework for AI In Psycho-Oncology



Developers play a critical role by designing AI systems using diverse, representative datasets and continuously evaluating them for bias and discrimination. Clinicians complement this work by determining whether AI tools have been appropriately developed and validated for the patients they serve and by recognizing barriers, such as technology or tool bias/discrimination, language, cost, internet access, or digital literacy that may limit equitable use.

Together, fairness and justice remind us that ethical AI is not simply about building accurate technologies, it is about ensuring those technologies improve care for all patients they intend to serve. [18,19]

Transparency & integrity

Transparency in AI and the mental health principle of integrity share a common goal: ensuring that AI technologies are honest, understandable, and worthy of patient trust. Developers promote transparency by documenting how AI systems are built, including their evidence base, intended populations, and known limitations. This information enables clinicians to critically evaluate whether a technology is appropriate for their patients and supports honest conversations about what AI can and cannot do.[18-21]

Developers should build AI using trustworthy evidence, while continually evaluating performance and openly reporting limitations. Mental health providers should understand this evidence before incorporating AI into care, recognize when human judgment remains essential, and communicate strengths and limitations clearly with patients.

Together, transparency and integrity ensure that trust is built not simply because AI provides an answer, but because developers create technologies that can be understood and mental health providers help patients under-

stand when those technologies should and should not be trusted.

Accountability & fidelity and responsibility

Accountability in AI and the mental health principles of fidelity and responsibility share a common goal: ensuring that responsibility for patient care always remains with people, not technology.

Developers should incorporate safeguards, monitor performance, and build systems that recognize situations requiring human intervention. Mental health providers should understand these safeguards, recognize their limitations, and ensure patients receive appropriate clinical care whenever AI reaches the limits of its intended role. [18,19,22-25]

Recommending an AI technology carries the same ethical obligation as recommending any other clinical resource. Developers remain responsible for monitoring and improving AI after deployment, while clinicians remain responsible for deciding when and how it should be used.

Together, accountability and fidelity remind us that while AI may enhance psycho-oncological care, ethical responsibility always remains with the developers who create these technologies and the mental health providers who incorporate them into patient care.

Privacy, security, and respect for people's rights and dignity

Privacy, security, and respect for people's rights and dignity share a common goal: protecting patients' personal information, autonomy, and right to make informed decisions about their care.

Developers should build AI technologies that minimize data collection, implement strong cybersecurity protections, and clearly communicate how information is collected, stored, and used. Mental health providers complement these efforts by understanding these protections and helping patients make informed decisions about using AI.[18, 19, 26-28]

Respect for patient dignity extends beyond protecting information, it also protects autonomy. Developers should design inclusive, understandable technologies that avoid unnecessary data collection, while mental health providers should ensure AI remains a choice rather than a requirement for care.

Together, these principles remind us that ethical AI is defined not by the amount of information it can collect, but by how responsibly it protects patients' information, autonomy, and trust.

Beneficence and nonmaleficence: The shared ethical goal

Although fairness, transparency, accountability, privacy, and their corresponding mental health principles each address different aspects of ethical AI, they ultimately share an objective: Beneficence and nonmaleficence, the ethical obligation to maximize benefit, while minimizing harm for patients.

These principles collectively guide the ethical development, implementation, and use of AI technologies in psycho-oncology, particularly for AYA survivors of cancer.[8-17f]

As AI continues to transform health care, the question is no longer whether these technologies will become part of psycho-oncological care, but how they will be integrated responsibly.

Although this framework was developed for adolescent and young adult survivors of cancer, its guiding principles may inform the ethical development and implementation of AI across other patient populations and healthcare settings.

As AI continues to evolve, ensuring innovation remains grounded in shared, collaborative ethical responsibility will be essential to realizing its greatest promise, not replacing human care, but strengthening our ability to deliver it.

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SPONSORED

Remote robotic surgery could redefine access to expert cancer care

By Yuman Fong, MD
Sangiacomo Family Chair in Surgical Oncology, Director, Center for Surgical Innovation, City of Hope

For generations, geography has been one of the biggest barriers to specialized surgical care. Advances in robotic surgery, telecommunications and cybersecurity may soon make distance far less relevant.

A recently published international consensus statement in the *World Journal of Surgery* outlines how health systems can safely implement remote robotic-assisted surgery, including standards for training, patient safety, cybersecurity, informed consent and emergency preparedness. The recommendations were developed by experts from 14 countries through a consensus conference organized by the Clinical Robotic Surgery Association.

Access to expertise without requiring travel

Momentum is accelerating. While not yet approved by the U.S. Food and Drug Administration, more than 1500 remote robotic procedures have been performed worldwide, and an upcoming study on a randomized trial will demonstrate that remote robotic surgery produces outcomes comparable to in-person robotic surgery for select urologic procedures. Experience across multiple countries has shown that surgery can be performed safely across significant distances using modern robotic platforms and secure communications networks.

For oncology, this raises a simple question: What if patients no longer had to choose between staying close to home and receiving specialized surgical expertise? Yet patients frequently seek care closer to home because of travel burdens, family responsibilities, insurance limitations, ongoing valued relationships with local oncologists, or limited access to specialty centers. Remote robotic surgery could help extend subspecialty expertise into community hospitals and geographically distant regions while allowing patients to remain within their local health systems and with their trusted oncologists.

At City of Hope, investigators have spent years evaluating long-distance telesurgery workflows in preclinical and animal models. The goal was to determine whether complex surgical procedures could be performed safely and reliably when surgeon and patient are separated by distance. In one study, surgeons in California remotely performed 20 procedures on models located in Illinois using a telecommunications network spanning more than 3,600 roundtrip miles. Procedures included nephrectomy, colectomy, cholecystectomy and gastric operations. All were completed without loss of robotic control, network interruption, audiovisual failure or intraoperative complications. Average network latency was 58 milliseconds, with no packet loss recorded. Most participating surgeons reported

that the remote experience was comparable to conventional robotic surgery.

Building the framework for clinical adoption

As promising as the technology is, implementation will require clear safeguards for patients and providers. The international consensus recommendations emphasize informed consent, standardized training, team credentialing, emergency preparedness, cybersecurity requirements and prospective outcomes tracking. The guidelines also call for institutions to record cases in registries to support ongoing evaluation of clinical, technical and network performance.

The recommendations represent one of the first internationally agreed frameworks for remote robotic surgery, a process coordinated through the City of Hope Department of Surgery. At the institutional level, success will depend on far more than purchasing a robotic platform. Health systems will need secure communications infrastructure, trained surgical teams, standardized workflows and participation in registries that track outcomes as the field evolves.

For decades, patients have traveled to expertise. Remote consultation popularized over the recent years now allow cancer treatment decisions to be rendered through telemedicine. Remote robotic surgery raises the possibility that therapeutic expertise could also increasingly come to patients. If the technology, training and safeguards continue to advance together, geography may become far less important in determining who has access to specialized cancer surgery. We will still need to optimize the surgeon-patient consultations to be sure that in addition to favorable cancer outcomes afforded by remote surgery, the human relationship between doctor and patient remains intact.

City of Hope®, one of the largest and most advanced cancer research and treatment organizations in the U.S., is leading the development of international consensus recommendations for remote robotic-assisted surgery. To learn more about City of Hope, visit: www.cityofhope.org. Discover the latest innovations in cancer research on City of Hope's new podcast, "On the Edge of Breakthrough: Voices of Cancer Research." Available on Spotify, Apple Podcasts, and at cityofhope.org/edge-of-breakthrough.

> If the technology, training and safeguards continue to advance together, geography may become far less important in determining who has access to specialized cancer surgery.

CANCER POLICY

Trump's vaccine executive order draws criticism from medical community, may put cancer populations at risk

By Claire Marie Porter

President Trump earlier this week issued an executive order that would drastically change the childhood immunization schedule—limiting recommendations, spacing out shots, and splitting the combined measles, mumps, and rubella vaccine into single-disease injections.

Trump said the move would provide American children with "gold-standard" protection and align the United States more closely with other developed countries that recommend fewer shots.

"Effective immediately, my administration is recognizing gold standard childhood vaccine recommendations for only 11 core vaccinations against the most serious and dangerous diseases, along with the MMR, which hopefully will be split up," Trump said in the Oval Office before signing the order on Aug. 10.

The executive order stipulates that children should get vaccinated for 11 diseases, down from the 18 immunizations that were recommended before Trump returned to office.

The details of this order mirrors HHS Secretary Robert F. Kennedy Jr. 's moves to overhaul the Centers for Disease Control and Prevention's schedule last year (*The Cancer Letter*, Oct. 10, 2025).

For the vaccines that are no longer recommended by the CDC, including shots for hepatitis A, hepatitis B, rotavirus, meningococcal disease, influenza, and Covid-19, the executive order directs families to talk to their doctors and make a "shared clinical decision" about whether their children should receive them.

ACIP voted in December to rescind its recommendation that all newborns receive a hepatitis B virus vaccine dose within 24 hours of birth (*The Cancer Letter*, May 1, 2026).

The decision will likely lead to hundreds of additional infections among children, according to studies published earlier this year in *JAMA Pediatrics*.

The rate of infants receiving a birth dose of the hepatitis B vaccine was already down 1.8%: 81.1% of babies born in 2019–2020 received the birth dose, while only 79.3% of babies born in 2021–2022 did (*The Cancer Letter*, April 3, 2026). This data was collected before fervent debate over vaccines, including the vaccine for hepatitis B, that has taken place in the last year.

Transfusion transmitted HBV in infants and children who rely on blood products is an overlooked area of risk, and removing the birth dose for infants born to birthing parents who are hepatitis B surface antigen–negative "creates a new cohort of vaccine-naive infants during a period when transfusion exposure may occur," according to one of the studies. "In practical terms, a universal birth-dose policy has become an option rather than a recommendation. This could lead to deferral or avoidance, therefore increasing risk for HBV transmission in pediatric patients."

Along with additional infections, the study predicts there will be more cases of liver cancer, death, and millions in added healthcare costs.

The executive order has drawn sharp criticism from the medical community, including the World Health Organization, which defended current immunization timelines as the product of decades of rigorous, evidence-based science.

A Survivor Views survey released earlier this year by the American Cancer Society Cancer Action Network found that vaccine-related confusion is already affecting patient decision-making, with nearly 1 in 6 cancer patients and survivors reporting that they delayed or skipped a recommended vaccine due to confusion.

In an Aug. 10 statement, Lisa Lacasse, president of the ACS CAN, said this order could undermine cancer progress and create confusion.

Said Lacasse:

> Preserving strong childhood immunization systems is essential to protecting public health and ensuring

that progress against cancer is not undermined. We are concerned that the executive order on vaccines will create further confusion for parents wanting to protect their children from vaccine-preventable diseases, including those that cause cancer.

Children today can be protected against more diseases with the same or fewer injections than in the past, including the HPV and HepB vaccines, which prevent several types of cancers later in life. Changes to the childhood vaccine recommendations could have a sweeping impact on American public health generally and on the health of patients with cancer and their families. Any changes to vaccine schedules must, therefore, be well-considered, evidence-based and made by qualified experts in the field.

ACS CAN supports fact-based vaccine policies that reduce the cancer burden and protect those affected by cancer through increased access and uptake of vaccines that prevent viruses that lead to cancer, like the HPV vaccine, treat cancer by boosting the immune system, and protect cancer patients and their families by maximizing community immunity.

The vaccine to prevent human papillomavirus remains on the recommended list of vaccines for children.

Senate passes stopgap bill that would ban OMB from finalizing rule that would politicize science

By Sara Willa Ernst

The U.S. Senate has passed a stopgap spending bill that, in addition to avoiding a government shutdown at the end of September, would preclude the White House Office of Management and Budget from finalizing a proposal that seeks to fundamentally redraw the ground rules for all federally funded research (*The Cancer Letter*, Aug. 7, 2026).

The bill passed with an overwhelming majority of senators (90-6) on Aug. 8, just before the chamber closed for a five-week summer recess.

The revision to Uniform Administrative Requirements, Cost Principles, and Audit Requirements for Federal Awards (commonly known as the "Uniform Guidance") attempts to make several policy changes, including expanding the power of political appointees in research funding decisions and restricting international collaboration among scientists.

Since the proposal was published in late May, the scientific community has responded with widespread opposition to the proposed changes (*The Cancer Letter*, June 12, 2026). Among the nearly 500,000 comments OMB has received during a public comment period were declarations of protest from prominent voices in oncology, including The Association for Clinical Oncology, The American Association for Cancer Research, The National Breast Cancer Coalition, and Association of American Cancer Institutes (*The Cancer Letter*, July 17, 2026).

The bill now goes to the U.S. House of Representatives, which will return from its summer recess on Aug. 31.

ACS CAN voter poll finds overwhelming support for affordable cancer care, high concern over tobacco usage

A national poll commissioned by the American Cancer Society Cancer Action Network found that likely 2026 voters from both parties overwhelmingly support people having access to cancer screening and care, as well as support for the federal government continuing to invest in cancer research.

The poll also showed that voters have concerns with the use of tobacco products in their communities.

According to the poll, 86% of likely voters nationwide believe that all Americans, regardless of the type of insurance they have, should have access to affordable cancer screening and treatment close to home. Further, nearly all (94%) believe that healthcare policies should make it easier—not harder—for people to get care.

The poll also found that 83% of likely voters believe the federal government

should prioritize strong and consistent funding for cancer research, prevention and early detection programs. Support for federal investment in cancer research and prevention remains strong, even when respondents prioritized reducing the federal debt and overall budget.

Conducted by Lake Research Partners and the Tarrance Group, this poll is a part of ACS CAN's national Cancer Votes campaign—the country's leading voter education program for cancer-related issues and policies.

"These findings underscore the broad public support for ensuring that where someone lives or how much money they make should not determine whether they can receive lifesaving care," Lisa Lacasse, president of ACS CAN, said in a statement. "As cancer remains one of the nation's leading causes of death, voters also recognize the importance of sustained federal investments that drive medical breakthroughs and expand screening opportunities."

The poll also highlights growing concern about tobacco use. 64% of likely voters state they are concerned about young people in their community using tobacco products, while 60% expressed concern about tobacco use in their communities overall.

"These concerns come at a time when tobacco is making a resurgence in pop culture and more increasingly addictive flavored products are entering the market," said Lacasse. "These trends threaten decades of progress in reducing tobacco use. Policymakers must take these concerns seriously by supporting science-based tobacco control policies and protecting future generations from a lifetime of addiction."

IN BRIEF

NRG Oncology names vice chairs and committee members

NRG Oncology announced changes in leadership across multiple committees.

Rebecca Arend was appointed gynecology oncologist vice chair of the NRG Translational Science Committee.

Arend is a gynecologic oncologist, surgeon-scientist, and clinical trial leader whose career has been dedicated to advancing translational research for ovarian, endometrial, cervical, and other gynecologic cancers.

Her research focuses on biomarker-driven therapeutics, molecular characterization of gynecologic cancers, and the development of innovative blood- and tissue-based biomarkers, including studies evaluating DNA, RNA, protein, and circulating tumor DNA for cancer screening, prognosis, and treatment response.

As associate director of Clinical Research at the O'Neal Comprehensive Cancer Center, she oversees clinical trial infrastructure, protocol development, workforce development, and translational integration across disease groups. Arend is a voting member of multiple NCCN Guidelines panels and has led numerous GOG Foundation, NCI-funded Cervical SPORE, and investigator-initiated multicenter clinical trials.

Within the NRG Oncology organization, Arend serves as the Translational Science chair of the Ovarian Subcommittee under the Gynecologic Cancer Committee.

Robin Lockhorst was appointed chair of the NRG Pharmacy Subcommittee.

Lockhorst is an accomplished oncology pharmacist, clinical research leader, and healthcare administrator with more than

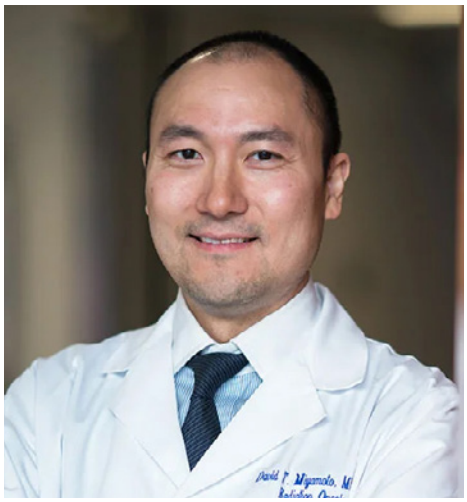
15 years of progressive experience at the Avera Cancer Institute. She currently serves as director of Clinical Research, Oncology at her institution, which is working on the growth of satellite research programs and the development of early phase clinical trial capabilities.

Lockhorst has maintained active involvement in protocol review, investigational drug services, and multidisciplinary staff development while leading operational improvements that have strengthened research quality and patient access to innovative therapies across the Great Plains region.

Her career has included roles as lead research pharmacist, oncology clinical pharmacy specialist, bone marrow transplant pharmacist, solid organ transplant pharmacist, and hepatology clinic pharmacist.

Additionally, Lockhorst has mentored several pharmacy residents and students and has led legislative and operational efforts for South Dakota's drug donation and repository pilot program, and secured grant support to advance research implementation in regional cancer centers.

Lockhorst currently serves as a member of the NRG Medical Oncology Committee and Ovarian Cancer Subcommittee, as well as previously served as a member of the NRG Pharmacy Subcommittee.



David Miyamoto was appointed Radiation Oncology vice chair of the NRG Translational Science Committee.

Miyamoto is a radiation oncologist, physician-scientist, and translational research leader at the Massachusetts General Hospital, an associate professor at Harvard Medical School, and an associate member of the Broad Institute of MIT and Harvard.

He has dedicated much of his career to advancing precision medicine for patients with genitourinary cancers by translating laboratory discoveries into practice-changing clinical applications.

As the director of an NIH-funded translational research laboratory in the Krantz Family Center for Cancer Research, part of the Mass General Brigham Cancer Institute, Miyamoto has led and pioneered the development of novel molecular biomarkers including liquid biopsy technologies, tumor genomic analyses, and advanced imaging approaches to better predict therapeutic response, treatment resistance, and disease progression in prostate and bladder cancers.

He has served as principal investigator on multiple NIH R01 grants, including an award to develop liquid biopsy and PSMA PET imaging biomarkers for patients receiving Lu-PSMA-617 radioligand therapy. He has also served as co-project leader on a P01 grant, collaborator on U01 and SPORE awards, and reviewer on multiple NIH and U.S. Department of Defense study sections.

Miyamoto has served as Translational Science chair or co-chair for major multi-institutional studies including NRG-GU015 (ARCHER), ECOG-ACRIN-NRG 8185 (INSPIRE), and the PARTIQoL trial, while leading biomarker investigations that have shaped the understanding of treatment response in bladder and prostate cancer. In addition to his work with NRG on the ARCHER study, he is a member of the NRG Translational Science Committee, Genitourinary Cancer Core Committee, and Theranostics Subcommittee.

Elena Nelson was appointed vice chair of the NRG Protocol Support Committee Clinical Research Associate Subcommittee.

Nelson joins NRG with over 15 years of experience in oncology clinical research at the University of Florida Health Cancer Center, where she has built a career centered on clinical trial operations, data management, leadership, and process improvement.

As the Data Management & Academic Research Consortium Network manager, she leads the team responsible for the quality, accuracy, and timeliness of data entry across approximately 150 solid tumor, hematologic malignancy, early-phase, and pediatric clinical trials at her institution.

Nelson is an expert in her field for NCTN and ETCTN studies and serves as a RECIST subject matter expert.

She has developed innovative data management workflows, implemented lasting operational improvements, and established standardized processes that continue to benefit the cancer center today.

During the COVID-19 pandemic, she created and implemented data management processes to ensure uninterrupted research operations while serving as a liaison between clinical and data management teams.

Nelson has worked closely with NRG before becoming a member of leadership as, under her supervision at University of Florida, their institution was to reach historic highs for NRG Oncology performance metrics demonstrating exceptional data quality and submission timeliness. She has been involved with the NRG RECIST CLASS project and has served as a member and a mentor in the NRG PSC.

Cortney Montgomery was appointed vice chair of the NRG PSC Mentorship Subcommittee.

Montgomery is an oncology research nurse and clinical trials professional with more than 25 years of progressive experience spanning academic medical centers, comprehensive cancer centers, and direct patient care.

Throughout her career, she has developed extensive expertise in coordinating phase I-IV clinical trials, including industry-sponsored, cooperative group, and investigator-initiated studies, with a primary focus on breast cancer, gynecologic oncology, and early-phase therapeutics.

In her current role at University of Pittsburgh Medical Center Hillman Cancer Center, she serves as both a clinical research coordinator and treatment nurse, overseeing patient screening, informed consent, investigational drug administration, chemotherapy delivery, protocol compliance, and multidisciplinary care while also leading implementation of policies to establish a new Clinical Translational Research Center.

Montgomery has maintained continuous GCP/CITI training and has contributed to the advancement of oncology research through leadership as a Clinical Trial Awareness and Outreach Advisor for the Carol Glock Foundation.

At NRG, Montgomery has served as a member and mentor in the PSC, as well as a liaison to the Breast Cancer Committee and Uterine Corpus Cancer Subcommittee.

Michelle Ozbun named associate director for basic research at UNMCCC

Michelle Ozbun was appointed associate director for basic research of the University of New Mexico Comprehensive Cancer Center.

Ozbun is a Distinguished Professor and the Maralyn S. Budke Endowed Professor in Viral Oncology in the UNM Department of Molecular Genetics & Microbiology with a secondary appointment in the Department of Obstetrics & Gynecology.

Ozbun was preceded by Alan Tomkinson, who was associate director from 2012 to 2026. He also served as interim center director and deputy director. During his tenure in these roles, the UNM Comprehensive Cancer Center recruited more than 18 faculty members and successfully renewed our NCI designation twice. Tomkinson's lab has been continuously funded by NIH for more than 30 years and has produced more than 100 publications.

Ozbun served two terms as treasurer and executive board member of the International Papillomavirus Society. She continues serving as chair of the IPVS Constitution Committee and as member of the IPVS Finance Committee and the IPVS Nomination Committee.

She is an elected fellow of the American Academy of Microbiology. At UNM, she currently co-leads the Cellular and Molecular Oncology Research Program for the UNM Comprehensive Cancer Center.

Ozbun's research focuses on HPV biology, replication, and transformation using advanced 3D organotypic "raft" cultures to propagate the virus—an ability few scientists possess.

Her research has been continuously NIH-funded since 2000 and she has obtained significant research funding from foundations and industry. Her landmark discovery identified the MEK signaling pathway, as a crucial regulator of HPV oncogene expression, revealing how carcinogens like tobacco smoke and estrogen promote HPV-driven cancers and reshaping understanding of HPV pathogenesis. Importantly, this work opened a novel translational path-

way to NIH and V Foundation supported preclinical work developing topical MEK inhibitors for HPV lesion treatment and cancer interception. Ozbun holds three U.S. patents with one patent pending.

Ozbun directs the NIH-funded T32 training program for predoctoral students and postdoctoral fellows in the biology of infectious disease and the American Cancer Society's Institutional Research Grant that provides pilot funding to early-career faculty in cancer research at UNM.

Stand Up To Cancer Nicolai Award will fund KRAS-targeted immunotherapy combination for pancreatic cancer

Stand Up To Cancer announced the recipients of the SU2C Nina Nicolai Pancreatic Cancer Innovation in Collaboration Award.

The approximately $225,000 in award funding will support a multi-institutional research team developing a potential new treatment approach for pancreatic cancer that pairs an mRNA vaccine with a KRAS-targeted cellular therapy.

The collaborative project is being led by Eric Tran, of the Providence Cancer Institute, and Di Liu, of Arizona State University. Tran leads the Adoptive Cell Therapy Laboratory in Providence's Earle A. Chiles Research Institute, and Liu is an assistant professor in ASU's School of Molecular Sciences and Biodesign Institute.

"The Nicolai Award supports innovative collaborations that we believe have great potential to lead to effective new treatments for pancreatic cancer," Julian Adams, SU2C president and CEO, said in a statement. "This year's recipients embody the spirit of this award—a partnering of talented young scientists who are pursuing a promising and novel immunotherapy-based approach to treating this lethal disease."

Researchers have trained much of their focus on a potential weak spot in pancreatic cancer: mutations in a gene called KRAS, which are present in tumors in nearly 90% of people with this disease. These mutations fuel the production of rogue proteins that help tumors grow and spread to other parts of the body.

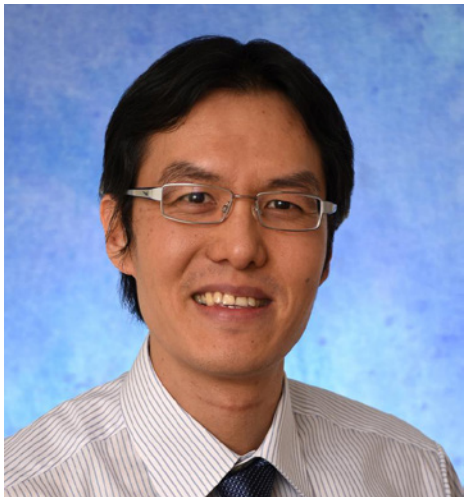
Although mutant KRAS proteins were long thought to be "undruggable," there are now two FDA-approved drugs to treat pancreatic cancer with KRAS-mutant tumors.

Both have had a modest clinical impact, however, with many patients' tumors not responding to the treatment at all and resistance quickly setting in among most patients whose tumors do respond.

And despite a proven track record against many other types of cancer, immune-based treatments have not worked against pancreatic cancer. Therapies known as mRNA treatment vaccines may buck that trend, with promising results seen in small clinical trials.

The treatment strategy being pursued by Tran and Liu targets tumors with KRAS mutations, but not by inhibiting the activity of mutant KRAS proteins. Rather, it uses two types of immunotherapy, including an mRNA vaccine. But rather than serving as the primary treatment, the vaccine is being used as an immune booster to a TCR T-cell therapy.

The receptor on the TCR T-cell therapy is genetically engineered to bind to cancer cells with KRAS G12D mutations, which are present in about 40% of people with pancreatic cancer.



Tran and his team at Providence have developed this TCR T-cell therapy and tested different iterations of it in a small number of patients, with some encouraging results, including one person with metastatic pancreatic cancer who had a year-long response.

Liu and his colleagues at Arizona State bring to the project their expertise and experience in developing mRNA vaccines. Funding from the award will support their efforts to engineer an mRNA vaccine with a specialized Cap2 structure, a chemical feature at the front end of mRNA, that is designed to help maintain antigen production and, thus, provide sustained stimulation for KRAS G12D-directed TCR-T cell therapy.

"In the setting of cancer immunotherapy, vaccine-induced innate immune activation can be helpful for stimulating antitumor immunity, but can also suppress mRNA translation," Liu said in a statement. "Our goal is to explore whether Cap2 mRNA can help maintain antigen production under these conditions and thereby better support TCR-T cell responses against pancreatic cancer."

According to Tran, the Nicolai Award will provide a platform for the partnership.

"We already have proof-of-concept that TCR T-cell therapy can shrink tumors in patients with pancreatic cancer. This grant is a catalyst for a new inter-institutional collaboration to help advance this exciting work," he said. "The resulting preliminary data will support future efforts to secure larger, long-term funding, ultimately accelerating our progress toward developing more effective treatments for patients with pancreatic cancer."

Stand Up To Cancer's scientific partner, the American Association for Cancer Research, will administer the grant.

USC researchers award $3.2M NIH grant to study age-related inflammation and cancer

Researchers at Keck School of Medicine at the University of Southern California have received a five-year grant of up to $3.2 million from NIH to further explore the role of thymulin in inflammaging and cancer, as well as its therapeutic potential.

As we age, chronic inflammation—or "inflammaging"—increases throughout the body and weakens our ability to fight cancer. But scientists have only recently started to uncover the biological processes that drive it.

Thymulin, a hormone produced by the thymus, keeps chronic inflammation under control, according to a Keck School of Medicine of USC study. As we age, thymulin levels drop and inflammation rises, weakening the immune system's ability to fight cancer. These findings were published in *Nature Communications*.

The project will use animal models and human cells to investigate how a naturally occurring hormone influences age-related inflammation and whether it can improve cancer immunotherapy.

"Scientists have traditionally viewed the aging thymus as important mainly because of its effects on one part of the immune system—T cells," Fumito Ito, professor of surgery and immunology and immune therapeutics at the Keck School of Medicine and principal investigator of the study, said in a statement. "Our findings suggest its influence is much broader, helping regulate chronic inflammation in ways that affect cancer."

Immunotherapy has revolutionized cancer treatment, but many patients still do not benefit—and Ito's findings may help explain why. In the new project, the researchers will explore whether thymulin can be used as an add-on treatment to help older individuals respond better to immunotherapies, including anti-PD-1 and anti-PD-L1 therapies. They will also test the hormone's potential for treating metastatic cancers. The preclinical studies will be conducted in aged mice with either breast cancer or melanoma, with additional testing done on human cells in the lab.

"By targeting one of the underlying drivers of inflammaging, we hope to help the immune system fight cancer more effectively, particularly in older individuals," said Ito, who is also vice chair of basic and translational science in the Department of Surgery.

In their *Nature Communications* paper, Ito and his colleagues showed that thymulin reduced inflammation, improved survival, and made immunotherapy more effective in older mice with cancer. While earlier studies had linked the thymus to inflammaging, Ito's group identified thymulin as a key regulator of that process. For the first time, they also established a causal chain connecting thymulin to inflammation, cancer progression, and immunotherapy response.

The grant provides funding to delve deeper into those findings, with three primary goals.

First, the researchers will investigate the precise molecular mechanism thymulin uses to control inflammation. To understand the biological signaling pathways involved they will study both mouse immune cells in living organisms and human immune cells in laboratory experiments. They will also identify which genes thymulin switches on and off to help control inflammation.

Next, the researchers will study how thymulin changes the immune environment inside tumors. In mice with forms of breast cancer and melanoma that do not respond well to immunotherapy, they will test whether the hormone helps the immune system mount a stronger attack against cancer. One key question: Is thymulin generating new anti-tumor immune responses, boosting an existing immune attack, or both?

Finally, Ito and his colleagues will test whether thymulin can work against metastasis, either by preventing metastatic tumors from forming or by slowing down established metastatic cancer.

Most cancers occur later in life, but much of what scientists know about

cancer immunotherapy comes from studies of young animals. By working with older mice, the team hopes to better understand how aging reshapes the immune system and to develop therapies more likely to translate successfully to older patients.

"To treat diseases of aging, we need models that reflect the biology of aging," Ito said. "Our goal is to make what we learn in the laboratory as relevant as possible to the patients most often affected by cancer.

Sethera Therapeutics and Roswell Park receive Breast Cancer Research Program Breakthrough Award from CDMRP

Sethera Therapeutics and Roswell Park Comprehensive Cancer Center have been awarded funding through the Breast Cancer Research Program Breakthrough Award, administered by the Congressionally Directed Medical Research Programs.

The award supports research aimed at advancing the prevention, diagnosis, and treatment of breast cancer.

The award will fund a Sethera Therapeutics and Roswell Park collaborative breast cancer research project, led by Katerina Gurova at Roswell Park Comprehensive Cancer Center and Karsten Eastman at Sethera Therapeutics.

Sethera Therapeutics has developed a polymacrocyclic peptide discovery platform designed to discover and engineer constrained peptide molecules with differentiated architectures and chemistries. The technology was first developed at the University of Utah with NIH support and licensed exclusively to Sethera Therapeutics. The pMCP platform offers an approach for pursuing difficult biological targets that have been challenging for conventional drug modalities.

The collaborative breast cancer project focuses on one of the most common and difficult problems in cancer biology: mutations in p53, a protein often described as the "guardian of the genome." In healthy cells, p53 helps prevent damaged cells from continuing to grow. In many cancers, including aggressive breast cancers, p53 becomes mutated and loses this protective function. These mutant forms of p53 can adopt abnormal conformations that allow cancer cells to survive, divide, and resist treatment.

Sethera will use its polymacrocyclic peptide platform to discover constrained peptide molecules that bind mutant p53 and stabilize conformations associated with restored tumor-suppressive activity. Rather than simply blocking a cancer target, the goal is to identify molecules capable of modulating mutant p53 structure and function in ways that are difficult to achieve with conventional modalities. This approach could support a new therapeutic strategy for breast cancers driven by p53 mutations, including forms of the disease that currently have limited targeted treatment options.

"This program represents an important external validation of both our platform and our strategy of applying architecture-diverse peptides to targets that have remained beyond the practical reach of many established drug classes," Karsten Eastman, CEO of Sethera Therapeutics, said in a statement. "Mutant p53 is an especially compelling test because its biological activity is closely linked to its three-dimensional structure. By working with Dr. Gurova and the Roswell Park team, we can evaluate not only whether our molecules bind mutant p53, but whether they can produce meaningful functional rescue in disease-relevant systems."

The Breast Cancer Research Program Breakthrough Award is designed to support studies that challenge existing paradigms and accelerate progress in breast cancer research. The FY25 award underscores the federal government's continued investment in transformative medical research and scientific collaboration.

Fred Hutch researchers receive multi-year funding from the V Foundation

Two Fred Hutch Cancer Center researchers have recently been awarded multi-year research grants from the V Foundation for Cancer Research.

Michael Haffner, associate professor in the Human Biology and Clinical Research divisions, received a V Foundation All-Star Grant, providing $1 million in research funding over 5 years. Haffner will study how a specific change to DNA in cancer cells could result in new therapeutic targets for FDA-approved cancer drugs.

Kevin Cheung, associate professor in the Public Health Sciences Division, received a V Foundation Translational Grant providing $800,000 over 4 years. Cheung will study ways to target triple-negative breast cancer cells, so named because they lack estrogen receptors, progesterone receptors and sufficient levels of HER2 protein, which promote the growth of cancer cells. Research into new potential targets is crucial because the drugs used to treat hormone-receptor or HER2-positive breast cancers are not as effective for those with TNBC.

Haffner's research focuses on the science of epigenetics, the changes that occur on top of strands of genetic material that can either enhance or repress the expression of specific genes. "Epi" is a prefix originating in the Greek language that means "over" or "above."

In DNA methylation, molecules called methyl groups are attached to portions of DNA, which hold the genetic code for producing cell proteins. With 20,000 genes located on the human DNA molecule, these epigenetic additions lead to a myriad of specific changes and form the basis of gene expression and cell identity.

"One thing that is pretty striking to me, and has been so since my training, both in the lab and then also as a pathologist, is that a key differentiating feature between cancer cells and benign cells is how the epigenome is structured," Haffner said in a statement.

During the COVID-19 pandemic when laboratory research slowed down, Haffner found himself with large amounts of time to read through existing research. He revisited literature on the epigenetics of cancer cells, especially DNA hypomethylation (a loss of expected methylation of DNA in specific cells), which had been observed in many different types of solid tumor cancer cells as early as the 1980s.

"Arguably the first description of an epigenetic change in cancer was that a lot of solid tumors lost DNA methylation," Haffner said.

However, studies that looked further into how cancer cells with DNA hypomethylation functioned were lacking. That led to the project for which the V Foundation awarded Haffner an All-Star Grant, "AKTing on DNA hypomethylation." The All-Star Grant is awarded to previous V Foundation grant recipients who are nominated by their institutions as the "best of the best" in their fields. Haffner previously received a V Scholar grant in 2021 for a project studying prostate cancer cells at the single-cell level.

AKT is a protein that acts as a growth signal in hypomethylated cancer cells. When AKT is blocked, cells turn to another signaling system known as Polycomb Repressive Complex 2 to survive.

Haffner's team previously demonstrated that when both AKT and PRC2 are blocked at the same time, cancer cells can be killed much more effectively. The goal of Haffner's new study is to develop a clinical trial using AKT and PRC2 blockers to treat cancer patients whose solid tumors show signs of DNA hypomethylation.

"If successful, this approach could lead to a more personalized treatment for patients with cancer," Haffner wrote in his grant application.

Targeting the machinery of the tumor cell itself is a promising new approach to attacking solid tumors. With a number of FDA-approved AKT and PRC2 blockers already available, Haffner believes that a breakthrough for DNA-hypomethylated solid cancers could be on the horizon.

He credits his frequent collaborator, Michael Schweizer, a Fred Hutch medical oncologist, with helping him to develop these ideas. Haffner also cites the critical work of Pallabi Mustafi, a postdoctoral researcher in his lab, who undertook the fundamental studies that demonstrated the vulnerability that hypomethylated cancer cells have to AKT inhibitors already in use for certain types of cancer. Those early findings and collaborative conversations set the stage for Haffner's current project.

"No one [else] had associated [AKT inhibitors] with DNA methylation at that point," Haffner said. The AKT inhibitors create "striking effects at very low doses of the drug, [and] only in the tumors that have low global methylation. That was our first insight that these tumors have a vulnerability that we can immediately go after with drugs that are [already] available that are reasonably well tolerated."

Further experiments showed that blocking AKT forces cancer cells to depend on a second pathway, known as PRC2, to stay alive. Since drugs targeting PRC2 are already being tested in patients, Haffner and his team were able to combine the two approaches. Together, the drugs were more effective than either treatment alone, offering a promising new strategy for treating advanced prostate cancer.

Haffner said he hopes that the first clinical trial, supported by the V Foundation grant, will demonstrate that using both drugs together to treat hypomethylated solid tumors will lead not only to new

treatments for solid tumors, but fewer side effects as well.

"We saw significantly increased effect [with both drugs]" while reducing the dosages of each drug, Haffner said. "So, not only do they work better together, but now you can spare a patient some of the side effects. The anticipation is that this combination of therapies will be very well tolerated."

Triple-negative breast cancer occurs in up to 20% of all breast cancer patients, and can be highly aggressive, dividing more quickly and exhibiting increased resistance to standard cancer treatments such as chemotherapy.

TNBC is particularly difficult to treat because of the absence of obvious markers that could be targeted with existing hormone-specific cancer drugs. Without receptors for estrogen or progesterone inside the cell, or significant amounts of the protein HER-2 on the cell surface, TNBC cells are harder to treat than other breast cancer subtypes. It's a predicament that keeps Cheung, the recipient of a V Foundation Translational Grant, up at night.

"I've been trying to understand how cancer cells, particularly breast cancer cells, metastasize," Cheung said in a statement. "Metastatic cancer cells have the aggression dial turned way up, making them spread rapidly, seed different sites, and resist therapies. What if you could turn the aggression dial way down?"

This is Cheung's second grant from the V Foundation. He previously received a 2017 V Scholar Grant for a project studying mechanisms of cancer metastasis. For his current project, Cheung is looking at molecular clues in cancers without obvious drug targets to take advantage of their cellular machinery to make them less aggressive.

While breast cancers identified by the presence or absence of hormonal receptors are known as "clinical subtypes," these cancers can also be described based on their molecular or morphological characteristics, such as their shapes and how they act under certain conditions. These so-called "molecular subtypes" include one type of tumor commonly seen in TNBC: the presence of cancer cells that resemble basal epithelial cells, a type of cell normally seen in the epidermis, the top layer of human skin.

The idea that a triple-negative breast cancer cell could resemble an epidermal cell suggested to Cheung that perhaps these cells could be coaxed into acting like them as well. That could provide a new avenue for the treatment of TNBC, by tricking these cancer cells into acting like cells that routinely die instead of multiplying uncontrollably.

Cheung's project, "Irreversible differentiation of triple-negative breast cancer via targeted UPS inhibition," targets a class of proteins known as the ubiquitin-proteasome system. The UPS system degrades old proteins in cells and recycles their remnants to build new proteins inside the cell. It is a key mechanism in cellular biology that allows cells to survive and multiply.

Cheung believes that UPS inhibitors, drugs with FDA approval that are in common use for multiple myeloma, could be used to identify and kill basal-like tumor cells in TNBC. He plans to use his grant to conduct critical experiments that will help in the design of a clinical trial for patients whose TNBC has already been successfully treated, in the hopes that the basal-like tumor cells that could seed a relapse could be eradicated before causing a recurrence of the cancer.

He credits breast cancer oncologist Sara Hurvitz, senior vice president and director of the Clinical Research Division, and myeloma oncology expert Andrew Portuguese, an assistant professor in the Clinical Research Division, for helping him conceptualize how these drugs can be repurposed for therapeutic use in TNBC. Hurvitz holds the Smith Family Endowed Chair in Women's Health.

"Once [TNBC cells] start acting like skin cells, they can't spread or grow," Cheung wrote in his grant application. "This approach could stop TNBC before it comes back and becomes life-threatening."

The implications for patients are substantial. Cheung notes that TNBC has the highest rate of relapse of all types of breast cancer within five years after the initial diagnosis. By the time a relapse is detected, many millions of TNBC cells will have already seeded the recurrence.

Cheung's project will determine whether UPS inhibitors can drive TNBC cells to differentiate into basal-like cells, and whether these cells normally digest and degrade the proteins known as transcription factors that drive cells to differentiate into basal skin cells. From there, he plans to determine how to identify TNBC patients that could benefit from UPS inhibitor-based therapy to prevent a relapse of their cancer.

The planned clinical trial aims to treat TNBC patients in remission with UPS inhibitors in the hopes that these drugs will degrade basal-like cells that could otherwise proliferate and create new tumors. Cheung will work in collaboration with cancer epidemiologist Christopher Li, senior vice president and director of the Public Health Sciences Division. Li holds the Helen G. Edson Endowed Chair for Breast Cancer Research.

"UPS inhibition has never been studied in the context of micrometastasis eradication [the eradication of small amounts of cancer cells before a diagnosable relapse occurs]," Cheung said. His hope is that by tricking basal-like cells into acting like skin cells that normally die off instead of proliferating uncontrollably, these studies will lead to a new class of treatments for cancer that look not at surface markers for drugs but cellular shapes and activities that can be disrupted.

THE CLINICAL CANCER LETTER

CLINICAL ROUNDUP

Traditional prostate cancer risk factors do not predict hormone therapy benefit, UCLA-led study finds

Traditional pathological features used to classify aggressive prostate cancer—such as high-grade disease, cancer extending outside the prostate and cancer involving the seminal vesicles—after surgery do not predict who will benefit more from adding hormone therapy to postoperative radiation, according to a study led by investigators at the UCLA Health Jonsson Comprehensive Cancer Center.

The study highlights the need for molecular biomarkers that can better predict treatment response and personalize treatment based on tumor biology.

The findings were published in *European Urology*.

After prostate cancer surgery, some patients receive radiation therapy if there is concern that their cancer may return. Doctors may add hormone therapy, which reduces the levels of hormones that can fuel prostate cancer growth, to improve outcomes for certain patients.

However, hormone therapy can cause side effects, including fatigue, hot flashes, sexual dysfunction, bone loss, and metabolic changes. Identifying which patients are most likely to benefit is important to ensure patients receive effective treatment while avoiding unnecessary side effects.

Doctors commonly use features found in the prostate tissue removed during surgery to estimate how aggressive a patient's disease may be. These features are known to predict outcomes, but it has remained unclear whether they can identify patients who are more likely to benefit from adding hormone therapy.

Researchers analyzed individual patient data from five phase III randomized clinical trials that compared postoperative radiation therapy alone with radiation therapy combined with hormone therapy.

The analysis included 4,781 patients who had undergone prostate cancer surgery and later received radiation therapy. The researchers developed an adverse feature count score based on four high-risk pathological findings:

- High-grade disease (Grade Group 4-5),
- Cancer that had spread into the seminal vesicles,
- Cancer that extended outside the prostate, and
- Positive surgical margins (meaning cancer cells were found at the edge of the removed tissue).

Patients received a score from zero to four based on the number of adverse features present. The researchers then evaluated whether this score influenced the benefit of adding hormone therapy for two key outcomes, overall survival and metastasis-free survival.

The researchers confirmed that patients with more adverse pathological features had worse outcomes. Patients with a higher adverse feature count had an increased risk of death and cancer spreading to other parts of the body.

However, the number of adverse features did not predict whether a patient would benefit more from adding hormone therapy to radiation therapy.

Even patients with multiple high-risk features, including high-grade disease and seminal vesicle invasion, did not experience a greater improvement in overall survival or metastasis-free survival from adding hormone therapy compared with patients with fewer risk factors.

The findings were consistent among patients with a prostate-specific antigen level of 0.5 ng/mL or less before radiation, a group in which previous research found limited overall benefit from adding hormone therapy.

The study shows that traditional pathological features are useful for identifying patients with a higher risk of re-

currence but do not indicate who will respond best to hormone therapy.

"These findings highlight an important distinction between predicting risk and predicting treatment benefit," Amar Kishan, executive vice chair of radiation oncology at the David Geffen School of Medicine at UCLA and the co-director of the cancer molecular imaging, nanotechnology and theranostics program at the UCLA Health Jonsson Comprehensive Cancer Center, said in a statement. "While pathology helps us understand which cancers are more aggressive, we need biomarkers that can tell us which patients are most likely to benefit from a specific therapy. By identifying which patients truly benefit from additional treatment, more personalized approaches could help improve outcomes while reducing unnecessary treatment-related side effects."

Half of prostate cancer focal therapy use falls outside current guideline-supported patient groups, study finds

As focal therapy gains popularity as a less invasive treatment option for some men with prostate cancer, a national study led by researchers at the University of Pittsburgh found that some men may be receiving treatment that is either unnecessary or not aggressive enough for their cancer.

The study suggests that about half of patients receiving the procedure fell outside the patient groups for whom its use is supported by current clinical guidelines.

The findings were published in *JAMA*.

"For appropriately selected patients with intermediate-risk disease, focal therapy is an appealing treatment option because it aims to preserve quality of life while treating the cancer," Quoc-Dien Trinh, senior author, professor, and chair of the Department of Urology at the University of Pittsburgh School of Medicine, said in a statement. "But as promising new technologies become more widely available, it is important to understand which patients are most likely to benefit so that treatment decisions are guided by evidence and aligned with clinical guidelines."

To understand how focal therapy is being used in practice, using the National Cancer Database, Researchers analyzed data from 1,179,384 men, age 50 and older, diagnosed with nonmetastatic prostate cancer between 2010 and 2023.

Among the 15,672 patients who received focal therapy, about half belonged to groups with low-risk disease, high risk, or very high risk disease, for whom focal therapy treatment was not recommended by the contemporary guidelines and for whom the treatment may not always be the best option.

For men with low-risk prostate cancer, focal therapy may constitute unnecessary treatment, as many can be safely monitored through active surveillance. In contrast, patients with high- and very high-risk disease may require more aggressive therapies with stronger evidence for long-term cancer control than focal therapy can currently provide.

The researchers emphasize that the study does not argue against focal therapy.

Rather, it highlights a broader challenge in cancer care: ensuring that promising new treatments are adopted in ways that are supported by evidence and targeted to the patients most likely to benefit.

While focal therapy may be appropriate for some patients, important questions remain about long-term cancer outcomes, retreatment rates, treatment-related side effects, and quality of life.

"Innovation is critical in prostate cancer care," said Trinh. "Our findings highlight the need to ensure that promising new treatments are adopted in ways that are supported by evidence and matched to the patients most likely to benefit."

As the use of focal therapy continues to expand, the researchers say additional data will help clarify those patients who are most likely to benefit from the approach.

While the National Cancer Database provides a broad national picture of treatment patterns, it does not capture participation in clinical trials or prospective registries, nor does it include information on long-term cancer outcomes, quality of life, side effects, retreatment, or cost.

Future studies examining these outcomes could help refine patient selection and inform the ongoing evolution of clinical guidelines. In addition, focal therapy performed outside Commission on Cancer-accredited centers may not have been captured in the analysis, meaning the number of patients who received focal therapy might be larger.

"Our main goal is to ensure that each patient receives the treatment that best matches the characteristics of their cancer and their individual needs," said Trinh.

HCC-LIVE consortium publishes treatment framework for hepatocellular carcinoma

Liver cancer experts at 17 cancer centers, part of a consortium of North American experts called HCC-LIVE, have compiled a guidance on the best treatments for hepatocellular carcinoma in North America.

The resource, called BEACON-HCC, was published in the journal *Hepatology*.

BEACON-HCC spells out treatment recommendations, supported by data from the medical literature, for each stage of HCC.

It incorporates the degree of tumor burden, invasion into the vascular system, tumor biology, and more to align treatment allocation with the practices of HCC experts in North America.

BEACON-HCC incorporates emerging modalities, such as external beam radiation therapy, a treatment that uses high energy beams of radiation to shrink or destroy cancer cells; transarterial radioembolization, a minimally invasive therapy that delivers radioactive beads directly into the blood vessels feeding a tumor; and novel combination therapies that work throughout the body and specifically target the tumors.

For nearly 30 years, clinicians around the world have relied on the Barcelona Clinic Liver Cancer staging and treatment allocation system, said Mark Yarchoan, BEACON-HCC co-author and an associate professor of oncology at the Johns Hopkins University School of Medicine. However, the treatment landscape for HCC has changed dramatically, necessitating new systems.

"The BCLC does not elevate all of the treatment paradigms that we have available to us, and promotes treatment decisions that are somewhat different from how we have practiced at our institution," Yarchoan said in a statement.

"HCC management is a complex multidisciplinary effort due to disease biology and the variety of treatment options," Jeffrey Meyer, co-author and an associate professor of radiation oncology and molecular radiation sciences at the Johns Hopkins University School of Medicine, said in a statement. "We wanted to lay out these issues and marshal together different approaches for each stage of the disease, reflecting our practices at Johns Hopkins and other centers."

The idea for BEACON-HCC arose as Yarchoan, Meyer, and colleagues at Johns Hopkins recognized that their management of patients with HCC was increasingly diverging from the BCLC recommendations.

"For example, BCLC classifies tumors that invade the blood vessels as advanced disease and recommends systemic therapy alone," Yarchoan said. "But in the modern treatment era, vascular invasion does not necessarily mean that remission is out of reach. In a prospective clinical trial at Johns Hopkins, we showed that selected patients with vascular invasion could still undergo potentially curative resection."

Meyer points to radiation as another example. Earlier versions of the BCLC did not recognize radiation as a major treatment option, but high-level clinical trial data now show that it can play "a very meaningful role" in HCC management, he says, either as the primary treatment or in combination with other therapies.

The team began reaching out to other experts in the U.S. who were making similar observations and decided to write its own guidance, a process that took nearly two years.

The 20 co-authors validated BEACON-HCC in two ways.

First, they pulled 29 de-identified patient cases from their institutions. Each submission included brief clinical information and tumor imaging. All co-authors independently reviewed each case and selected their recommended initial treatment approach from options such as surgical resection, liver transplantation and other therapies. They also shared the same cases with 18 North American HCC clinical experts who were not involved in the development of BEACON-HCC to get their feedback on the best course of treatment. Then, they compared the percentage of agreement of both groups with BEACON-HCC recommendations and BCLC 2025 treatment recommendations. The experts' treatment decisions were 96.6% in alignment with the BEACON-HCC recommendations but only 72.4% in agreement with the BCLC recommendations.

"Our hope was to explain to the broader community how we currently manage HCC in our own multidisciplinary clinic," Yarchoan said. "Hopefully, it can influence the way that people think about this cancer."

HCC is the third-leading cause of cancer-related death worldwide and the leading cause of cancer-related death in patients with cirrhosis. The five-year survival for HCC remains below 25% despite improvements in screening and treatment.

BEACON-HCC provides a framework to consider each patient at their stage and appreciate all of the different treatment options that are available.

"It summarizes what we have available but also recognizes some of the outstanding questions for patients," Meyer said. "I think it will help provide a good framework for tumor board and multidisciplinary clinic discussions."

"As systemic and locoregional therapies continue to evolve, BEACON-HCC provides a dynamic, adaptable framework that can grow alongside our expanding therapeutic armamentarium for HCC," Marina Baretti, an assistant professor of oncology and the Jiasheng Chair in

Hepato-Biliary Cancer Research at the Johns Hopkins University School of Medicine, said in a statement. "What excites me most about BEACON-HCC is that it reflects the reality of multidisciplinary HCC care: No single factor determines treatment, and a classification system should reflect that complexity, while remaining practical and clinically actionable."

Baretti, co-director of the Liver and Biliary Cancer Multidisciplinary Clinic at the Kimmel Cancer Center, was one of the experts who helped validate the tool.

Baylor researchers develop drug aimed at overcoming cancer drug resistance

Researchers at Baylor College of Medicine have developed a drug called CS18 that disrupts the ability of cancer cells to survive therapy.

The findings were published in *Science Advances*.

"Therapeutic resistance is a main obstacle to achieve effective and durable cancer treatments," Weei-Chin Lin, corresponding author and professor of medicine in hematology and oncology, and of molecular and cellular biology at Baylor, said in a statement. "While some therapies are effective at the beginning, many patients eventually relapse because cancer cells can activate compensatory and convergent biological pathways that allow them to overcome the toxic effects of therapy, promoting survival."

In the current study, the researchers' goal was to develop a drug that would target a 'biological switchboard'—topoisomerase IIß-binding protein 1—that controls several cancer-driving pathways at once and determine whether this strategy could deliver durable responses and overcome resistance.

"Of all the 'biological switches' on TopBP1, switch BRCT7/8 interacts with several key regulators of cancer growth, including MIZ1, a suppressor of cancer driver MYC; mutant p53, which can acquire cancer-promoting functions; and PLK1 and CIP2A, proteins that help cancer cells survive and divide," said Lin, a member of Baylor's Dan L Duncan Comprehensive Cancer Center. "All together, these diverse roles position TopBP1-BRCT7/8 as a promising target for intervention."

The team screened thousands of chemical compounds using computer modeling and laboratory testing to identify molecules that could bind to the BRCT7/8 switch and block its cancer-promoting activities. They found compound 3B6, which they subsequently modified and tested many versions until they found CS18, the most effective candidate.

"When CS18 binds to BRCT7/8, the cancer-promoting activities of MYC and mutant p53 decreased, proteins involved in DNA repair became less active and cancer cells were more likely to die," Lin said. "In addition, CS18 increased the activity of genes that stop uncontrolled cancer growth. Altogether, CS18 appears to reduce several of the defenses that help cancer cells survive therapy."

The researchers observed these effects in several cancer cell types, including triple-negative breast cancer, ovarian cancer, lung adenocarcinoma, lung squamous cell carcinoma, and acute myeloid leukemia, while the drug was less toxic to non-cancerous cells. Importantly, combining CS18 with cancer drugs currently in use such as PARP inhibitors or osimertinib killed cancer cells more effectively than either drug alone.

"In the case of lung cancer cells that were already resistant to osimertinib, adding CS18 restored the cells' sensitivity to osimertinib, increasing cancer cell death," Lin said. "We observed a significant reduction of tumor growth in animal models with no major weight loss or other signs of toxicity."

The researchers propose CS18 is a candidate for further development as a drug that could become part of combination treatments to prevent or overcome cancer drug resistance.

SANRECO phase II study of divesiran in polycythemia vera meets primary endpoint

The SANRECO phase II trial of divesiran, a first-in-class siRNA, in 48 phlebotomy-dependent patients with polycythemia vera, met its primary endpoint and secondary endpoints. The 36-week, randomized, double-blind, placebo-controlled portion of the trial administered divesiran subcutaneously (6 mg/kg) every six weeks or every twelve weeks.

Divesiran is sponsored by Silence Therapeutics.

Key findings from the study include:

- The primary endpoint was met, with a significantly higher proportion of clinical responders among divesiran-treated patients with PV compared to those who received placebo (88% for divesiran versus 19% for placebo; p<0.0001). The primary endpoint was the proportion of patients achieving a response, which was defined as the absence of phlebotomy and maintenance of hematocrit below 45% during weeks 18-36.

- Importantly, both divesiran dose groups showed substantial primary endpoint efficacy with response rates of 93.8% and 81.3% for Q6W and Q12W, respectively.
- The key secondary endpoint of phlebotomy rate during weeks 0-36 was also met with the mean number of phlebotomies per patient in the divesiran groups significantly reduced compared to placebo (0.2 for divesiran versus 2.1 for placebo; p<0.0001).
- Divesiran groups also showed improvements in hematocrit control, iron markers including ferritin, and patient reported outcomes using the MPN-SAF Total Symptom Score.

Divesiran was observed to be well tolerated and safety was in line with previous trials. No new safety findings were observed in the trial. Injection site reactions were infrequent and self-limiting. There were two investigators who reported grade 1 anemia adverse event cases.

"Across the SANRECO phase I/II program, divesiran has been well tolerated and has consistently delivered durable hematocrit control in phlebotomy-dependent patients with PV, regardless of risk level or disease severity," Marina Kremyanskaya, associate professor of Medicine, Hematology and Medical Oncology, at the Icahn School of Medicine at Mount Sinai, said in a statement. "These compelling results highlight divesiran's potential to transform PV management with convenient, infrequent dosing that reliably controls hematocrit and addresses longstanding unmet needs for patients."

"The SANRECO phase II trial delivered our best-case outcome, confirming the impressive results observed in phase I with dosing every six weeks and demonstrating equally robust and durable effects with quarterly dosing," Curtis Rambaran, chief medical officer at Silence, said in a statement. "These results reinforce divesiran's potential to become the first and best-in-class siRNA treatment for PV. We look forward to initiating phase III development and bringing divesiran to patients as quickly as possible."

Silence plans to present full results from the phase II SANRECO trial at an upcoming medical congress.

DRUGS & TARGETS

FDA grants accelerated approval to iberdomide with daratumumab and hyaluronidase-fihj and dexamethasone for multiple myeloma

FDA granted accelerated approval to iberdomide (Zenbexus) in combination with daratumumab and hyaluronidase-fihj and dexamethasone for adults with multiple myeloma who have received at least one prior line of therapy including a proteasome inhibitor and an immunomodulatory agent.

Iberdomide is sponsored by Bristol-Myers Squibb Company. Full prescribing information for iberdomide will be posted on Drugs@FDA.

Efficacy was evaluated in EXCALIBER-RRMM (NCT04975997), a two-stage, randomized, multicenter, open-label trial in adults with relapsed or refractory multiple myeloma (RRMM) who had previously received one or two prior lines of therapy. Patients who had disease refractory to prior anti-CD38 monoclonal antibody therapy, or to prior bortezomib were excluded.

A total of 939 patients were randomized to one of three dose levels of iberdomide in combination with daratumumab and hyaluronidase-fihj and dexamethasone (IberDd) or to daratumumab and hyaluronidase-fihj, bortezomib and dexamethasone (DVd) in stage 1 (n=279); or to iberdomide 1 mg in combination with daratumumab and hyaluronidase-fihj and dexamethasone (Dd) or DVd in stage 2 (n=660).

The major efficacy outcome measure was minimal residual disease (MRD)-negative complete response (CR) at any time. The primary efficacy population included the first 420 patients randomized to iberdomide 1 mg in combination with Dd (n=207) or the comparator DVd arm (n=213) across stages 1 and stage 2. The MRD- negative CR rate at any time was 41% (95% CI: 34, 48) in the IberDd arm and 21% (95% CI: 15, 27) in the DVd arm (p-value <0.0001).

The prescribing information includes a boxed warning for embryo-fetal toxicity and serious venous and arterial thromboembolism, as well as warnings and precautions for neutropenia, infections, and secondary primary malignancies. Because of the risk of embryo-fetal toxicity, iberdomide is available only through a restricted distribution program called ZENBEXUS Risk Evaluation and Mitigation Strategy.

This review was conducted under Project Orbis, an initiative of the FDA Oncology Center of Excellence. Project Orbis provides a framework for concurrent submission and review of oncology drugs among international partners. For this review, FDA collaborated with Switzerland's Swissmedic.

FDA advisory committee to vote on GRAIL's multi-cancer detection test, Galleri

FDA announced a forthcoming hybrid meeting of the Molecular and Clinical Genetics Panel of the Medical Devices Advisory Committee on Sept. 23 to discuss, make recommendations, and vote on information regarding the premarket approval application for the Galleri test sponsored by GRAIL, Inc.

The Galleri test is a prescription-only qualitative, next-generation sequencing-based in vitro diagnostic test intended to detect cancer-specific methylation patterns in cell-free DNA isolated from peripheral whole blood. The Galleri test is intended for screening for the early detection of multiple types of cancer in adults aged 50 years or older. The test is also intended to predict where a detected cancer signal may have originated in the body and should be followed by a diagnostic workup by a qualified health care professional.

The FDA is establishing a docket (FDA-2026-N-8004) for public comment on this meeting. The docket will close on Sept. 16 at 11:59 ET. The electronic filing system will accept comments. Late, untimely filed comments will not be considered.

In the event that the meeting is cancelled, the FDA will continue to evaluate any relevant applications or information, and consider any comments submitted to the docket, as appropriate.

FDA approves companion diagnostic supporting patients with advanced melanoma

FDA approved Labcorp's PGDx elio tissue complete CDx as a companion diagnostic to help identify patients with advanced melanoma with certain BRAF variants who may benefit from treatment with FDA-approved targeted therapies.

Targeted therapies are an important treatment option for patients with advanced melanoma whose tumors have a BRAF alteration. As a companion diagnostic, PGDx elio tissue complete CDx helps clinicians identify which melanoma patients carry these BRAF V600E/K variants and may benefit from treatment with FDA-approved BRAF inhibitors and BRAF/MEK inhibitor combination regimens.

As a kit-based solution, the companion diagnostic can be implemented directly within hospitals and health systems, expanding access to testing while enabling organizations to retain samples and data that may inform future clinical research.