CURALINK

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thecurafoundation.org

Welcome to CuraLink—a newsletter for innovators building a healthier future for all.

Dear Cura Community,

Robin L. Smith, MD
Founder, President and Chairman, Cura Foundation

Welcome back to CuraLink, a newsletter and interview series featuring the most pressing issues in human health, unmet medical needs and the emerging innovations and technologies directed to address them.

In February, we heard from physician and author, Dr. William Li, about his upcoming book, *Eat to Beat Your Diet*, and his anti-diet approach to longevity. Dr. Li shared how to embrace food as a tool to improve metabolic health without sacrificing pleasure. Access that interview at bit.ly/CuraLink-12.

This month, we spoke with Dr. Laura Esserman who is shifting field-wide paradigms in oncology to optimize breast cancer screening and treatment. Through her clinical practice and various groundbreaking research endeavors, including the WISDOM study, I-SPY trials and the Athena Breast Health Network, Dr. Esserman hopes to redirect the population-based model of cancer care toward a more personalized, patient-centered approach.

This conversation is for anyone blazing a new trail in their field in an effort to make real change. We hope you enjoy reading.

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A conversation with Dr. Laura Esserman

Over the last century, scientists and clinicians have made major strides in understanding how to mitigate breast cancer's insidious health effects. Still, it remains the second leading cause of cancer death in women, despite breakthroughs in screening and treatment.

Dr. Laura Esserman, an internationally recognized breast surgeon, breast oncology specialist and visionary in personalized medicine, refuses to accept this reality. As a professor of surgery and radiology at the University of California, San Francisco (UCSF) and the director of the UCSF Breast Care Center, Dr. Esserman's breast cancer work spans the spectrum from basic science to public policy issues and, ultimately, reveals how multiple sectors intersect to shape a patient's health.

By listening intently to the concerns of her patients and gathering pivotal evidence to challenge the status quo in the field, Dr. Esserman is revolutionizing breast cancer screening and treatment worldwide. She is currently leading WISDOM, a large-scale study that uses genetic testing to determine an individual's risk to personalize and optimize their breast cancer screening schedule. Eventually, Dr. Esserman and her team will evaluate how outcomes from tailored screening compare with those resulting from the current standardized guidelines.

Laura J. Esserman, MD, MBA, Alfred A. de Lorimier Endowed Chair in General Surgery and Director, UCSF Breast Care Center, University of California, San Francisco

Along the road to redesigning breast cancer detection and care, some skeptics considered Dr. Esserman's ideas radical. But according to the oncologist and researcher, her approach is common sense. "We should be aspiring to be better," Dr. Esserman says. Without constant experimentation and evolution to improve care, clinicians are failing their patients, she adds.

In Issue 13 of CuraLink, Dr. Esserman shares the importance of implementation in making real change, why the field needs to shift toward shared decision-making and how to ensure clinical research is accurately representative of all communities.

What initially sparked your interest in caring for patients with breast cancer?

I love science, and I also love the ability to implement scientific advances in a way that will positively impact lives. Sometimes when people do basic science work, they struggle to apply the findings in a way that matters. Throughout my medical training, research and early practice, I was particularly frustrated by the slow pace of change in medicine.

After medical school, when I was in business school, I realized that you could have a vision about science and medicine, but if you can't get people to implement new ideas and make them actionable, you can't make an impact. So I've had this long-standing desire to dig deep, understand the science and figure out how to apply new ideas through trial design, policy or other levers that will make a difference.

In the late 1970s, I actually put myself through medical school doing disease modeling in the engineering department. At the time, we were modeling the optimal timing for cervical and breast cancer screening. We predicted cervical cancer screening should occur every 3 years and presented our disease model to the head of the OB/GYN department at Stanford. He responded: "Well, I don't think my ladies could remember to come in every 3 years. So I'll just stick to the annual guideline."

It took almost 40 years for cervical cancer screening guidelines to transition from annual to every 3 years as our model predicted.

The experience at Stanford frustrated me then, and later when I was hearing that same argument about breast cancer (that women could not remember when to come in for screening), I nearly lost it. That should not be what drives decisions about when to screen.

What made you rethink the standard approach to breast cancer screening? Why should the field move toward precision medicine?

When I was in training in the early 1980s, radical mastectomies were prevalent. Women were really angry. They were going into the operating room not knowing whether they had cancer or not. And if they did, they would wake up having had a radical mastectomy—no choice or discussion on the matter.

In the 1990s, everyone was recommended to get chemotherapy for even a 1 centimeter tumor. Now we use a multigene diagnostic test to determine who really is going to benefit from this therapy.

Even as things started to change, and there were early trials of lumpectomies and other procedures, there was still no way to coordinate care for breast cancer patients. Everyone was working in silos; medical oncology worked separately from the surgical teams. Patients would come in for different visits and hear conflicting guidance from each provider. I realized that we needed to create a patient-centered model, where various disciplines communicated and patients could come to one single space for care.

At the time, a team from Dartmouth and I also started pushing for shared decision-making. We started reflecting on what a medical opinion really means. It's a clinician's personal threshold for intervention. It's not the patient's threshold for intervention. These vary from clinician to clinician and from patient to patient.

What patients need to understand is: "What are the different treatment options and their outcomes? What are the trade-offs?" One person might value something far more than another. Someone might want to do chemotherapy for a 1% benefit, while someone else would say: "No way."

All of my best ideas come from patients. For example, from in-depth, intense conversations, and a challenge to improve the way we performed mastectomies, we developed the idea and techniques for saving all the skin of the breast, including the nipple, to improve reconstruction (we call it total skin sparing mastectomy).

"We have to get rid of this ingrained notion that everybody has to have the same screening and treatment."

Early on in my career, I worked with Dr. Nola Hylton, who was building the sequences that later became foundational for breast MRI technology. I thought this technology might help us answer the question of whether all cancers responded the same. We saw that all cancers aren't the same. They don't look the same or respond the same to the same treatment. So how is it that we have this one-size-fits-all approach? We thought that MRI could be used to help patients and their clinicians customize treatment protocols. This was the impetus for the I-SPY study.

What inspired you to conduct the WISDOM study, and what do you hope to learn?

We now know much more about breast cancer than when I started. There is a large spectrum of cancers. Some are non-threatening. People are very frightened of breast cancers, but not all of them are scary. Part of my job is to reset people's expectations and help them understand what their risks are as well as the appropriate potential interventions for the best outcomes, with the least toxicity, so they can get back to their lives.

I just operated on someone who had a 3 millimeter tubular cancer with no nodal involvement. She thought that she was dying. But her cell turnover was so low, it was barely measurable. Her life was not threatened. Someone else who has a fast-growing, 6 centimeter tumor that's not responding to standard therapy is in big trouble. These are completely different stories. These patients don't need the same treatment. So why are we screening everyone as if they are at risk for the same disease?

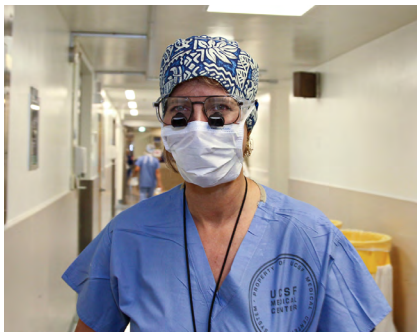
Everybody wants to believe that early detection saves lives. It's a great phrase. It's very simple and fits on the side of a bus. But with 30 years of taking this screening approach, there are still 40,000 women a year dying of breast cancer, and breast cancer rates continue to rise.

Breast cancer is the most common cancer in women. So for the 40,000 women who are dying of breast cancer annually, 230,000 are being diagnosed with the disease. Some patients have tiny tumors that aren't going to kill them. But they're getting mastectomies, and they're made to feel like they are dying. This can be terrifying for people.

There is so much room for improvement. I can't sit idly by and just watch. It's time to design a whole different paradigm for early detection. The idea that it is what it is and we can't do any better seems patently ridiculous to me.

People initially found WISDOM so radical, but really it's common sense. What's wrong with wanting to improve

screening and make prevention a priority? We need to ask: "Are we getting to the people who have the highest risk? Where has screening missed the boat?" This is not like we're burning the house down.



Dr. Laura Esserman is an internationally recognized breast oncology specialist and surgeon, who is rethinking the future of breast cancer screening and treatment. She now leads WISDOM, a large-scale study that uses genetic testing to determine an individual's risk to personalize and optimize their breast cancer screening schedule

How do you respond to skeptics who worry that shifting away from annual screening toward personalized screening may lead to missed cancer cases or more women being diagnosed with advanced cancers that aren't treatable?

Rethinking conventional wisdom in the field is the hardest thing to tackle because there is this almost impenetrable wall. Most people are told that to avoid getting cancer, you have to start getting annual mammograms at 40. That this scheduled screening will fix everything.

Screening works best for slower-growing cancers. That's true in cervical cancer, colon cancer and prostate cancer. When you have a fast-growing cancer, screening is not going to make that much of a contribution. It's not like, "Oh, if I have a screen-detected cancer, my life is saved. If I don't, I'm dead." It doesn't work that way. And we have lots of effective medicines to help manage and even prevent these cancers.

Everyone has to rethink this. We also have to do a better job of messaging. It's very hard to change 30 to 40 years of public health messaging. If you are getting screened every other year, and then you had cancer in your second year, the natural reaction is thinking you should have come in last year. In fact, your outcome is almost certainly likely to be the same if you had come in the year before, because of what we know about the biology of cancer and its response to therapy.

I'm a systems person—I like to look at other fields of medicine that have made great strides. When I started in the faculty at UCSF in the early 1990s, the biggest killer of women, by far, was heart disease. Today, your risk of dying of cancer is higher than your risk of dying of heart disease. How did this happen?

Over time, with the Framingham study that started in the late 1940s, cardiologists and primary care physicians began to understand what drove risk for developing heart disease—high blood pressure, family history, high cholesterol and lack of exercise. Early endpoints, such as change in cholesterol or blood pressure, were then tied to late endpoints like stroke risk and cardiac events. Trials were run with these embedded endpoints. All of these models have contributed to cutting the risk of having a heart attack in half. It has led to important interventions, like statins and antihypertensives, to reduce risk. Dr. Dean Ornish's work on lifestyle choices to improve cardiac health, proved that how you live your life impacts your risk of chronic heart disease. We can learn a lot from this dynamic approach to heart disease and apply it to breast cancer to think about a prevention strategy.

What do initial findings from WISDOM suggest about the outcomes of personalized screening?

We have yet to complete the trial. Our first readout is in 2 years. But there are four key things that we know so far.

First: We were told that all women want annual screening starting at 40. We've seen that the vast majority of women want something personalized and want to know their risk. In the WISDOM trial, we asked people if they were willing to be randomized and about 60% were. If you didn't want to be randomized, we still wanted you to join the trial. We wanted to be inclusive of everyone and learn from everyone. For the women who chose their screening arm, 85% chose the personalized arm, so women wanted to learn more about their personal risk.

Second: As many as 60% of people who have a mutation associated with breast cancer risk don't have a family history of the disease. People may have small families, may not know their family history or may be adopted. Women who have an inherited predisposition frequently have early onset breast cancer under 40. And today, we are not finding these people. This is not a big portion of the population, but it's the low-hanging fruit. If we can screen them better, then we can develop better tools to prevent early onset cancer, not just respond with prophylactic surgery.

Understanding your risk, how you should be screened and what you can do to prevent breast cancer is super important. If you carry a CHEK2 gene mutation and you're at risk for developing a hormone-positive breast cancer, what's the best thing to do when you're 30? Should we screen people more frequently? Or should we get them on the very medicines that will reduce their chance of getting breast cancer?

"The goal isn't just to find cancer. The goal is to prevent it."

Third: Our data safety monitoring board has given us the greenlight to proceed. We have been going long enough that if this was super risky and we had a higher rate of more advanced cancers in the personalized arm, the trial would be shut down. Do we know the best way to personalize? No. That's what the next phase of what the trial is about. But we do know that it's likely as safe as annual screening.

Fourth: There's a lot to be learned from ethnic and racial diversity and who's at risk for what kind of cancer. Breast cancer is less common in African American women, but the mortality rate is 40% higher.

The bulk of breast cancer risk models include mostly people of European ancestry, which aren't helpful to more diverse groups. We cannot take what we're doing and apply it to only one portion of the population. Because every woman is at risk.

We've learned, both from our trial and from the European trials, that polygenic risk scores (looking at many genes in combination) can predict cancer risk as well as whether a cancer will be fast- or slow-growing. If you're at risk for a slow-growing cancer, we have ways to reduce your risk, and now we know that much lower doses of medicines like tamoxifen (an FDA approved drug for breast cancer prevention) are much more tolerable and just as effective at reducing risk.

How might personalized screening influence the overall health burden and costs of current breast cancer screening guidelines?

Currently, we're spending about $12 billion dollars on screening annually. And if we use the American College of Radiology guidelines and screen everybody, it would be about $24 billion. With the WISDOM method, we could bring that down to about $8 billion.

So you really want to use models that indicate who's at high risk to guide screening. Women who are super high risk are not common. They make up less than 10% of the population. About 2% of people have mutations, and another 1 to 2% of people have really high polygenic risk scores. Then about 5% of people can majorly reduce their risk by taking endocrine risk reduction medication (in the same way that people at risk for heart disease or stroke take a statin).

Those at lower risk have the burden of screening. You have a 50% chance of having a biopsy and a 75% chance of getting a call back if you screen for 10 years. If you are in that group of people who have low polygenic risk, low density breast tissue and don't hit any thresholds for risk, surely you don't need to be screened every year. With this low-risk group, we are applying a 3-year screening rule similar to the strategies the UK and the Netherlands have adopted.

What can be challenging is that people are willing to do more but are afraid to do less. But sometimes, less is better.

In our under-resourced communities especially, we want to make sure that we are targeting the people who need it most and leaving people alone who don't need it. We want to use our resources where they will make the biggest difference and do the least harm.

In 10 years, what if we could cut the chance of getting breast cancer in half? I think that is actually quite possible, but we have to make it a priority.

How does the WISDOM study have potential applications to other countries' screening protocols, and how is it influenced by other countries? Could personalized screening enable a more efficient and targeted approach to breast cancer in low- and middle-income countries?

In most of Europe, screening starts at 50 and it is every 2 or 3 years. Their mortality rates are not higher than ours, so that helps us to know that for some women, a longer screening interval should be just fine. If we also find that a more personalized approach is better, it is likely countries in Europe as well as Australia would adopt it.

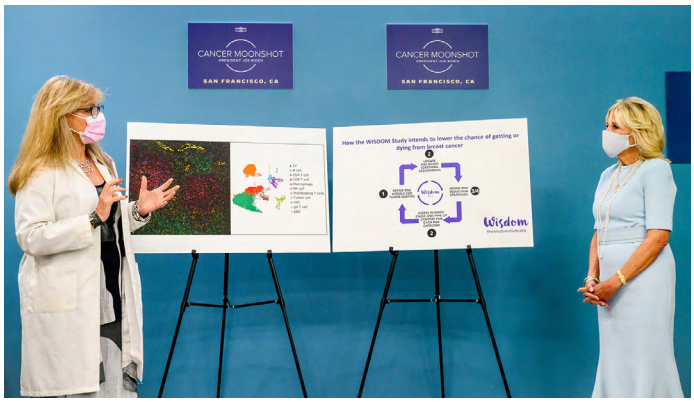
In West Africa, Southern Africa and the Caribbean, it looks like there's a higher risk for women in their 30s coming in with cancer. One of the things that I am super frustrated about is that people say: "Let's just import a screening mammo-van and send it around." How is that going to help? Women in their 30s have very dense breast tissue, and thus those mammo-vans are not the right approach.

"You have to understand your population and you cannot leave people behind."

There are a lot of things that we've done for many years that aren't very effective that we are shedding. So you want to be careful not to take the ineffective things that we do and make it the standard of care someplace else.

If a health system doesn't have the resources to take care of somebody with cancer very well, what will make the biggest impact on the mortality of the population? Is it improving screening or improving treatment?

Ideally, you wouldn't have to choose. But if you can reduce the risk by 30% with better treatment, and you can make a difference of maybe 2% by screening, you want to focus resources on the treatment. You first want to make sure that you have all the pieces in place to do the most good for the most people.



Dr. Esserman speaking with Dr. Jill Biden who visited the UCSF Breast Care Center in October 2022

There actually is enough money in the system in the U.S. But you have to ask: "Can I deploy resources differently and get a better result?" You don't want to do painful, emotionally difficult procedures, like bilateral mastectomies, when someone doesn't need them. Maybe a patient just needs to take a low dose of tamoxifen, and they will be fine.

There is a lot of financial toxicity in this country. Health care is the number one cause of personal bankruptcy. How is that acceptable? Are patients understanding what their medical providers are ordering—the real costs and benefits? If you order an MRI as a screening test that costs several thousand dollars and they're paying a 20% copay, can someone afford that?

Everyone should want to achieve healthcare value—the same or better outcomes with less burden and less emotional, physical and financial cost.

What did the process of recruiting for WISDOM teach you about your own inherent biases, and what have been the major challenges to recruiting racially diverse participants?

I thought that all we had to do was open the WISDOM trial up to everyone and that would work. Nothing could have been further from the truth.

I was surprised by how much distrust of the medical system there is by different groups of people. Many people might not know what clinical studies or trials are. Based on the Tuskegee study and other historical examples, people think they will become guinea pigs if they participate in a trial. Listening and trying to understand what people's fears are is essential.

To ensure that a trial represents the true population in the U.S., we have to get the message out and make it possible for everyone to participate.

"You have to be persistent in wanting to move forward, but patient enough to listen and change your approach."

In 2019, 2 years after we launched the trial, we had about 1.7% African American participation. That was unacceptable. So we have used multiple strategies to increase diverse recruitment and worked with colleagues like Dr. Olufunmilayo Olopade and Dr. Maren Scheuner at the Veterans Affairs as well as community advisory boards. Partnering with folks in the community and advocates who are leading this fight is really important. In our last quarter, we had 16.7% African American participation. This is what we were hoping for, and we are gratified that so many women have put their trust in us and the WISDOM study.

If you want people from a community to be part of your initiative, you need trusted voices in that community to be involved in the design and implementation from the get-go. Having that seat at the table from the beginning is critical to shape how we investigate what matters most to the community. For over a decade, we've included patient advocates in our work, but it is important to make sure that they are representative of the community at large as well as other communities that may not always be at the table.

Medicine is a learning system and everyone should be constantly working to improve and evolve their practice. When clinicians are just following the status quo, and not improving care, we are letting down the public.

We should be aspiring to be better and not settling for doing the same thing over and over again. You can never expect a better future if we persist in just standing still.

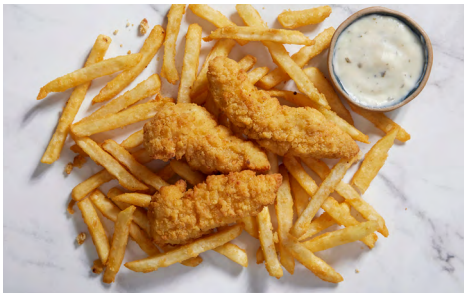
This interview has been edited for length and clarity.

Insights, Perspectives & Ideas

The Cause of Depression Is Probably Not What You Think

Quanta, January 2023

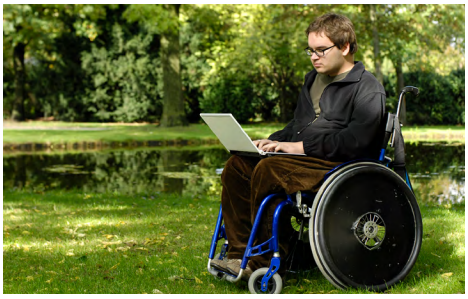
For decades, depression has been frequently blamed on low levels of serotonin in the brain. However, the strongest research to date testing that chemical imbalance hypothesis suggests the causal explanation has been overstated. Science writer Joanna Thompson describes how the latest findings are spurring scientists to not only rethink depression treatments, but the underlying disease mechanisms themselves.



Fat, Sugar, Salt ... You've Been Thinking About Food All Wrong

Wired, February 2023

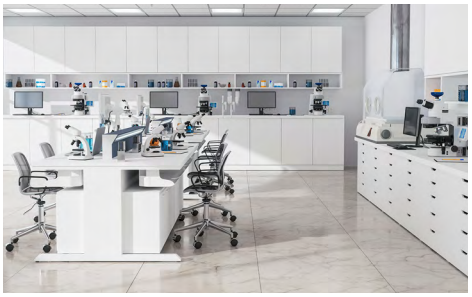
In the realm of nutrition and health, few foods get as bad a rap as ultra-processed ones, which are often packaged, deep fried and chock-full of additives and preservatives. Read the fascinating exploration from Matt Reynolds into the controversial science, toxic health effects and complex classification of ultra-processed foods.



What Does Wellness Mean When You're Fighting an Incurable Disease

GQ, February 2023

In a deeply personal column packed with data, science writer Andrew Zaleski shares his experience dealing with muscular dystrophy at 31. On top of a range of mysterious and life-altering physical symptoms, Zaleski reflects on what health means when you are living with an incurable and rare disease. This article gives insight to anyone facing a chronic illness as well as the clinicians treating them.



The Fight To Keep Ukrainian Science Alive Through a Year of War

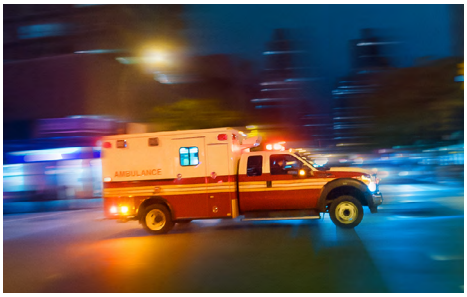
Nature, February 2023

As Ukraine enters the second year of conflict, tens of thousands of scientists in the country are striving to keep their research going, Aisling Irwin reports. Most of the country's researchers—who totaled 60,000 before the war, with some 35,000 scientific support staff—have remained in Ukraine. Some have died fighting on the front line or lost family members. Others have been internally displaced because their workplaces are damaged, destroyed or impossible to operate in due to lack of power. Some have lost jobs, project funds or a proportion of their salary as money is repurposed for the war effort. Ukrainian researchers inside the country say science is "bleeding," and they need support to keep it alive.

Acting Out Dreams Predicts Parkinson's and Other Brain Diseases

Scientific American, February 2023

When we sleep, our brain begins to cycle through various stages of activity, Diana Kwon describes. REM sleep is a distinct period marked by vivid dreaming. While we dream, muscles are temporarily immobilized to prevent acting out those dreams. But for people with REM sleep behavior disorder (RBD), one of the earliest signs of Parkinson's disease, this sleep-time paralysis is lifted. A look at the lived experience of and science behind RBD to better understand opportunities for early intervention.



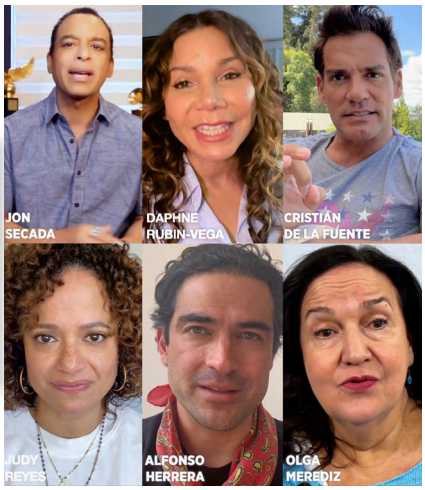
Patients Still Have No Protection Against Surprise Ambulance Bills. And There's No Solution in Sight

STAT News, February 2023

Ground ambulances were excluded from the federal law that banned most types of surprise medical bills starting in 2022—even though roughly 85% of all emergency ambulance rides are out-of-network for individuals. This means that people are often hit with steep ambulance bills that aren't covered by insurance. *STAT*'s Bob Herman investigates the messy battle between ambulance companies, insurers, regulators, policymakers and patients.

Updates & Events

- #UniteToPrevent PSAs in Spanish and English—La Familia & La Communidad—won 2 Anthem Awards this year receiving Silver in Best Influencer Endorsement (Health) and Bronze in the Nonprofit Campaign (Health) categories. The Anthem Awards honor purpose and mission-driven work of people and organizations globally. The PSAs featuring Grammy winner Jon Secada and actors Alfonso Herrera, Cristián de la Fuente, Daphne Rubin-Vega, Judy Reyes and Olga Merediz continue to be circulated in the U.S. reaching more than 140 million people via over 90,000 TV airings.



  #UniteToPrevent is a U.S.-based multimedia campaign that raises awareness of the continued need to act safely, together, to stop the spread of COVID-19. To help improve vaccination rates among Hispanic Americans, the Cura Foundation released an expansion to the #UniteToPrevent PSAs in March 2022. The campaign has been supported by Sanford Health, Akkad Holdings, Aspire Capital and Alliance Global Partners and produced by RonMar Studios.

- The Cell & Gene Meeting on the Mediterranean is scheduled for April 12-14 in Barcelona, Spain. The conference brings together the cell and gene therapy community from Europe and beyond. More than 80 presentations will cover a range of commercialization topics from market access and regulatory issues to manufacturing and financing. Learn more at meetingonthemed.com

CELL GENE
MEETING ON THE MED

- On April 30 to May 3, the 26th Annual Milken Institute Global Conference will bring together thought and industry leaders around the theme of "Advancing a Thriving World." From gene therapies to renewable energy, AI to infrastructure and DEI to FinTech, attendees will gain valuable insights and make crucial connections to drive progress and prosperity. Learn more at milkeninstitute.org/events/global-conference-2023

- The STAT Breakthrough Summit will occur on May 3-4 in San Francisco. The Summit will discuss how to unlock the full promise of emerging medicines, technologies and sources of data to improve patients' health. Speakers include Dr. Jennifer Doudna, Nobel Laureate and co-inventor of the CRISPR/Cas9 technology and President of the Innovative Genomics Institute; Stephen Gillett, chief executive officer of Verily and Dr. Vineeta Agarwala, General Partner at Andreessen Horowitz. Learn more at bit.ly/2023_Breakthrough_Summit

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