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CANCERWORLD

THE LIFE JOURNEY OF

Giuseppe Curigliano

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NOT FOR SALE

CancerWorld *is a platform for telling human stories that unfold across science, politics, and society, going beyond the investigation of cancer biology and therapy.*

In our October 2025 issue, we open with one of two cover stories: the profile of **Prof. Giuseppe Curigliano**, *soon to become President of ESMO, whose journey from Rome to Milan to global leadership, from pioneering early-phase trials to shaping international breast cancer practice and nurturing a new generation of oncologists, tells a story of science, courage, and mentorship.*

The second cover story features **Prof. Fedro Peccatori**, *whose career has been defined by transitions, from fertility preservation to treating cancer in pregnancy to advocating for adolescents and young adults. His work reminds us that oncology is as much about listening and humanity as it is about science and medicine.*

We also bring a powerful profile of **Dr. Felicia Marie Knaul**, *who sheds light on the inequities women in low- and middle-income countries continue to face in accessing cancer prevention, diagnosis, and treatment. The daughter of a Holocaust survivor and a cancer patient herself, Dr. Knaul has built a career of advocacy rooted in lived experience, shaping health systems, and advancing the principle that cancer outcomes should not depend on geography, gender, or income.*

Scientific knowledge runs strongly through this issue. We examine how **artificial sweeteners may interfere with immunotherapy**, *urging us to reconsider even the most ordinary elements of modern life. We also report on new evidence that respiratory infections such as* **influenza and COVID-19 can awaken dormant breast cancer cells in the lungs**, *with implications for prevention and survivorship.*

We feature a compelling profile of **Prof. Paul Mischel**, *which not only explores his groundbreaking research on extra-chromosomal DNA but also reveals the life and person behind the science.*

We turn to the **social dimensions of cancer care**. *A report from sub-Saharan Africa shows how initiatives like* **Hope & Courage International** *are helping families overcome one of the biggest barriers to treatment for children with cancer: the sheer distance to hospitals.*

At the same time, we explore how **AI is reshaping radiology**. *Once predicted to replace radiologists entirely, AI is instead finding its role as an indispensable assistant, supporting diagnostics, streamlining workflows, and raising new questions about trust, training, and integration into daily practice.*

We also highlight two additional perspectives: **Dr. Jovana Mijucic** *on the challenge of transforming social media from a source of misinformation into a tool of truth for oncology patients, and* **Dr. Christos Tsagkaris** *on why musculoskeletal health, mobility, strength, and independence must be seen as integral to the cancer journey.*

Finally, we acknowledge the immense pressures faced by those on the frontlines of cancer care. **Burnout** *among oncologists and healthcare providers is not a private matter; it affects the quality of care, the sustainability of health systems, and ultimately the well-being of patients.*

The stories in this issue underline a simple truth: cancer care is about more than medicine. It is about connecting science with compassion, and innovation with fairness. Progress depends not only on the next breakthrough, but on how we bring that breakthrough into real lives.

Adriana Albini, Co-Editor-In-Chief, CancerWorld

From Rome to Milan to ESMO's presidency — a story of science, courage, and mentorship.

THE LIFE JOURNEY OF
GIUSEPPE CURIGLIANO

FROM BECOMING AN EXPERT TO MAKING EXPERTS

By Amalya Sargsyan

I am in Yerevan. Giuseppe Curigliano is in Milan, just back from Asia.

"JSMO, CSCO, Korea, Japan, China..." he sighs, then laughs.

"Too much travel?" I ask.

"Traveling all over the world is not easy," he replies, his voice warm, quick, full of energy. "But this is what we love about our job. And now we need to be ready for ESMO."

And just like that, the interview slips into something else, not questions and answers, but a story. He begins to rewind his life for me: a student in Rome, searching for opportunity; a young Italian doctor stepping into a specialty that hardly existed; and, years later, preparing to lead one of the largest oncology societies in the world.

Rome: Where it All Started

"I didn't grow up dreaming of being an oncologist," he begins. "But already in the first or second year of medical school, I felt something. Oncology patients were different — their needs were unmet, their suffering was greater. And at that moment, Italy had just opened its first School of Medical Oncology. That was 1980s Italy. For me, it was an opportunity." He recalls those years with clarity.

"I went to **Catholic University in Rome, Policlinico Gemelli**, because it offered a college where you could live without paying, and you had free access to studies. That was the only way I could continue."

He pauses. "Every step of my life came because there was an opportunity — and I tried never to miss it."

His thesis was on colorectal cancer, studying the role of p53. "I remember very well — I did everything myself: cutting sections, performing immunohistochemistry, quantifying the expression. It was hard, but it gave me what I needed most — methodology. And methodology is everything. You learn to create a hypothesis, test it, and accept the result. That mindset later makes you both safe and creative in the clinic."

Charleston & New York: The World Opens

"After Rome, I wanted to see more. My first stop was the USA, Charleston, South Carolina, in 1991. One of the oldest American cities, full of Civil War history. But what mattered to me was the lab. I was working with flow cytometry, analyzing urine from patients with bladder cancer. In a way, it was an early liquid biopsy."

It was his mentor in Charleston, Mariano Lavia, who encouraged him to go further. "'You should go to a larger lab,' he told me. And he called a friend in New York. That friend was I. **Bernard Weinstein** at Columbia University. Weinstein was a giant. He was the first one to introduce the concept of oncogene addiction."

New York became a turning point. "Brooklyn was full of Italians, so I lived there and traveled every day by subway to Columbia. Giuliani had just become mayor, the city was completely different — clean, vibrant, like a diamond. And Columbia... it was science at the highest level."

He smiles as he remembers. "In Weinstein's lab, I worked on bladder cancer, studying DNA adducts of 4-aminobiphenyl. That became my first publication, in Carcinogenesis. We literally mailed the manuscript by post. There was no internet. America Online had just appeared. Imagine that world..."

And then, more seriously:

"As a postdoc in New York, I earned five times what you could earn in Italy. For a young man, just starting a career, that was life-changing. It gave me the freedom to focus only on science."

Back to Italy: Liquid Biopsy Before its Time

"After New York, I came back to Rome," he says, his voice slowing as if rewinding the film of his life. "I set up in a lab with Giovanna Flamini and Achille Cittadini. And there we started something that, at that time, seemed almost impossible."

They began isolating tumor DNA from body fluids.

"Urine for bladder cancer, stool for colorectal, bronchoalveolar lavage for lung cancer. We had no NGS, no commercial kits. Everything was manual — DNA isolation by hand, gels to prove it was there."

He smiles. "But we published three papers. And we had guidance from Bert Vogelstein's group at Johns Hopkins. It was before anyone even used the term 'liquid biopsy.' We didn't know it, but we were already doing it. It was pioneering. It was beautiful science."

And then his face grows serious. "But you know, in Italy in the 1990s, there was something you couldn't avoid — military service. It was mandatory. And that is what came next."

Milan: Estiny Knocks

"They sent me to the Air Force, in a base close to Milan," he recalls. "I had no choice. But destiny was kind. Because at that very moment, a new institution had just been created in Milan — the European Institute of Oncology, founded by Umberto Veronesi. And the head of medical oncology there was Aron Goldhirsch."

He laughs as he tells the story. "I applied to meet him. But when I arrived, another doctor tried to do the interview instead. I said: 'No, I applied for Goldhirsch. I will wait.' It was strange, maybe rude — but it worked. Aron accepted me. He offered me a very small salary, and he told me: 'You can work with me, but only in the clinic. No more lab.' And I said yes immediately."

That choice — to move into the clinic — was decisive. But it also came with a personal crossroad. "At that time, my wife — well, she was not yet my wife — was already working in Rome. She had a secure, permanent position as an intensive care physician. And I had to choose: do I go back to Rome, where she was safe? Or do we take the risk of Milan, where nothing was guaranteed?"

He stops, his voice softening. "She chose to leave her job and come with me to Milan. That was courage. Without her, nothing would have been possible. **Twice I was lucky in my life — once in my career, and once in my love.**"

Prof. Curigliano with his wife, Maria Grazia Calabrò, head of the Cardiac Surgery Intensive Care Unit at San Raffaele Hospital in Milan

Early-Phase Medicine, Italian Style

"Looking back, I realize everything in my career came down to choices, chances, and the people around me," Curigliano says. "At IEO, I was lucky to work with Filippo de Braud. He was incredibly creative. He was the first in Italy to use gefitinib in EGFR-mutant lung cancer, the first to use cetuximab in head and neck and colorectal cancer, and the first to try trastuzumab not only as an antibody but as a radioconjugate, working together with Giovanni Paganelli, another genius of nuclear medicine. This was 1998 — they were already doing radioligand therapy, precision medicine before it even had a name."

His own first trial with Filippo was ET-743 (trabectedin).

"I still remember completing something like 7,000 CRFs by hand. I was the second author on that JCO paper, with Nicoletta Colombo as first. We took the drug from Phase I, to Phase II, to Phase III, in ovarian cancer. For me, it was the first time I saw the whole journey of a molecule — from a new idea in a Phase I unit to a published late-phase study."

And what stayed with him was the sense of community.

"At that time, only a handful of people in Europe were doing Phase I studies — Franco Cavalli and Cristiana Sessa in Lugano, Jean-Jacques Armand at Gustave Roussy. We were very few, but we were connected. And in the US, I had the chance to collaborate with Pat LoRusso in Detroit. It was a small world of pioneers."

He pauses, then adds quietly:

"You realize quickly that science is not just data. It is trust, mentorship, and friendship. That is how you grow."

Breast Cancer and the Art of Asking the Right Question

"Those years with Filippo and the early-phase community taught me how a drug is born. It was invaluable. But at some point, you understand that you need to narrow your focus. You cannot do everything. You need to go deeper into one disease."

And that is when **Aron Goldhirsch** returned to the center of his story. "Aron was already a leader in breast cancer." Working with Aron gave me the chance to ask different questions. Not only about new drugs, but about how to best use the therapies we already have."

He remembers one of the first.

"I was thinking whether all HER2-positive tumors need the same treatment. What about the small ones — less than one centimeter? What we showed was that maybe, for these very small tumors, you could consider de-escalation," he says.

"I remember very well, when I did that study I moved for several months to the **Dana-Farber Cancer Institute**, where **Eric Winer** was leading the service. I presented my data, he looked at it and said:

"This deserves a trial."

Sara Tolaney designed what became the APT study. And today, short-course paclitaxel with trastuzumab is the standard for small HER2-positive tumors.

He smiles at the memory. **"That's how things are connected. You start with a retrospective analysis in Italy. You bring it to Boston. A trial is born, and practice changes worldwide. All from one question."**

Prof. Curigliano with Prof. Humaid Al-Shamsi, President of Emirates Oncology Society

Leadership and Responsibility

"I continued my training at the **European Institute of Oncology**. I went from assistant, to vice director, and finally to co-director of Aron's division. Those years were full of energy. We were working side by side, managing patients, building clinical research, and shaping the future of the department. For me, it was a time of growth."

He pauses. *"Working with Aron gave me discipline and vision. But there is always a moment in your career when you feel the need for independence — when you must take responsibility for your own direction."*

That independence came gradually, through international work. "During those years, I became more and more involved in St. Gallen, which was, and still is, the most important meeting on early breast cancer. At first, I was just helping — analyzing, preparing, learning. And then came the turning point. When Aron and Richard Gelber decided to step away, the committee asked me to take on the role of scientific chair. I was only 42."

"Suddenly, I was no longer the junior collaborator — I was the one who had to lead."

He smiles at the memory, half with pride, half with awe. "To organize **St. Gallen** meant bringing the very best people together, building consensus, making recommendations that would shape practice worldwide. It was daunting, yes. But it was also the turning point when I understood that I was ready to stand on my own."

The Power of Peers

He leans back, a smile spreading across his face as if a scene from long ago has returned. "I remember in 2002 or 2003, we were in Romania, at a very small meeting. There were legendary leaders **Edith Perez and Martine Piccart** — and then a group of very young doctors presenting cases.". There were four of us, very young then: **Fabrice André, Javier Cortés, Nick Turner**, and me. "

He smiles. "Now, twenty years later, Fabrice has been ESMO President, Javier and Nick are international leaders, and I will also soon be president of ESMO. You see how these paths cross, how the young doctors presenting cases in a small meeting become the ones leading global oncology." He calls it "a career of intersections."

"In life, you meet people who shape you. Some inspire, some push you to be better.

Working alongside colleagues like Fabrice or Javier, and Nick — who I honestly believe are even better than me — gave me energy. You learn from their ideas, and you try to improve yourself."

He reflects quietly. "That is the essence of science: the exchange of ideas. Learning from people who see something you don't. That is what moves us forward."

Becoming a Professor, Becoming a Mentor

In 2014, Curigliano was appointed **professor at the University of Milan**. "That was another turning point," he says. *"When you move into an academic leadership role, your perspective changes. It's no longer only about your own career — it's about the people who are starting theirs."*

He leans forward, speaking with quiet conviction. "When you become a leader, you must understand: your real job is to work for other people. To build the careers of those younger than you. To support them, sponsor them, protect their dreams."

He names them one by one: **Paolo Tarantino, Dario Trapani, Antonio Marra, Paola Zagami, Stefania Morganti,** and many more. *"They came as residents, and now they are making their own mark globally. That is what matters most to me — to give them what I didn't have, to see them go further than I could."*

And then, almost tenderly:

"Some of them, I see like children. My wife and I don't have children, but I feel this same responsibility toward my mentees — to help them grow, to make sure they have the opportunities they deserve. That is the real legacy."

Prof. Curigliano and his mentees, ESMO Congress 2024, Barcelona, Spain

He laughs suddenly, remembering a moment from the ESMO elections.

"At ASCO in Chicago, OncoDaily organized a party. They made a poster with my picture — I didn't even know about it. I wasn't there. But suddenly my phone kept buzzing with messages from my fellows. They were taking pictures with the poster, sending them to me: 'Professor, look, it's you!'"

He shakes his head, smiling. "For them, it was joy, pride. And for me, that was worth more than any election. To feel their excitement, their belief — that was the real victory."

Milan Today, ESMO Tomorrow

Now, settled in Milan with his wife, he reflects on the road ahead. "Milan has transformed. It is one of the great cancer hubs of Europe, with thousands of patients. For oncology, scale matters. That is why I stayed here."

As he prepares to lead ESMO, his voice softens.

"The true engine of oncology is not the senior professor giving the keynote. It is the young doctor finishing a CRF at midnight, having a better idea for the next patient. They are the future. My job is to give them the tools, the mentorship, and the belief to change the world."

He reflects on the arc of his life.

"Every stage has its role. First, to be challenged. Then to ask questions. Then, to change things. Later, to give space to support others, to let them grow, to build something that lasts."

And finally:

"Believe me," he says. "Every achievement in my life came from people around me — mentors, peers, my wife, my students. **If I am remembered, I hope it is not for my titles, but for helping others rise.**"

From a young student cutting slides in Rome to the next president of ESMO, Giuseppe Curigliano's story is proof that oncology is not built on dogma, but on questions, courage, and the will to lift others higher.

FELICIA MARIE KNAUL

A RESEARCHER SHAPED BY EXPERIENCE

By Yeva Margaryan

Hello, Dr. Knaul, it's a great honor to…

"Please, call me Felicia," she interrupted immediately, her warmth cutting through the formality.

Felicia Marie Knaul is one of the world's most influential voices in cancer care advocacy, a leader who doesn't rely on formal titles or depend on life-saving treatments from the world's top clinics to do her work. What she does rely on to inspire her work are real-life stories and lived experience: her own, her father's as a Holocaust survivor, the children from the streets of Guatemala and Colombia, the patients she meets and their families, and the professionals she has worked alongside in the health sector.

This article is about the life and advocacy of Felicia Marie Knaul, who, after overcoming immense personal challenges, now dedicates herself to helping others survive and live with dignity in the aftermath of their own battles.

I'm a Mix of Different Things…I'm All of These Things

"I'm a mix of different things," Felicia explains with a humble smile, embracing the complexity of her career. Trained in economics with a PhD from Harvard University, she is an advocate for cancer patients, a researcher, and a mother who has faced her own personal battle with cancer. "I do not usually introduce myself as 'Professor Knaul,' or 'associate of the chancellor and distinguished professor of medicine at UCLA,' or even 'president of Tómatelo a Pecho,'" she continues, "I'm all of these things together, and that gives me the chance to use evidence to help make change."

Dr. Knaul's work spans various sectors: "I've worked in both government and non-governmental organizations, and my research has always focused on making a difference through policy, whether in the public, private, and not-for-profit sectors," she says.

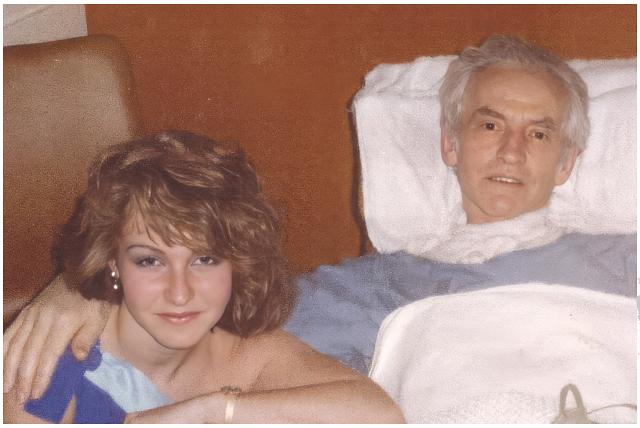
Her journey into advocacy began at a young age. Growing up with the heavy legacy of a father who survived the Holocaust, Felicia learned early on that the world could be a hostile place, particularly for marginalized communities. "I grew up with an awareness that the world can be unsafe for so many people," she reflects. "That understanding motivated me to do whatever I could to help make life safer for others, no matter their religion, faith, or ethnicity."

It was this deep sense of justice that led her to work with street children in Latin America, an undertaking that would lay the foundation for her future endeavors as a researcher and advocate focused on public health.

"It lived with us in my childhood home: the mute cry of the Holocaust that was tattooed on my father's forearm and marked my family. It was part of my upbringing. That fear had lived with me since I was a little girl of about five. Ever since the night I had woken up, crept down the stairs, and heard my father reading the stories he had written and talking with friends – also Holocaust survivors – about his experiences in the Nazi labor and concentration camps.

"When I was a small child, my cartoon-like nightmares were about Nazi witches. In these nightmares, I always tried to save my father, to rescue him from the concentration *camp, while desperately attempting not to be captured and imprisoned myself."*

From "Beauty Without the Breast" the book authored by Felicia Marie Knaul



Dr. Knaul with her father, shortly before his passing.

Those Who Shaped Me

Throughout her career, Dr. Knaul has been guided by a constellation of mentors. "There were many along the way," she notes. "My mom's life was very different from mine. She didn't have the opportunities I was fortunate to have when it came to education, but she was an unwavering force—always making it possible for me to pursue my education. Few people have shaped me as deeply as she has," she states proudly.

One of her key mentors was Amartya Sen, a Harvard University professor and Nobel laureate in economics, whose work on poverty and inequity deeply influenced her perspective on economics. "I was incredibly fortunate to have Professor Sen as my mentor at Harvard, along with several other wonderful individuals. What inspired me most was his profound vision of why and how we could address poverty and inequality, and his guidance continues to resonate with me today," she says.

Her academic journey was also shaped by Albert Berry, a professor emeritus at the University of Toronto, who convinced her that economics could be a path to make a difference, even when she initially aspired to become a doctor. "I wanted to be a doctor, but I quickly realized organic chemistry was not my strength," she laughs. "Albert helped me see that economics could also be a powerful way to drive meaningful change."

Another formative influence was the late Rabbi Dow Marmur, the senior rabbi at her synagogue in Toronto, who helped her navigate many challenges and career decisions. "Rabbi Marmur was an incredibly inspiring Jewish leader who thought about the suffering of all people, and what we can do about it. He was open, non-judgmental, encouraging, supportive, and he helped me in so many ways, especially after my father passed away from cancer, just after I turned 18," she shares.

She also speaks proudly and with a sense of loss of the women who have inspired her throughout her journey. Renata Block, a social worker who supported her and her father as he battled cancer, became a close friend and guide as she struggled to identify a pathway for herself rooted in social justice.

Felicia's work in Mexico was greatly influenced by Sor María Suárez, a nun and a leading figure in the professionalization of nursing in Mexico. "She was one of my closest friends and a huge inspiration," Felicia reflects. Our friendship began while working together to guarantee access to education for hospitalized children but evolved into two journeys with breast cancer that only Felicia would survive.

I'm an Atypical Economist… In Many Ways

Dr. Knaul doesn't fit the mold of a typical economist. For her, economics isn't primarily about mathematics or numbers; it's about people. While most economists focus on analyzing how people and countries with wealth choose to spend their money, she centers her attention on those who live without the luxury of choices. She focuses on the people who struggle daily to survive and meet basic needs, with little or no ability to make choices, because they don't have enough money to make any.

The passion driving her work is rooted in a deeply personal history. "I started my career working with street children, specifically in Guatemala," Felicia shares. "I am the child of a concentration camp survivor. My father was interned in several camps, including Auschwitz-Birkenau, from the age of 15 to 20, and my grandparents and most of my family were murdered. Almost everyone." This painful family history fueled her determination to change the world for the most vulnerable, particularly children forced into labor.

But as her career progressed, a new chapter awaited. A move to Colombia to undertake her doctoral dissertation research on street and working children marked a pivotal turning point. There, Felicia became immersed in the country's health reform efforts, a challenge that would redefine her path and lead her to focus on healthcare, eventually becoming a key advocate for cancer care. "When the health reform called Ley 100 started, and I was offered a position with the Colombian government, the equivalent of the Ministry of Finance, it was an incredible opportunity to learn, grow, and actually be part of something so impactful," she says.

For Felicia, her involvement in health reform fulfilled a deeply personal longing. "It helped satisfy my unmet desire to work in health care and make sure that people had access to health care," she admits.

The Idea That Income Determines Access is Unacceptable to Me

As she transitioned into cancer care advocacy, Felicia's approach was shaped by her strong belief in universal access to healthcare. "I simply can't accept, perhaps partly because I'm Canadian, that income should determine whether someone receives healthcare, for cancer or for any other health condition," she asserts. "I believe very fundamentally that access to high-quality healthcare and medicine is a right. The idea that survival depends on income is just unacceptable to me."

Felicia's most recent work, co-chairing The Lancet Commission on Cancer and Health Systems, has allowed her to push for structural changes in healthcare systems worldwide. "There are ways to make this possible in our world," she explains, "and with stronger and better health systems that are more thoughtful, we can get exactly what we want: more and better economic growth, with and through better access to healthcare."

Listen to Their Suffering and Act

Knaul's approach to global health is defined by a commitment to action, as well as research to generate the evidence to guide that action. "I'm probably unable to design something like a controlled experiment or a pilot initiative that doesn't involve actually stepping in and doing something," she admits. For Felicia, encountering a need in public health is a moral obligation. "When you do global health and witness suffering, you're morally obligated to act, and the research objectives may become secondary," she insists.

Her unwavering belief in action is deeply personal, shaped by the painful memory of her father's final days. Despite being in Toronto with full access to care, in 1984, Felicia was unable to secure the pain medication her father so desperately needed. "I had to request the pain medication over and over and then administer it myself the night before he passed," she recalls. "For years, I wondered: What would I have done if they hadn't given me that medication? I knew I had done the right thing, but there was also a lingering fear that I had done something wrong."

That experience became a turning point, driving her to advocate for global access to palliative care. "Even in Toronto, where there was access, I couldn't get access," she reflects. "That moment haunted me for decades and continues to shape my work."

Felicia's focus on empathy over detachment guides her approach. "What moves me is listening to people, whether it's a patient or their family," she explains. "Listening to their suffering, being with them in their homes, and watching how they cope with a dying child or a child with long-term care needs, those real-life encounters teach me far more than reading thousands of articles ever could."

Felicia not only studies the problems; she embraces lived experience and responds through action. Her commitment to global health is rooted in the belief that real change comes from more than observing, but from stepping in and making a difference.

Breast Cancer Gave Me a Voice

It was her own diagnosis with breast cancer that solidified Felicia's commitment to cancer advocacy. "Before my diagnosis, I was a researcher. I didn't walk the talk," she admits. "Afterward, I could speak with authenticity. It gave me a voice."

Choosing to receive most of her treatment in Mexico rather than the United States or Canada was an important decision, she says.

"Living the disease in Mexico publicly gave me the voice I needed to push for change," she reflects. "I knew that while I had the choice to go elsewhere for treatment, most women don't have that luxury. I wanted to demonstrate that high-quality care is available in Mexico, and that Mexican women and their families don't need to go bankrupt to access treatment. ."

Felicia's experience as a patient changed her perspective on cancer care. "Cancer isn't just about survival; it's about the long road of survivorship," she explains. "Policymakers need to understand that cancer patients are not just fighting for their lives, they are fighting for the opportunity to live their lives to the fullest and to thrive." Felicia, advocacy means building a system that supports patients through every stage of their journey, from diagnosis to long-term care.

Dr. Knaul with her daughter, Mariana, while undergoing treatment.

Her journey through cancer not only shaped her professional mission but also led her to a deeper, more empowered self-awareness.

"In my mirror, I see a stronger woman than the one I used to see." "And I like the woman reflected in that mirror," I added to myself, without uttering the words out loud. "I like myself, more than I did before the cancer.

From the "Beauty Without the Breast" book authored by Felicia Knaul

Dr. Knaul in Miami, July 2022, before her mastectomy.

A Triumph of Advocacy and Lasting Impact

When asked about a moment in her career she considers a personal and professional triumph, Dr. Knaul said proudly: "One of my most significant triumphs came with the founding of an NGO in Mexico, which continues to operate successfully today. **Tómatelo a Pecho**, AC was officially founded in 2011, but began its work on breast cancer in 2008. To have been able to establish and lead an organization that matches research with advocacy and policy is a truly special combination. It's small but mighty, providing us the chance to project our research into tangible change."

Her passion for making lasting, systemic changes is evident in her pride over another major initiative: the **Sigamos Aprendiendo en el Hospital** program. Felicia helped establish schools in every tertiary hospital in Mexico, ensuring that children undergoing treatment, including cancer patients, had access to education. "We were able to legally guarantee children in hospitals the right to education, including those battling cancer, burns, organ transplants and others," she says. "It still continues today, and I'm incredibly proud to see it entrenched in the Mexican health and education systems."

Two books she authored, *Closing the Cancer Divide and Beauty* Without the Breast, also stand as pillars of her career. "When I look at those books, I see more than just words on pages," she reflects. "That's actually an enduring legacy."

Looking ahead, Felicia is focused on two critical global health initiatives in her work on cancer control: reducing violence against women that exacerbates cancer outcomes and developing an *economics of hope* framework, which would demonstrate the broader benefits of investing in cancer care systems. She firmly believes that improving and extending cancer care will save lives and also boost the economy by keeping people out of poverty and ensuring they live long and healthy lives.

She also advocates for a more integrated approach to health advocacy. "We need to stop thinking about health in silos," she insists. "If we advocate for breast cancer, we should be advocating for women's health as a whole. Cancer is just one piece of the puzzle."
Felicia's legacy will undoubtedly leave a lasting impact on the world of public health, but it is her

Dr. Knaul with her husband, Chancellor Julio Frenk during her breast cancer treatment.

deep empathy for patients and her relentless drive to bring about change that sets her apart as a trailblazer in cancer care.

As the conversation winds down, Felicia reflects on the impact of her work. "We need to create a world where health is a right, not a privilege," she concludes. "If we can break down the barriers and globalize healthcare markets, we'll be able to drive down costs and improve access for all."

Blitz Round: Who is Felicia Knaul?

Personal Motto or Quote You Live By?

There are many, but one I live by is by Elie Wiesel: 'In the face of suffering, one has no right to turn away, not to see.' That's what drives me every day.

Favorite City?

Paris or Lisbon. But the place that has truly wowed me is Guatemala, particularly the more remote regions.

Most Used App on Your Phone?

Sadly, it's probably WhatsApp. It's much faster than texting or anything else.

Favorite Book and Movie?

'Born Free' is my favorite movie. It might surprise you, but it's a classic about freedom and life. As for books, I'm fascinated by 'The Covenant of Water' and 'Cutting for Stone.'

Best Piece of Advice You Ever Received?

If I am not for myself, who will be for me? If I am only for myself, what am I? And if not now, when? A quote from Abba Hillel.

One Thing People Would Be Surprised to Learn About You?

I love to crochet and do needlework, though I don't have much time for it these days. And, I also horseback ride!

Comfort Food?

I don't have just one comfort food, but I do love fruit, muffins, coffee, sometimes popcorn. And yes, sadly, I adore red meat, especially bison.

Most inspiring person you've met in oncology?

Mary Gospodarowicz, former Medical Director at the Princess Margaret Cancer Centre in Canada, Julie Gralow, the Chief Medical Officer at the American Society of Clinical Oncology (ASCO), and Carlos Rodriguez-Galindo, the Executive Vice President, Chair of the Department of Global Pediatric Medicine, and Director of St. Jude Global at St. Jude Children's Research Hospital.

If a Biography Were Written About Your Life, What Would the Title Be?

A Wandering Jew. Or maybe, 'The Wondering Jew.'

Artificial Sweetener Reduces Response to Immunotherapy

By Janet Fricker

Could artificial sweeteners undo the benefits of immunotherapy? A study published in Cancer Discovery, July 30, found that melanoma and non-small cell lung cancer (NSCLC) patients who consume high levels of the artificial sweetener sucralose have worse responses to immunotherapy than those whose diets are low in sucralose. In mouse studies, the investigators showed that supplements boosting levels of the amino acid arginine can prevent the negative effects of sucralose.

"It's easy to say, 'Stop drinking diet soda,' but when patients are being treated for cancer, they are already dealing with enough, so asking them to drastically alter their diet may not be realistic," says lead author Abby Overacre, from the Department of Immunology at the University of Pittsburgh and UPMC Hillman Cancer Center, Pennsylvania. "We need to meet patients where they are. That's why it's so exciting that arginine supplementation could be a simple approach to counteract the negative effects of sucralose on immunotherapy."

While immunotherapy has shown remarkable success in various cancers, a significant percentage of patients do not respond to treatment, a finding that has stimulated research into contributory factors. Recently, the gut microbiome has emerged as a tumour-extrinsic regulator of response to immunotherapies (including checkpoint inhibitors and CAR T cell therapy). After a study published in Nature in 2023 showed that mice fed high levels of sucralose experienced lower T cell responses, attention shifted to artificial sweeteners. "We already knew artificial sweeteners shift the microbiome in a negative way and that the gut microbiome is critically important for immunotherapy responses. So, we decided to bring these ideas together and explore for the first time whether artificial sweeteners can influence immune therapy," Overacre tells Cancerworld.

For the study, the team focused on sucralose, their reasoning being that out of the six non-sugar sweeteners approved by the FDA, sucralose is by far the most commonly used. Sucralose, made by replacing 3 hydroxyl (oxygen and hydrogen) groups in sucrose molecules with chloride atoms, is used in low-calorie snacks, diet drinks, chewing gum, sugar-free desserts, and protein supplements.

Mouse Model Demonstrates Link to Arginine

To explore mechanisms by which sucralose might hinder the effectiveness of immunotherapy, Overacre utilised two mouse models of cancer - MC38 (adenocarcinoma) and B16 (melanoma). First, mice in the experimental group were exposed to sucralose in their drinking water (0.09mg/mL, ~0.45mg/day, equivalent to three human packets) while control mice received normal drinking water. A few weeks later, all mice were injected with tumours and underwent three separate treatments with an antiPD1 inhibitor. Mice in the sucralose arm continued to receive sucralose throughout treatment. **Results showed that 40% of mice who received sucralose were able to clear their tumours, versus 80% of mice in the control group who did not receive sucralose. Furthermore, flow cytometry and single cell RNA sequencing revealed significant reductions in the number of T cells infiltrating the tumours of mice receiving sucralose.**

To explore the effect of sucralose on the microbiome, the team performed 'shallow shotgun sequencing' of mouse stools to provide compositional and functional sequencing of the microbiome. Results showed that mice who consumed sucralose had relative outgrowth of gram-positive bacteria, including Clostridiaceae and Lachnospiraceae, and also had high levels of the arginase enzyme (which breaks down the amino acid arginine) and low levels of arginine. "These data would suggest that ICI [immune checkpoint inhibitor] resistance after sucralose consumption is possibly due to phenotypic or functional shifts in the gut microbiota and is associated with an outgrowth of gram-positive bacteria," write the authors.

Strikingly, mice that did not consume sucralose but received faecal transplants from sucralose-fed mice developed resistance to immunotherapy. Conversely, restoring a healthy microbiome through faecal transplants from ICI-responsive mice rescued treatment response, even in the presence of sucralose. "What this showed us was that the sucralose-driven microbiome changes were sufficient to drive immunotherapy resistance," explains Overacre.

Finally, the team showed that supplementing the diet with arginine or citrulline (a precursor of arginine) was sufficient to restore arginine levels and reverse T cell dysfunction, thereby improving immunotherapy response in animal models. "So, it appears that sucralose consumption shifts the gut microbiome in a way that leads to reduced arginine levels, which in turn appears to be critically important for T cell function, the immune cells harnessed by immunotherapy to kill tumours," explains Overacre.

Human Dietary Studies Reveal a Negative Impact on Immunotherapy

In an entirely separate project, Diwakar Davar, from the University of Pittsburgh Department of Medicine and a medical oncologist at UPMC Hillman Cancer Center, had already been administering dietary questionnaires to cancer patients undergoing immunotherapy. "We had been exploring the simple question of whether patients who eat well do better," explains Davar. Since the semiquantitative Diet History Questionnaire III (DHQ III) food frequency questionnaires included information about sucralose intake, the project offered the perfect opportunity for Davar and Overacre to join forces to explore the effects of sucralose in immunotherapy patients.

Davar looked at three separate cohorts of patients from the Hillman Cancer Center - 91 patients with advanced melanoma receiving anti-PD-1-based immunotherapy; 41 patients with advanced non-small cell lung cancer (NSCLC) receiving anti-PD-1-based immunotherapy or chemoimmunotherapy; and 25 patients with high-risk, resectable melanoma receiving neoadjuvant treatment with anti-PD-1 and innate agonist vidutolimod.

Bioinformatic approaches identified an optimal cutoff (defined as > 0.16 mg/kg per day), and this cutoff across all three cohorts showed that high sucralose intake was associated with worse survival compared to low intake patients (defined as <0.16mg/kg/day).

- In patients with melanoma who received anti-PD-1-based immunotherapy or chemoimmunotherapy, median progression-free survival (PFS) was 8 months with high sucralose versus 13 months with low sucralose (HR, 2.23; 95% CI, 1.03-4.84; P =0.037).

- In patients with NSCLC who received anti-PD-1-based immunotherapy or chemoimmunotherapy, median PFS was 7 months with high sucralose versus 18 months with low sucralose (HR, 2.78; 95% CI, 1.03-7.5; P =0.034).

- In melanoma patients treated with an ICI and vidutolimod, median relapse free survival (RFS) was 19 months with high sucralose versus 25 months with low sucralose (HR, 6.69; 95% CI, 1.33-33.76; P=0.012).

"Our study bolsters the growing notion that artificial non-nutritive sweeteners, even those manufactured from sugar like sucralose, are not inert and can have broad immunomodulatory effects that adversely affect patient outcomes," write the authors.

Davar was surprised by the magnitude of the effect. "Simply by avoiding something that is bad, patients were doing 40% better. This is low-hanging fruit, giving up sucralose would be comparatively easy for patients to implement, and could make an enormous difference to their outcomes," he tells Cancerworld.

Cancer Patient Diets Need to be Spoke

Oncologists, Davar believes, need to be questioning patients more carefully about their diets. "Rather than just telling patients 'To eat healthy,' we need to become more specific about exactly what they should be consuming. Cancer medicine is bespoke, so why shouldn't patients' diets also be bespoke?"

In terms of next steps, Davar and Overacre hope to initiate a clinical trial to investigate whether citrulline supplements might mitigate the immunotherapy-dampening effects of sucralose. They also want to explore the impact of other sugar substitutes (aspartame, advantame, neotame, saccharin, and acesulfame potassium) on immunotherapy.

Independent Expert Comment

Jotham Suez, a microbiologist from Johns Hopkins

Bloomberg School of Public Health (Baltimore, MD) who specialises in microbiome research, discusses the implications of the study with CancerWorld.

1. Could you comment on the overall significance of the study and what you see as the clinical importance of the findings?

This study is important because it shows us, for the first time, an unexpected connection between artificial sweeteners and the efficacy of cancer immunotherapy. We and others have shown that various artificial sweeteners can alter the human gut microbiome in a manner that increases an individual's risk of developing diabetes. Multiple research groups have reported that the microbiome plays a crucial role in the efficacy of cancer immunotherapy and that person-to-person heterogeneity in the gut microbiome composition can lead to variation in immunotherapy efficacy. This study connects the dots between these pieces of information. It nicely complements observations in patients with interventions in mice that allow the authors to establish causality between the impact of sucralose on the microbiome and cancer immunotherapy efficacy. If the same causal links occur in patients, this could provide an additional means of improving immunotherapy efficacy through dietary changes.

2. What do you see as the unanswered questions arising from the study and what further research would you like to see undertaken?

The combination of the human and mouse work makes it plausible that artificial sweeteners, and sucralose specifically, can reduce responsiveness to immunotherapy in humans. However, experiments where microbiomes from individuals with high versus no sucralose consumption are transplanted to mice would be helpful to strengthen this link and support the hypothesis that the mechanism shown in mice is also the reason for reduced immunotherapy responsiveness in humans.

Also, whether other artificial sweeteners besides sucralose have similar impacts on immunotherapy efficacy is currently unclear. Consumers of non-nutritive sweeteners often consume more than one type of sweetener, and therefore, it is difficult to isolate the contribution of a single type of sweetener. This is even more challenging when using food frequency questionnaires, which may not be sufficiently granular to identify the consumption of specific products and sweeteners they contain (e.g., specific types of diet soda). The authors did not test other types of sweeteners in their preclinical work; therefore, it is possible that the effects are not unique to sucralose, but more work is needed.

We do know from our own research that not everyone's microbiome is impacted similarly by sucralose, and some microbiomes are more ‘resistant' to its impacts. Therefore, it is unclear in what percentage of patients sucralose (or other artificial sweeteners) produces a microbiome that impairs immunotherapy efficacy.

3. What would you say to cancer patients concerned about the findings of this study?

The preclinical data are compelling, but more work is needed to determine whether the causal link between sucralose and reduced immunotherapy response is applicable in humans. Overall, this is an important first step that needs to be followed up by additional human work with larger and more diverse cohorts, with an emphasis on establishing causality in humans. Given the currently speculative evidence, but with a potential risk, patients should consult their doctors to weigh the benefits and risks. Beyond response to immunotherapy, there are already data that non-nutritive sweeteners may be detrimental to health in at least some individuals. However, excess sugar consumption is also detrimental. If patients can reduce their intake of artificial sweeteners without increasing sugar consumption, that would be the safest option.

A PLACE TO SLEEP A CHANCE TO HEAL

How Hostels and Transport Help Children Beat Cancer in Africa

By Diana Mwango

Catherine Wambugu (Katrina), Founder of Hope & Courage International

For parents of children battling cancer, finding a place to stay that is both affordable and close to the hospital is not just a convenience; it can mean the difference between life and death. Without accommodation, families are often forced into impossible decisions: endure long, costly commutes, fall into financial ruin, or abandon treatment altogether.

Childhood cancer studies done in sub-Saharan Africa reveal how common this is. In Zambia, approximately 46% of children with cancer abandon treatment; in Kenya, it's 54%, and in Malawi, 36%. A key non-medical factor is the long distance to hospitals and the inability to afford transport and accommodation.

For Bigirimana Benotte, a Burundian mother of four, the shock of her son's Ewing sarcoma diagnosis, a cancer of the bone and soft tissue, was quickly overshadowed by another fear: how to get him to Kenya, over 1,150 kilometers away, where he had a chance at survival.

"My biggest worry wasn't even the diagnosis," she says. "I had no relatives in Kenya, and I couldn't afford a hotel."

Burundi has only one public cancer hospital with no functional radiotherapy machine. After six chemotherapy sessions, her son was referred to Kenya for radiation.

It took her nine long months to raise just $155 for the journey, a modest amount, but the one barrier between her son and treatment. With that, and the promise of free accommodation, they finally travelled to Kenya for treatment, joining the many Burundians forced to seek radiotherapy and other cancer care abroad due to limited services at home.

"A doctor connected us to a hostel in Kenya for parents and their children. We stay here for free, and they provide free transport to Kenyatta University Teaching, Referral and Research Hospital, seven kilometres away," she says. "We'll be here for two months while my son completes 30 radiotherapy sessions."

Her story is not unique. I met her and others like her at **Hope & Courage International**, a hostel that offers more than shelter. It also provides a sense of community and hope to parents with children with cancer who meet monthly.

Bigirimana Benotte, a Burundian mother, whose young son is receiving treatment for Ewing sarcoma in Kenya

At 3.30pm, Bigirimana is in the kitchen washing dishes. Her son is playing chess. Some children are sprawled on the floor painting. There is also a TV room and a Zumba space.

The hostel was founded by Catherine Wambugu, a leukemia survivor, and whose son died of non-Hodgkin's lymphoma. She rents the house for $465 a month, converting it into six rooms, including three bedrooms with nine beds for the children and their caregivers.

Her goal: To help children complete their treatment

Catherine knows this burden too well.
"I used to struggle to find a place to stay when I took

my adopted son for treatment," she says. "We'd travel far, only to be told the chemo drugs were out and to return the next day. With nowhere to go, we slept on hospital benches. Sometimes, I had no money for food, just enough to come to the hospital and get back home."

She saw other mothers go through the same. "Some travelled over 500 kilometres for radiotherapy, only to find the machine broken. They'd be told to return in a week. With nowhere to go, they slept on hospital grounds during the day and on casualty benches at night," she says.

After losing her son and facing a recurrence, Catherine decided to act. "I just wanted to ease the pain, even if it's for one parent," she says.

Since June this year, she has hosted seven Burundians and several Kenyans from far-off places, about 600 kilometres to the city.

"The youngest patient I have now is a one-and-a-half-year-old baby with retinoblastoma in both eyes," she says.

But running a cancer hostel isn't easy. Catherine relies entirely on donations for rent, food, transport, and other expenses, limiting her to four to six children a month.

One case still lingers in her memory, an eight-year-old Burundian boy brought to Kenya to have a facial tumour examined. When the doctors confirmed it was cancer, his father broke down.

"He told me, 'If it's cancer, I honestly don't want the child. Even if we start treatment, where will I live?' He said the only other option was to send the boy back home to die. That's how I ended up legally adopting my son," Catherine says quietly. "He lived with me, and I'd take him for treatment until he passed away at 14."

A study done in five hospitals in sub-Saharan Africa (in Kenya, Malawi, Cameroon, Harare, Zimbabwe and Ghana), found that providing free treatment, transport, lodging, and meals significantly reduced abandonment. In Malawi, abandonment among Wilms tumour patients dropped to just 7%, with full support. In Brazil, it dropped from 16% to 0.5%.

Dr Festus Njuguna, the Head of Paediatric haemato-oncology unit at Moi Teaching and Referral Hospital, which treats children from Western Kenya, Uganda, South Sudan, Tanzania, and Democratic Republic of Congo, said **survivorship of childhood cancer in Africa remains low, just 20% to 30%, compared with 80% in high-income countries.**

"To prevent abandonment, LMICs need better access to insurance, transport, financial aid, and parental education," he says. "The good news is, survival is improving. For example, acute lymphoblastic leukemia survival has risen from 19% to 32%, and Wilms tumour from 40% to 60% [success rates that he attributes to many factors, including access to insurance]."

He says the hospital partners with Living Room in Eldoret, which provides shelter for the children and their caregivers. "For the past four years, we've covered their transport costs through donor funding, and it has helped," he adds.

The good news is that more people are stepping in to help. In August, Childhood Cancer International announced plans to build or fund housing in six countries, Ethiopia, Kenya, Mexico, Nepal, Peru, and Ukraine, to fight treatment abandonment.

"We are confident these six projects will combat abandonment and help achieve the WHO's goal of 60% survival by 2030," the organisation said.

In Uganda, New Hope Hostel in Kawempe has, for over seven years, provided shelter for children with cancer and their caregivers who travel from remote areas to Kampala. The need is overwhelming and financially demanding. With only 30 beds, it is sometimes forced to turn families away.

Catherine believes more hostels like hers could be game-changers. "Without support, Bigirimana might have had to choose between her four other children and her sick son," she says.

How AI is Assisting, Not Replacing Radiologists

By Sophie Fessl

Nine years ago, one of the leading artificial intelligence scientists, Geoffrey Hinton, made a startling prediction: **"We should stop training radiologists now."** He believed that within five years, machines would outperform humans at reading medical images. Nearly a decade later, radiologists are not only still here, they're proving why their role is more essential than ever.

"This perspective was too simplistic", Prof. Daniel Truhn, the radiologist and developer of AI solutions for clinical routine, working at RWTH Aachen University in Germany, says. "The clinical reality of radiologists is obviously a lot more complex than just looking at images and making diagnostic yes-no decisions. In complex situations, AI is far from replacing radiologists."

Excelling in 2D, Struggling in 3D

Truhn points to mammography as the one area where AI is beginning to match radiologists. The reasons are clear. First, the field benefits from enormous datasets: millions of images gathered through national screening programs were used to train AI models. Second, mammograms are produced under strict quality standards, which means the images are highly consistent and directly comparable. And third, the data is two-dimensional (2D), the format that AI systems have been trained to classify for over a decade and handle best.

In Sweden, where mammograms are double-checked by two radiologists, researchers tried an experiment: what if one of those human experts were swapped for AI? The result: the machine held its own. "Indeed, in this setting, AI can replace one radiologist", Truhn comments. "But this is currently the only case in which AI can replace radiologists in high-volume studies – and it is only one part of our job." Currently, AI is mainly used to support radiologists, for example by suggesting findings – such as indicating fractures -, prioritizing urgent examinations to make workflows more efficient, or enhancing report texts.

By contrast, AI still struggles with complex 3D studies such as CT or MRI, where every slice must be integrated into a full volumetric view, Truhn adds. "Here, AI is good at routine tasks that require little cognitive work – like indicating and measuring angles in images or measuring lesion volume in brain MRI."

Reimbursement, Reliability, and Trust

Most models haven't made it into broad clinical use, Truhn observes. One barrier is reimbursement. "AI is only effective for radiologists if it actually saves us time, which has not yet been reliably demonstrated – and initially, implementing models costs money. There is no standardized system in place to claim reimbursement of costs; such a system is still under development."

Another barrier lies in the models' narrow focus. Most AI models are specialists in answering one particular question – while radiologists carry out a range of diagnostics to answer different questions. "It is of little use if, out of 1,000 reports, AI can only handle 23. These are still individual solutions that cannot yet be integrated into workflows on a larger scale." Truhn envisions the future of radiology in "app stores" for clinical AI solutions – building on existing platforms, but advancing them into widely accessible and seamlessly integrated tools within PACS systems.

But Truhn wants to take AI even further: In his start-up Synagen, he is developing so-called agent-based systems for oncology, capable of carrying out multiple-step processes. "Oncology is a complex field, no one expert can have an overview of all guidelines and updates in all fields." Instead of simply reviewing an image once and providing a single report, such systems would combine imaging findings with clinical guidelines and additional patient information. "Because decision-making requires the integration of imaging, genetic profiles, and histopathology, we need agent-based systems to replicate such multi-step reasoning."

His wish for AI? "AI models should feel like always having an experienced colleague by our side, to discuss our decisions and consult with – thereby increasing diagnostic accuracy."

However, the AI expert still sees hurdles in achieving this ideal. The "black box" nature of AI poses a major challenge. "An AI-generated report must be transparent enough that the radiologist can confirm it and build trust in its accuracy", Truhn postulates. "For example, in fracture detection, the system is able to highlight the fracture, allowing the radiologist to visually verify the finding: the AI indicates a fracture, the radiologist checks the image, and indeed, the fracture is there."

While this works relatively well in such straightforward cases, interpretability can be a challenge in complex situations. "This lack of transparency is a key barrier for radiologists to trust such models. AI must first demonstrate that it can deliver reliable predictions and, critically, provide ways for those predictions to be verified."

Trust also has another side: the risk of relying on AI too readily and uncritically. So-called "AI automation bias" has already been demonstrated. "A study showed that radiologists can get used to AI being right when the model initially delivers correct results. When incorrect results show up, the bias is to still trust the AI", Truhn reports. "That's why it's critical to make sure that any AI model we use is at least as accurate as the radiologist themselves."

Training Radiologists in the Age of AI

One major challenge Truhn foresees is training the next generation of radiologists. Early training typically involves repetitive tasks and grappling with complexity—working through the "valley of tears," where much must be learned and much remains unclear. "If an AI model is available at the workstation from day one, and already outperforms what a beginner can achieve in the first weeks, there is a real risk that trainees will not develop the necessary skills themselves."

Introducing AI only later in training may be one solution. "We may need to restructure training programs so that trainees first work independently, with AI acting as a second reader rather than a crutch."

For experienced radiologists, the key will be to build practical familiarity with the models, Truhn adds. "Much like the way many users have grown accustomed to ChatGPT—initially mysterious, but gradually better understood by just regularly working with it—radiologists will learn the strengths and limitations of AI by using it. While training courses are available, expert knowledge about the potential and the limits can only be gained by using AI models."

How the future of AI in radiology unfolds depends on the pace at which AI develops. "If progress continues at the speed we have seen over the past two years, then in ten years a large share of professions could be replaced," Truhn is certain. "The key question is whether this exponential growth will truly continue. It may not. But at the very least, we can expect AI models to become our reliable, ubiquitous colleagues in radiology."

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CANCERWORLD

Between Science and the Human Heart

FEDRO
PECCATORI

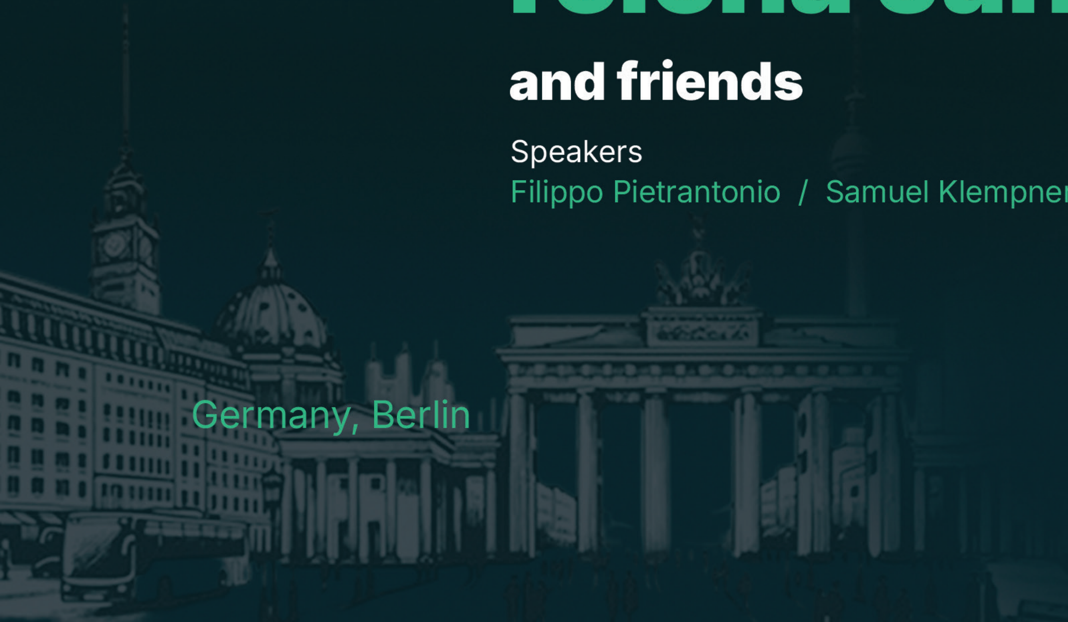
OncoDaily Grand Rounds
at ESMO

GI Edition with

Yelena Janjigian

and friends

Speakers
Filippo Pietrantonio / Samuel Klempner / Elena Elimova



Germany, Berlin

When I first connected with Professor **Fedro Peccatori**, the line between us was anything but fixed: he was calling from a moving train between Padova to Milan, between obligations. Yet the instability of the connection seemed fitting. His entire career has been about navigating transitions—between disciplines, between life and illness, between science and humanity.

Peccatori, now a globally respected oncologist and educator, insists he never planned it this way.

"I always wanted to be a doctor," he tells me, "but oncology came serendipitously."

FEDRO PECCATORI

BETWEEN SCIENCE AND THE HUMAN HEART

By Amalya Sargsyan

Building a Career of Crossroads

He was training in gynecology in Milan, than in Monza in the late 1980s when a visit to Bellinzona placed him in the orbit of **Franco Cavalli** and **Cristiana Sessa**. *"They had the intuition,"* he recalls. *"All the specialists around one table, each case considered in its whole context. Even the nurses spoke first sometimes—they knew the patient's social story."* Decades before tumor boards became routine, Peccatori witnessed the embryo of multidisciplinary care: **oncology not as a solo sport, but as an orchestra**. It changed the scale of his thinking.

After completing his degree at the University of Milan in 1988, Peccatori deepened his training with a PhD at Sapienza University in Rome. He spent research years in the Netherlands, where, as he recalls, *"the cultural differences were not dramatic, but the scientific approach was. It taught me how to ask questions differently."* As a young fellow at the Mario Negri Institute under **Silvio Garattini**, he had already gained a grounding in research that would shape the rest of his career.

Back in Milan, at the **Istituto Nazionale dei Tumori (INT)**, he walked straight into the hardest questions of that era: high-dose chemotherapy in breast cancer that looked promising until the data said otherwise. "INT was the best place to test and to stop," he says. That small verb—*stop*—says much about his method. For Peccatori, rigor is as much about restraint as it is about invention.

By 1995, he crossed town to the **Istituto Europeo di Oncologia (IEO)** where he would truly build his legacy. It was there that his clinical focus on **fertility, pregnancy, and young adults** began to crystallize. *"It was something new, something deeply tied to patients' futures," he explains.*

A Future Patients Could Still Claim

In the 1990s, few spoke about fertility after cancer. For men, sperm banking was known and available. For women, options were complicated and rarely discussed and often introduced too late. Peccatori and his colleagues began to make fertility preservation part of oncology, not an afterthought.

"For many young women, fertility preservation wasn't about a child immediately," he says. "It was about a future they could still name."

Since 2011, Peccatori has led the Fertility and Procreation in Oncology Unit at IEO in Milan, turning what was once a fragile hope into an integral part of cancer care.

Cancer in Pregnancy

Perhaps the next big step in his career, maybe the most delicate one came when he and his team began treating **cancer in pregnancy**. For decades, the default response had been termination.

"We didn't know what was possible," he said. "Could we do surgery safely? Could we give chemotherapy without harming the baby?"

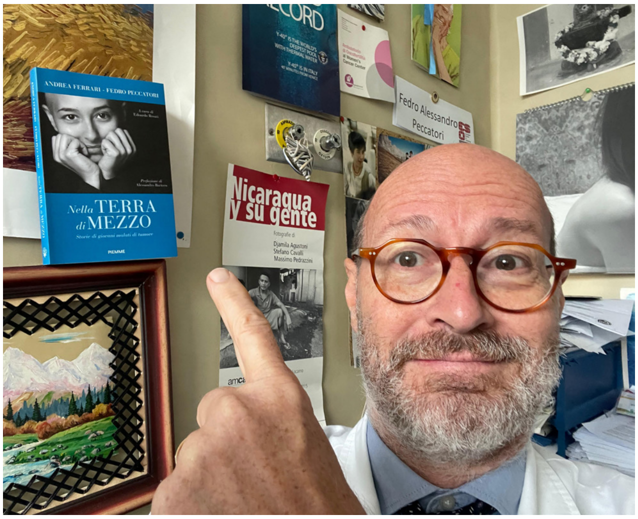
He remembers a 36-year-old pregnant woman with neuroblastoma, a tumor almost never seen by adult oncologists. "Everyone came," he says simply. "Pediatric oncologists, obstetricians, pathologists. We asked: *how many weeks can we safely give her? How do we balance the mother and the child?* The solution was not a miracle so much as choreography: buy weeks safely, monitor closely, match tempo to biology and gestation. "The victory," he suggests, "was time—time converted into possibility."

Today, IEO and Mangiagalli in Milan are recognized as a referral centers for cancer during pregnancy, but Peccatori is quick to point out that it was never a solo effort. *"You never do something by yourself in medicine. It was always cooperation—oncologists, pathologists, obstetricians,neonatologists and,* *most of all, the patients."*

For Peccatori, these cases embody both the beauty and the difficulty of his work. *"The most rewarding part is giving women the possibility of a future—beyond cancer, with family, with life. The hardest part? Accepting that sometimes medicine cannot go as far as we wish."*

The Land In-Between: Adolescents and Young Adults

The third chapter of his work focuses on **adolescent and young adult (AYA) oncology**—patients too old for pediatric wards, too young for adult clinics, group too often lost "in the land in-between," as he calls it. "Their outcomes are worse than children's, worse than older adults".



Together with colleagues like **Andrea Ferrari**, he built initiatives at both the Italian and European levels. They developed guidelines, created networks, and advocated for these patients who, in his words, "are not just statistics—they are young people who deserve someone to listen."

Listening is a word he returns to often. "Patience, patience, patience," he says, almost like a mantra. "The ability to listen is as important as any drug we prescribe." Young people wanted explanations, choices, honesty. They wanted doctors who treated not just their cancer, but their lives—school, work, relationships.

A Teacher, a Mentor a Builder

Teaching, Peccatori admits, came "a little by chance, like many things in my life." First a fellow, then eventually Scientific Director of the European School of Oncology (ESO), he spent ten years shaping programs that would become a backbone of European oncology education. "I owe a special thank you to **Alberto Costa**, who wanted me to join ESO. We made a very nice trip together, and I hope I gave my contribution, however humbly, to improving the quality of oncology education in Europe."

What made it so important, he explains, is that oncology itself is still young. "It hasn't always been its own discipline. In the past, organ specialists treated their cancers — pulmonologists for lung, gynecologists for gynecological malignancies, surgeons for many others. Building oncology meant not only building training programs, but building identity."

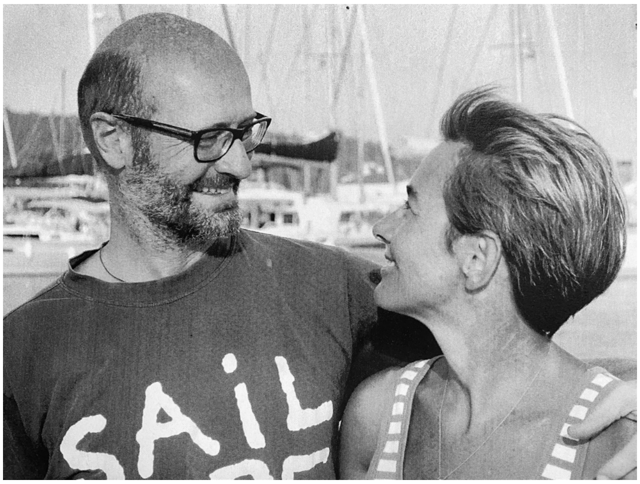
Through masterclasses, clinical training centers, and specialized courses, he helped generations of young oncologists learn not only the science but also the posture of the profession. "Mentorship is not just about techniques," he says. *"It's the way you approach a patient, the way you listen, the way you carry yourself as a doctor. That is the legacy."*

He also remembers the influence of Umberto Veronesi, founder of the Istituto Europeo di Oncologia. "Veronesi had this fantastic and unique personality—charisma with patients, but also with collaborators. He showed us that science and humanity can walk together."

Fatherhood, Mountains, and the Future

Peccatori is also a father of five and husband of pediatrician. Two of their children are doctors,

one a pediatrician. “Wetried to stay neutral,” he laughs. “But maybe, unconsciously, they absorbed something from both their parents.” He speaks of role modeling not only in families but in institutions. *“Being a model means showing that you can be a good doctor, but also a good father, a good partner. Investing in all those things is a good investment.”*



“‘Retirement?’ he repeated when I asked. ‘I think there is a time for everything—a time to study, a time to work, and a time to care for yourself. For me, it will be the mountains. I imagine nature, quiet, reconciliation. But I will never abandon what shaped my life. Even then, I will stay connected to research, to education. There is still so much to do.’”

Lessons for the Next Generation

When I ask what advice he would give to his younger self—or to the many young oncologists who look up to him—his answer is immediate:

“Curiosity. Humbleness. And a little bit of boldness. Be courageous in your choices. Don’t say: ‘This is too much for me, I will never succeed.’ Try. Give yourself the chance. Sometimes it’s about persistence, sometimes about courage. But always about **believing in your future**.”

Optimism, for him, is not naïveté—it is discipline. A deliberate choice to believe in people, in medicine, and in life beyond cancer.

In the end, what defines Fedro Peccatori is not only his scientific contributions, but the humanity he brings to every interaction. “Patients are not only cancer patients,” he tells me. “They are persons, with their own priorities. *Our job is to listen, to guide, to walk with them."*

On a train, between cities, between moments, his voice carries the calm conviction of someone who has devoted his life not only to curing disease, but to honoring life. And perhaps that is his greatest lesson for all of us: ***that oncology, at its heart, is not only science—it is a profoundly human art***.

Does Uncertainty Inherently Cause **Burnout** Among Oncology Care Providers?

By Adrian Pogacian

Oncology is both one of the most inspiring and one of the most demanding fields in medicine. Unlike other specialties, the emotional and professional boundaries in oncology are often blurred. Many of us feel that our lives are devoted to a single purpose: caring for people with cancer. But this raises a painful question—who cares for the caregivers when our emotional resources are not enough?

Oncology is not just another branch of medical care. For many providers, it is not a profession that can be switched off at the end of the day. It becomes a life.

The Uncertainty

Chronic uncertainty has become a defining reality in oncology, affecting both patients and professionals. For patients, uncertainty often centers on fear of recurrence or disease progression. For providers, uncertainty fuels a quieter fear: what will happen to my patients if I step away?

"According to a 2024 workforce study, 67% of nurses who delayed resigning cited 'fear of what would happen to their patients' as the primary reason. The longer we remain under such terms, the more we risk losing not just nurses, but entire professional identities."

Mark Carter, CEO and Founder,
MACH Health (LinkedIn post)

This fear often translates into guilt, which becomes one of the most powerful drivers of burnout.

Guilt

Burnout in oncology doesn't simply feel like exhaustion or the need for rest. It feels like guilt.

As oncology nurse navigator Alessandra Alvarez explains:
"Burnout in nursing often carries a heavy sense of guilt, especially in oncology. It's not only the physical and emotional exhaustion but also the internal conflict of feeling like you're not doing 'enough' for patients who are already going through so much. We hold ourselves to very high standards, and when we can't give 100% every day, guilt creeps in. Compassion fatigue is very real—and that guilt can sometimes be harder to carry than the exhaustion itself."

Her words echo what many of us silently carry. When patients suffer, we feel that we should have done more. When patients die, we wonder if we missed something. Even when we give everything, the sense of responsibility lingers, turning exhaustion into guilt, and guilt into burnout.

Compassion Fatigue

Compassion fatigue is not just about being tired. It is about being overwhelmed by caring. For psycho-oncologists, nurses, and physicians alike, it means balancing empathy, trust, and hope while coping with inevitable loss.

Unlike in other specialties, oncology often fosters deep, long-term relationships with patients and families. This closeness is meaningful, but it makes loss even heavier.

As Alessandra Alvarez notes:

"Patients rely on us to guide them through overwhelming systems and decisions. Walking away isn't just about taking time off; it feels like abandoning someone in the middle of a storm. Many of us stay not out of strength, but out of commitment and concern for what might happen if we weren't there."

This captures the paradox of compassion fatigue: we remain, not out of resilience, but out of fear of letting go.

Living in Two Worlds

Behind every statistic, every clinical trial, and every treatment protocol are human beings with dreams, worries, sacrifices, and fears. Patients and families live them. But so do we, the providers. Healthcare providers are often torn between professional duty and personal life, drawing strength from loved ones even as they remain tethered to patients' needs.

We live divided lives, between professional duty and personal identity, between grief for lost patients and love for our own families, between exhaustion and hope. Our families wait for us, often worrying about how much we can bear. Yet many of us stay late, unable to leave a patient in danger, unable to silence the inner voice that says, If not me, then who?

This dual existence, living in two worlds at once, creates the conditions for chronic burnout. It is not only the workload, but the ongoing internal negotiation between caring for patients and caring for ourselves.

Alessandra emphasizes another truth:

"It is absolutely essential that healthcare professionals speak up every day for patient safety. In oncology, even small delays or missed details can have serious consequences. Nurses and physicians are often the first to notice risks, gaps, or barriers, and our advocacy makes a real difference. Raising our voices isn't just about procedural safety—it's about ensuring patients feel seen, heard, and protected. Consistent advocacy creates a culture where safety is prioritized at every level, from the bedside to the boardroom."

Advocacy is both a responsibility and a coping mechanism. It is a way of transforming uncertainty into action, of turning fear into vigilance. Yet it also adds to the weight we carry. When every small oversight can have life-changing consequences, the stakes of daily work are relentless.

Reframing the Question

So, does uncertainty inherently cause burnout? Not necessarily. Uncertainty is an inseparable part of oncology, and it cannot be eliminated. But when uncertainty is paired with inadequate support, chronic guilt, and compassion fatigue, it becomes a catalyst for burnout.

Uncertainty is not only about medical outcomes. It also exists in the form of administrative pressures, systemic barriers, and organizational demands. Providers face strict timelines, electronic documentation burdens, and staffing shortages, all of which compound the emotional weight of patient care.

Burnout cannot be solved by individual resilience alone. Institutions must create conditions where healthcare providers can share responsibility, find rest, and seek support without guilt.

So, the challenge is not to escape uncertainty, but to share it, to transform it from an isolating burden into a collective reality. When uncertainty is acknowledged openly, when teams and institutions provide space for reflection and recovery, it can foster resilience instead of collapse.

Burnout in oncology is not just an individual failing; it is a shared responsibility. The duty of care extends not only to patients, but also to those who dedicate their lives to caring for them.

Oncology professionals need permission to say: I cannot carry this alone. Patients need caregivers who are present, not perfect; resilient, not guilty; human, not superhuman.

Uncertainty will always shape the work we do. The question is whether it drives us into guilt and burnout, or whether, with proper support, it strengthens our commitment and our humanity.

If institutions, colleagues, and communities stand together, oncology professionals can continue their mission, not out of fear or guilt, but out of capacity to care.

HASHTAGS AND CLARITY

TRANSFORMING SOCIAL MEDIA INTO A SOURCE OF TRUTH FOR ONCOLOGY PATIENTS

By Jovana Mijucic

In recent years, global health statistics have shown two significant upward trends: on one hand, in 2020, there were 19.3 million newly diagnosed cases of malignant disease worldwide. [1] On the other, the ever-expanding use of social media, which, just three years later, reached 4.88 billion active users.[2]

Data from the Global Cancer Observatory indicate that in 2020, Serbia reported 42.039 newly diagnosed cases of malignant disease, reflecting a modest decline relative to earlier trends, yet still placing the country among those with the highest incidence rates in Europe, [3] a situation further compounded by relatively delayed diagnosis and the insufficient implementation of organised screening programs.

Today, social media is the fastest-growing source of oncology-related information, offering a broad spectrum of content: from essential resources for patients and their families, to updates for physicians and researchers, advocacy groups, and even relevant stakeholders in the healthcare industry. However, the increasing integration of social media and artificial intelligence (AI) into daily life has fundamentally reshaped how patients engage with cancer-related information. While these technologies provide unprecedented opportunities for patient education and empowerment, they also amplify the risk of exposure to misinformation, which can significantly influence patients' attitudes, behaviors, and treatment decisions, sometimes even before the first clinical consultation takes place.

The internet and social media, now enhanced by their powerful new ally AI, have transformed the patient journey and outpaced us, especially in areas where we oncologists hesitate, stepping in to explain what we did not manage and offering extensive access to information about risk factors, treatment options, clinical trials, and survivorship. This modern triad is providing our patients, effortlessly and instantly, with information of often dubious accuracy – data frequently unsupported by evidence and derived from unreliable sources.

Public health studies [2,4,5] consistently demonstrate that misleading health-related posts often generate more engagement (likes, shares, hashtags), becoming more visible to a wider audience, when compared to accurate, evidence-based information. AI-driven algorithms, designed to amplify the profit by maximizing users' engagement, unintentionally intensify this effect by prioritizing sensational claims over scientifically valid ones. This trend creates an environment where incomplete or incorrect data spreads rapidly, reaching patients who often lack the medical background or critical tools needed to evaluate it properly. Such exposure shapes unrealistic expectations, fosters misplaced trust, and can directly affect clinical outcomes. Moreover, additional misinformation patients encounter frequently arises from misinterpretations of texts that are insufficiently tailored to readers without previous medical knowledge, as they search for answers to questions we may have overlooked during multidisciplinary board meetings.

Impact on Everyday Clinical Practice

The anxious fingers of patients newly introduced to cancer quickly search online, only to be overwhelmed by unfamiliar terms: phenotype, biomarker, predictive factors. This is often a first step in the perpetual loop we find ourselves caught in, between the lack of time for each patient, the use of inadequate terminology that we are personally not fully aware of and the unfiltered stream of medical information online, usually written by incompetent individuals lacking the realistic clinical perspectives. Once misinformation takes root, correcting it is difficult, and trust in the oncologist can erode. Faced with oversimplified, unverified and misleading explanations, patients often develop fear not only of their illness, but unfortunately also of the oncologists sitting across them. They come back to us usually seeking an innovative therapy they found online, convinced it is highly specific to their type of malignancy – a therapy that, despite their belief, we cannot offer. As a result, we are faced with a frightened and angry individual, someone whose trust has been shaken and whose expectations have been betrayed. From them pours a stream of fragmented bits of information, lacking the medical context necessary for critical interpretation.

This later continues not only with distrust, but also higher toxicities, poor treatment adherence, delayed symptom reporting, and an overall decline in cancer-related quality of life.

Instead of remaining stuck, as a hamster on a wheel, oncology professionals should proactively harness the potential of social media to bridge this growing knowledge gap. We should not (unfortunately sometimes with unavoidable arrogance) criticise the incomplete (mis)information they have encountered, nor repeatedly express surprise at its consequences – rather, we could respond to their natural curiosity by providing accurate and understandable answers via social media.

Building a National, Patient-Centered Online Platform

One promising approach is the development of a national, patient-centered online platform that delivers accessible, evidence-based and regularly updated content and bridges the language barrier. Even though some similar platforms already exist *(OncoDaily.com, cancer.gov, and the NIH)*, our patients would undoubtedly benefit from a platform adapted to their needs.

Although previous attempts to establish online support in our country have not been fully implemented, patient associations (particularly those of women with breast and cervical cancer "Zenski centar Milica" *eng. Female center Milica*) have succeeded in establishing and continuously improving additional channels of communication and information exchange with their oncologists, resulting in interactive seminars, podcasts, a website and an Instagram profile – which may provide a foundation for further advancement of digital support through interactive platforms designed to address a wider spectrum of malignancies. It must be inclusive,culturally sensitive and adapted to diverse socioeconomic realities and educational backgrounds.

At the same time, it enables us to avoid harmful mistranslations of medical information into the native language through the use of terminology that may not be readily understood by people without prior medical education. Such a platform should address not only treatment protocols but also everyday quality-of-life concerns that patients frequently hesitate to raise during medical consultations: "Will I lose my hair?", "Can I go on holiday?", "What should I eat?". Concise, easy-to-understand answers provided by oncologists, nurses and verified patient advocates are essential, alongside moderated patient-to-patient exchanges to foster safe and protective communication. Importantly, healthcare institutions, academic societies and patient advocacy organizations should collaborate to ensure both the credibility and sustainability of such initiatives.

By meeting patients where they are and providing trustworthy information through the same channels they already use, we create a safer, supportive, and collaborative environment. Social media, when leveraged responsibly, can become a bridge between medical professionals and patients, enabling us to dispel misconceptions that emerge during late-night web scrolling, redirect fears toward reliable resources and empower individuals to actively participate in their care.

In an era where misinformation spreads faster than scientific evidence, ignoring the digital realities of our patients' lives is no longer an option. By embracing digital platforms and shaping them into credible, patient- centered resources, we can improve health literacy, strengthen the patient-oncologist relationship, and ultimately enhance both treatment adherence and quality of life.

Today, it is no longer enough to treat disease alone; we must also treat information. So our patients can feel seen, so they can feel heard.

Acknowledgment

This article was written by Dr. Jovana Mijucic, one of the two winners of the **ESO College Voices Contest 2025**, on the topic "Social media: friend or foe for cancer patients?".

This year's contest once again proved that doctors can also be excellent cancer writers. We received 27 proposals from ESO College members across 20 countries, each exploring the chosen theme.

After careful deliberation, guided by **CancerWorld's editorial standards**, as well as criteria of clarity, relevance, originality, potential impact, and our hallmark style of weaving in interviews and firsthand perspectives, ***Dr. Mijucic was selected as one of the winners, and we are proudly publishing her impactful voice.***

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TO STAND
TO MOVE
TO LIVE

MUSCULOSKELETAL HEALTH AS PART OF THE CANCER JOURNEY

By Christos Tsagkaris

At a cancer forum not long ago, after I introduced myself as an orthopaedic surgery resident, someone asked — with genuine curiosity — *"But why are you here?"* The question stayed with me, because it revealed a paradox: musculoskeletal health professionals are often seen as peripheral to oncology, yet bones, muscles, and movement lie at the heart of living with and beyond cancer. Patients sustain pathological fractures, lose mobility, struggle with sarcopenia. Their independence and dignity, their ability to stand on their own feet, often depend on musculoskeletal health. This brings us to the real question for the cancer community: is it pragmatic, is it plausible — and above all, is it needed — to expand the mandate of musculoskeletal health professionals in cancer prevention, control, and care?

Current Status

Musculoskeletal professionals are already involved in cancer care — but in disease-specific ways that may be fragmented from the continuum of cancer care. Orthopaedic oncologists provide highly specialised surgery for bone and soft-tissue sarcomas, a rare field centralised in a few expert centres. Orthopaedic and spine surgeons treat metastatic bone disease, often faced with controversies such as whether biopsies should be routine during vertebroplasty to detect occult cancers. Physiotherapists and rehabilitation physicians play an important supportive role throughout treatment, yet their services may remain unevenly integrated and underfunded.

There is however space and need for more action from musculoskeletal health professionals. ***Bone metastases affect approximately 54 and 89% of patients with advanced breast or prostate cancer respectively, while skeletal-related events such as fractures or spinal cord compression drive morbidity and cost.[1] Sarcopenia and frailty, affecting 30–50% of cancer survivors, predict poorer outcomes and limit treatment options.[2]*** Despite this, cancer rarely features in the core curricula of orthopaedics, rehabilitation, or physiotherapy training — apart from focused modules in subspecialties such as musculoskeletal oncology or paediatric orthopaedics. The result is a professional community that has a potential to accompany the cancer journey, but without systematic preparation, recognition, or policy mandate to do so.

A Play in Three Acts – Clinic, Research and Policy

Contemporary cancer care emphasizes both survival and quality of life, rendering the services of musculoskeletal health professionals essential. Standardising musculoskeletal follow-ups could prevent debilitating complications. These include early detection of bone metastases that precede fractures, routine frailty and fall-risk assessments, and proactive physiotherapy or surgical stabilisation where indicated. Simple tools such as DXA scans, FRAX adapted for oncology, and functional assessments like the Timed Up and Go test could be embedded into survivorship clinics as readily as blood counts are checked in oncology visits. Beyond complication management, the musculoskeletal health community could drive prevention — aligning with Europe's "Cancer Code" recommendation on physical activity. Active social prescribing of exercise, safe-sport counselling, and community programmes led by rehabilitation specialists would strengthen both primary prevention and survivorship care.

"Be physically active in everyday life. Limit the time you spend sitting."

European Code Against Cancer (2014, EC/WHO/IARC)

A stronger evidence base is essential. Musculoskeletal outcomes could be systematically captured in cancer registries, tracking fractures, mobility, falls, and quality of life using validated instruments such as the MSTS score, PROMIS mobility, or the EORTC QLQ modules. Translational research could link the effect of chemotherapy, radiotherapy, and hormonal therapy on bone and muscle biology to indications for physiotherapy, assistive devices, or even prophylactic surgery. In exercise oncology, musculoskeletal expertise is crucial to refining which regimens improve not only cancer-specific outcomes but also independence and function.[3] With musculoskeletal data integrated into cancer registries, the evidence gap that sidelines musculoskeletal health professionals could be bridged.

Finally, musculoskeletal health needs to be recognised in cancer strategies at the policy level. Formal involvement in national cancer control plans, WHO rehabilitation frameworks, and survivorship guidelines would legitimise and fund these roles. Representation in conferences, consultations, and research consortia can strengthen cross-sector links — from orthopaedics and rehabilitation to sports medicine and industry. Athletic events could serve as platforms promoting exercise as prevention. Harnessing partnerships with implant and surgical planning ventures could create momentum mobility interventions focused on cancer patients and survivors. Policy presence often serves as a lever transforming isolated good practice into system-wide change.

"Rehabilitation is relevant to the needs of people with many health conditions and those experiencing disability across the lifespan and across all levels of health care."

WHO Rehabilitation 2030 initiative, 2017

Recommendations – The Way Forward

The way forward requires both structure and experimentation. A top-down approach would mean developing frameworks, curricula, and guidelines: oncology modules in orthopaedic and physiotherapy training, multidisciplinary working groups within cancer societies, and inclusion of musculoskeletal indicators in national cancer registries. International working groups and dedicated sessions at major oncological and orthopaedic conferences could set shared agendas and track progress through yearly reports.

At the same time, a bottom-up approach is equally necessary. Pilot programmes in hospitals and communities could test practical models: joint survivorship clinics that integrate physiotherapy and orthopaedics, structured exercise prescription embedded in routine oncology visits, or twinning programmes increasing mutual understanding of healthcare professionals in oncology and musculoskeletal health and care. Patients themselves should be invited to shape these initiatives, ensuring that services reflect real needs and lived experiences.

The most pragmatic path is a combination of both: a framework that provides legitimacy and resources, and grassroots use-cases that prove feasibility and generate evidence. A concrete start could be an inaugural "Call to Action" published jointly by cancer and musculoskeletal societies, followed by structured exchanges of knowledge, annual progress reports, and international twinning opportunities for the next generation of professionals.

Conclusion

Expanding the role of musculoskeletal professionals in cancer care is not about rivalry or reshaping hierarchies — it is about collaboration. By joining forces across disciplines, we can prevent avoidable fractures, preserve independence, and embed exercise and rehabilitation into every stage of the cancer journey. The goal is simple but powerful: better care, together, for every patient living with and beyond cancer and for every individual who can diminish their cancer risk.

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RESPIRATORY INFECTIONS TRIGGER METASTATIC BREAST CANCER IN THE LUNGS

By Janet Fricker

Common respiratory infections, including COVID-19 and influenza, can awaken dormant breast cancer cells that have spread to the lungs, setting the stage for new metastatic tumours.

The study published in Nature, 30 July, included findings obtained in mouse models that were supported by human observational data showing increases in death and metastatic lung disease among human survivors of cancer who experienced COVID-19 infections.

"Dormant cancer cells are like the embers left in an abandoned campfire, and respiratory viruses are like a strong wind that reignites the flames," says James DeGregori, co-lead author from the University of Colorado Anschutz Medical Campus. The study, he adds, indicates that individuals with a history of cancer may benefit from taking precautions against respiratory viruses, such as vaccination when available.

In 2024, the **Journal of the Natitionall Cancer** Insitut reported changes in cancer-related mortality during the COVID-19 pandemic in the US that could not be fully accounted for by COVID-19 deaths or delayed screening and treatment. Such observations prompted DeGregori and colleagues to hypothesise that pulmonary viral infections could be increasing cancer deaths by triggering the development of metastases from dormant cancer cells. The theory was supported by earlier studies suggesting that inflammatory processes can awaken disseminated cancer cells (DCCs)—cells that have broken away from a primary tumour and spread to distant organs, which can lie dormant for extended periods.

Awakening Cancer Cells: Testing the Hypothesis in Mouse Models

The current study involved two parts: a mouse model of dormant DCCs in breast cancer and the analysis of human observational data from two databases. "We choose to focus on breast cancer because there's epidemiological evidence that it can relapse after many years and we also had good mouse models of dormant breast cancer," DeGregori explains to **CancerWorld**.

First, the team used the MMTV-erbB2/neu/HER2 mouse model (MMTVHer2), where the HER2 oncogene is expressed in the mammary glands of mice. The result is a slow-growing primary tumour that within 12 to 14 weeks seeds the lungs, and then for up to one year remains largely as dormant single cells before progressing to overt metastatic disease. "This model recapitulates the persistence of dormant DCCs in lungs and bone marrow in individuals who remain in remission for years to decades," write the authors.

The team then exposed the mice to the influenza virus or SARS-CoV-2, and went on to use immunofluorescent antibodies directed against HER2 to quantify the number of metastatic cancer cells that appeared in the mice.

Results showed that within two weeks, there was a large increase in HER2-positive cells in mice exposed to influenza (as opposed to mice not exposed) and in HER2-positive cells in mice exposed to SARS-CoV-2 (as opposed to mice not exposed.) The

HER2 increase persisted for up to nine months for influenza and 28 days for SARS-CoV-2.

Next, the team performed a cytokine array that revealed dramatically increased levels of interleukin 6 (IL-6). Significantly, metastatic growth was found to be slower in mice that had been genetically engineered to be without IL-6. "Given that IL-6 is known to be involved in cancer pathogenesis and we were seeing marked increases, we thought it represented a good candidate for the culprit behind reawakening," says DeGregori.

When areas of the lung with immune filtration (known as DAPI dense regions) were probed, they found increased immune markers for CD4+ T cells and reduced markers for CD8+ T cells. Depletion of CD4+ T cells led to regression of the tumour, but when they additionally depleted CD8+T cells the tumour returned. "The CD4+ T cells appear to be keeping the CD8+ T cells in check and preventing them from killing cancer cells," explains DeGregori. The findings, adds DeGregori, suggest that the mechanism behind the metastasis is driven by IL-6–mediated inflammation and dormant cancer cell awakening and expansion, followed by immune reprogramming where $CD4^+$ T cells suppress $CD8^+$ T cells, thereby corrupting the immune system and preventing it from killing cancer cells. "We haven't shown whether IL6 mediates this immune reprogramming," says DeGregori.

COVID-19 Provides Opportunity for Real-World Data

The SARS-CoV-2 pandemic provided the opportunity to use real-world data to investigate the hypothesis that respiratory viral infections can promote metastatic disease. The team had access to two large data bases - the UK Biobank and US Flatiron Health database.

From the UK Biobank database, researchers analysed information from 4,837 people who were diagnosed with early-stage cancer before January 2015 (five years prior to the start of the pandemic).

Results showedpeople who tested positive for COVID-19 before December 1 2020 (the day vaccination started) had a nearly twofold increase in cancer mortality compared to those who were not documented to have been infected (odds ratio, 1.85; 95% CI: 1.14–3.02). The Flatiron Health database includes information about women diagnosed with breast cancer from 280 cancer clinics across the United States. The researchers looked at data on women diagnosed with breast cancer in January 2011 or later. Results showed that women with breast cancer who later contracted COVID-19 were about **40% more likely to develop lung metastases** than those who did not catch the virus, even after adjusting for age, race, and ethnicity (hazard ratio of 1.44; 95% CI: 1.01, 2.05; P = 0.043).

"Our studies reveal how respiratory virus infections can increase cancer recurrence risk and underscore the need for public health and clinical strategies to mitigate the increased risk of metastatic progression associated with SARS-CoV-2 and other respiratory virus infections," conclude the authors.

DeGregori stresses that their goal is not to create fear. "We don't want every cancer survivor to be worried about stepping outside their front door. But if I was a cancer survivor, I'd make sure to be vaccinated against major respiratory viruses where there are good vaccines available," he says.

As well as primary prevention strategies, treatments for managing severe COVID-19 have been approved by the FDA (including antagonistic antibodies against IL-6 and orally available JAK1/2 inhibitors), raising the prospect of interventions that could be used to reduce the risk of infection-induced metastatic cancer progression.

The next steps, says DeGregori, will be to explore whether interventions such as vaccines and managing COVID symptoms, could minimise the risk of reawakening metastatic cells. They also hope to understand more about the mechanisms by where CD4+ T cells increase and CD8+ T cells decrease. "Ultimately, we'd like to develop interventions that could be given to cancer survivors to prevent the reawakening," says DeGregori.

Unanswered Questions

Although only breast cancer was modelled in the mice and metastatic sites in the lung were explored, the authors believe that the findings are likely to be applicable to other types of cancer, and also to other metastatic sites such as the brain and liver. "We also want to ask whether infections beyond viruses, such as bacterial infections, can cause awakening in the lungs or other tissues, and understand just how general this phenomenon is," says DeGregori.

PAUL MISCHEL

CALMING FULL CIRCLE

By Yeva Margaryan

It was an interview during which I simply couldn't stop smiling, amazed by the brilliance of Prof. Paul Mischel, yet he speaks about his discoveries with such ease, clarity, and enthusiasm that you can't help but be carried along. Here is a man whose work promises to reshape the future of cancer care and save countless lives, speaking with such lightness and grace that you almost forget the scale of his impact. When strangers ask what he does, his reply is modest:

"I'm a doctor and a scientist and I do cancer research."

Beneath those few words lies a lifelong mission, to understand why so many treatments fail, and to find a way to make them work.

"I was always very interested in this idea of personalizing therapy," he explains. The hope was that by decoding a tumor's genetic makeup, doctors could design treatments tailored to each patient. But for too many people, that promise never materialized. The question of why pulled Prof. Mischel into discoveries around extra-chromosomal DNA.

The pursuit is personal. Prof. Mischel was just 14 when his father died of stomach cancer. "It was terrible. He died a very painful death," he recalls. That searing loss crystallized his purpose. In his college essay, he had already declared his dream:

"I wanted to be a doctor and a scientist to do something about cancer."

Prof. Mischel with his father, taken when he was five years old

My Uncle Told Me

Orphaned of a father, Prof. Mischel found guidance in another, his uncle, Walter Mischel, the psychologist famous for the marshmallow test. *"Walter pretty much rescued me and was a father figure to me,"* Paul says, his voice catching even now. *"He became a mentor. And then ultimately, he became a friend."*

Walter was more than an uncle, he was a role model whose wisdom shaped the course of Paul's life. Throughout the interview, Prof. Mischel returned again and again to the lessons his uncle had shared. But one stood above the rest, a principle he now passes on to the younger generation:

"Never make the work about you. It's never about you. You don't need to look out for yourself, you need to be looking out for the integrity of the science, for the work itself, for the people you train, those you collaborate with, and ultimately for people with cancer."

Prof. Paul Mischel with his uncle, Prof. Walter Mischel.

Prof. Mischel's wife, physician-scientist Deborah Kado, also became a mentor in the truest sense, an intellectual partner since the first day of medical school, and a wise voice at every crossroads. Along the way, Mischel drew strength from a constellation of teachers: Harry Vinters at UCLA, who guided him into pathology; Dr. Clarence Kado, his father-in-law, who bluntly told him his descriptive papers weren't "real science" and pushed him toward training; and Dr. Louis Reichardt at UCSF, who took a chance on a 34-year-old doctor picking up a pipette for the first time. In Reichardt's lab, alongside future Nobel laureate Ardem Patapoutian, Prof. Mischel learned molecular biology from scratch.

The list of mentors grew longer: Drs. Harvey

Herschman, Charles Sawyers, Webster Cavanee, Carolyn Bertozzi, Chaitan Khosla, Howard Chang, Ben Cravatt, and many more. Each one gave him not only scientific insight but also a model of generosity, courage, and vision. *"I liked the idea of being mentored your whole life,"* he says. And he paid it forward, mentoring generations of scientists. *"The real secret here that nobody understands is that it goes both ways. The amount that I learn from these brilliant people in my lab, they don't even know how much I get from working with them."*

The Ptolemy's Map of the Solar System

In 2014, Mischel and his colleagues published a discovery that would ripple through oncology: oncogenes driving aggressive cancers were often found not on chromosomes, but on rogue circles of DNA outside them, extra-chromosomal DNA, or ecDNA.

The realization came from puzzles in glioblastoma, a deadly brain cancer. Tumors showed genetic chaos and swift resistance to therapy that classical genetics could not explain. "The aha moment was the realization that maybe we actually don't know where genes are," Mischel recalls. Looking at dividing cells, they saw amplified oncogenes residing on ecDNA.

That finding transformed the map of cancer biology.

"It's like Ptolemy's map of the solar system, the measurements were correct, but the map was wrong because they put the earth at the center. Is it possible that in some cancers, their genome map is completely wrong because of this?"

The implications were profound: ecDNA, lacking centromeres, segregates randomly, creating explosive genetic diversity, the raw material for Darwinian evolution inside tumors. *"Now you have a situation in which these extra-chromosomal DNA elements are allowing tumors to become highly heterogeneous," he explains. "That explains why this is actually happening, allowing them to hit very high copy and allowing them to change their genomes very rapidly because of this non-Mendelian genetics."*

For Mischel, that was the real breakthrough: what seemed impossibly complex suddenly snapped into focus. "If you step back and see it from this lens, it's actually remarkably simple," he says. "They're following Darwinian evolution, but they're not following Mendelian genetics."

The first person he shared the discovery with, outside the lab, was his wife. "Of course," he says with a smile. Her response was simple but steadying: "She said, this is paradigm shifting."

Prof. Mischel and his wife, Dr. Deborah Kado, Chief of Geriatrics Research at Stanford, Faculty Co-Director of the Stanford Longevity Center, and Chief of the Geriatric Research, Education, and Clinical Center at the Palo Alto VA.

It is a Matter of Time Now

When Paul Mischel speaks about extra-chromosomal DNA, his eyes light up with the same enthusiasm he felt at the moment of discovery. *"Extra-chromosomal DNA with a big exclamation point,"* he says, recalling the discovery in your career that has surprised you the most.

Science, he reminds us, is slow by design: *"First* *you actually have to show, and show again with more data. Then others need to see it too."* What began as an obscure observation in 2014 has now crossed a threshold, no longer "interesting," but unquestionably important.

The work, first met with skepticism, is now embraced as a paradigm shift. "Everybody realizes that this is important,"Prof. Mischel says. *"It is a matter of time now. I have great confidence that we collectively will figure out how to target this unique biology for the benefit of patients."*

The next challenge is action. Through Boundless Bio and other emerging companies, drugs targeting ecDNA are already in clinical trials. For patients, the message is both simple and powerful. *"For some people with very aggressive cancers that resist treatment, extra-chromosomal DNA is quite possibly behind it. Knowing this may let us identify those patients and treat them differently, and the drugs to do that are being developed as we speak."*

Maybe Terminal Doesn't Mean What It Meant Anymore

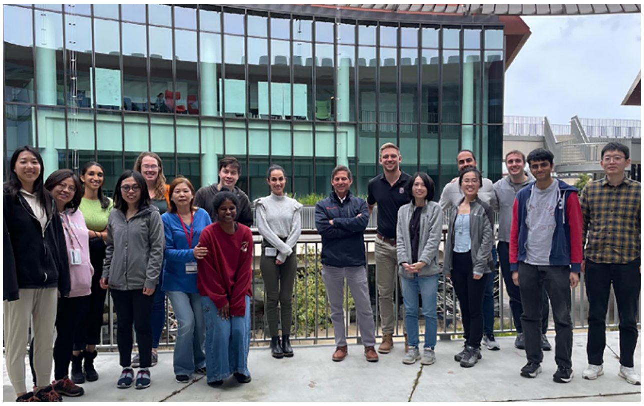
For Mischel, the science is never far from the personal. He still remembers seeing the word "terminal" stamped on his father's chart. That word has stayed with him ever since. Today, he believes research is beginning to rewrite its meaning. **"Maybe terminal doesn't mean what it meant anymore. Maybe that's what we should really be, part of what we should be changing."**

He points out that medicine doesn't talk about curing heart disease or curing diabetes. Instead, the focus is on helping patients manage the condition and continue living meaningful lives. He envisions cancer in the same way. *"We need to be talking and thinking through how we manage it, how we let people continue to live meaningful lives even if they have cancer,"* he says. Already, research is pushing that frontier forward, people with terminal cancer are living longer, spending more years with their families, raising children, working, and being present. For Prof. Mischel, that progress is proof that science can transform despair into possibility.

Inside his own lab, he works to cultivate not just breakthroughs, but also a culture. He urges young scientists to practice *"courage, humility, collaborativity,"* and never to forget that *"human relationships are amplifiers."* Ideas aren't handed down by command; they emerge in dialogue.

"I never tell anyone in my lab what to do because if I do, I'm not harnessing inherent creativity or their knowledge. So it's by conversation. We arrive at shared interests and they take their projects. There's intellectual creativity and ownership. That's the beauty of it. It's hard to do, but it is really important."

And the lesson he passes to them, inherited from his uncle Walter and carried through his own journey, is always the same: *"Never make the work about you. It's never about you. You don't need to look out for yourself, you need to be looking out for the integrity of the science, for the work itself, for the people you train, those you collaborate with."*



The research team of the Paul Mischel Lab.

The Blitz Round: Who is Paul Mischel?

To end our conversation, we turned to something lighter, a rapid-fire round of questions meant to reveal the person behind the white coat. Let's uncover, together, the hobbies, principles, and passions that shape Paul Mischel beyond the lab.

A quote you live by?

I don't know a quote, but I do know a principle, right? (We all know that now)

A family photo: from left to right, Prof. Mischel and his wife, Dr. Deborah Kado; their daughter, Dr. Anna Mischel, an internal medicine resident at Stanford, and her fiancé, Dr. Jay Meisner, a pediatric surgery fellow at UCSD; and their daughter, Sarah Mischel, with her partner, Steven Shin, both first-year medical students at the University of Pennsylvania.

Favorite book and movie?

A book called Stoner by John Williams. It's about the beauty and meaning of scholarship. My wife read it, my daughters read it, and we all had tears in our eyes. For movies, I'd say Hoop Dreams, a documentary about boys with dreams of becoming basketball players and the hardships they endured. It's a beautiful film about resilience.

Comfort food?

Bread, cheese, salad, and a glass of red wine.

A hobby you've always wanted to try?

Singing. I'd love to learn, and to sing with others.

What's a personal accomplishment that you're quietly proud of?

Both of my daughters would say Dad was always there for me when I needed him.

Something that would surprise people?

I do high-intensity interval training with my wife and my two daughters.

Most inspiring figure in oncology?

Dr. Charles Sawyers. His generosity as a scientist and as a human being and the bravery with which he translates fundamental science into live saving treatments for people with cancer has always inspired me. I would also say that my colleague Dr. Howard Chang inspires me with his brilliance and deep sense of purpose.

Who should we interview next?

Alice Shaw, head of oncology at Dana-Farber. Alice is a truly wonderful person.

Paul Mischel is a scientist whose brilliance is matched by humility, whose breakthroughs are driven by loss and hope, and whose greatest pride is not in papers or prizes, but in being present for the people he loves.

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