UCLA Health RADIATION ONCOLOGY JOURNAL

SPRING 2024 RADIATION ONCOLOGY JOURNAL



4 CHAIR'S LETTER

6 KEHINDE WILEY Painting the "Grand Manner" of a Black future.

18 NICK FLYNN The importance of human connections.

24 DR. LAURIE SANTOS Cultivating Happiness with

Yale Professor and Happiness Icon, Dr. Laurie Santos.



Changing healthcare with

46 DR. UMA NAIDOO

Exploring the scientific connection between nutrition and mental health with Dr. Uma Naidoo of MGH and Harvard.

66 A NOVEL APPROACH TO METASTATIC PROSTATE CANCER

A novel treatment for metstatic prostate cancer with Dr. Amar Kishan and the SATURN Trial.

A PATIENT'S EXPERIENCE 54 A patient's experience with Dr. Thomas E. McWilliams.



56

MARK GRATTAN

Exploring the connection between well-being and the power of where you put yourself in a space with multidiscplinary designer Mark Grattan.

CHAIR'S Letter

Dear All,

As we near the end of the first quarter of 2024, this issue of the *UCLA Radiation Oncology Journal* explores ideas, research, and conversations beyond our department and bigger than ourselves—ideas, research, and conversations that aim to enrich our experience.

Our Featured Artist, Kehinde Wiley, President Obama's official presidential portraitist, re-visions Old Masters' and, through his work, paints the exquisite "Grand Manner" of a Black future. Dr. Trudy Wu and Dr. Beth Neilsen, the next generation of Radiation Oncologists, share their contributions to the treatment of non-small cell lung cancer. Featured Poet, Nick Flynn, drives home the importance of human connection. Dr. Ann Raldow and Kathleen Mier, LCSW, catch up with Yale's iconic "happiness professor," Dr. Laurie Santos, about how we can all cultivate more joy in 2024. Dr. Travis Courtney's article from Seminars in Radiation Oncology lays out the UCLA Department of Radiation Oncology's work to advance care through MRI-Guided Radiation Therapy (MRgRT). UCLA Radiation Oncology's Registered Dietitian, Lydia Chau, MS, RDN, CNSC, sits down with Dr. Uma Naidoo, Director of Nutritional and Lifestyle Psychiatry at Massachusetts General Hospital (MGH), to delve into the scientific connections between nutrition and mental health. Our Editor-In-Chief explores the intersection of well-being and the "power in where you put yourself in a space" with the multi-disciplinary and transcendent designer Mark Grattan. And Dr. Amar Kishan provides an update on his SATURN Trial-demonstrating a paradigm shifting approach for the treatment of metastatic prostate cancer.

And now, following Dr. Laurie Santos' advice regarding letters of gratitude, let me take this opportunity to express my heartfelt gratitude to our faculty, residents, fellows, research associates, and staff for the dignity and professionalism they exhibit every single day as they uphold and embody UCLA Health's vision "to heal humankind, one patient at a time, by improving health, alleviating suffering, and delivering acts of human kindness."

Be well and stay safe,

Michael Steinberg, M.D. Professor and Chair









P A I N T I N G T H E " G R A N D M A N N E R " O F A BLACK FUT U R E

KEHINDE WILEY

"...if someone is alive in the world, they already have something quite grand going for them"

hen I began studying painting and drawing at the San Francisco Art Institute (SFAI) in 2005, Kehinde Wiley was 28 years old and already a rising star in the art world, quickly gaining international attention. A 1999 graduate of SFAI, Wiley stood out from the long list of famous alums because he was young, Black, and making paintings that were said by art critics to bridge Hip-hop culture with Old Masters' prowess and command. In fact, Wiley's trips to the Huntington Library's galleries during his youth were instructive; he was fascinated by the British Grand Manner painters' elevation of portraiture, the idealization and opalescence both in what was portrayed within paintings as well as the boldness of color and models' poses, manner, and attire. This included The Blue Boy, a painting by Thomas Gainsborough that is in the Huntington's collection, and that Wiley's connection with would very recently be solidified in current art history.

By the time his official Presidential painting of former President Barack Obama was unveiled in 2018, Wiley's work had already exhibited widely, including at the Smithsonian American Art Museum in Washington, D.C. Now, 25 years since his time at SFAI, you will never hear Wiley's work referred to as "Hip-hop," but you will hear his work referenced often in complex conversations about race, identity, and how we use language when discoursing on the concerns, cultures, and identity of, and continued systemic roadblocks and violence upon Black and brown people. While it is true that Wiley has painted Black models in the poses of paintings by Old Masters such as Jean-Baptiste Carpeaux, Artemisia Gentileschi, and more, it is important to note that this is a continually relevant and intentional point of entry on Wiley's part for three reasons: his desire for Black people to be able to see themselves on the walls during visits to museums and galleries, his knowledge that museums and other cultural institutions would die if they were unable to continue to entice new generations to join as members and engage as visitors/viewers and performers/artists, and, perhaps most importantly, his desire for the root causes for harm of Black lives to be addressed.

For Kehinde Wiley: An Archaeology of Silence, the major exhibition San Francisco's de Young Museum mounted last year, Abram Jackson, the inaugural Director of Interpretation for Fine Art Museums of San Francisco, collaborated with a team he curated of "local community interpretation partners" for building the narrative and public-facing materials to present and accompany Wiley's exhibition. André Bloodstone Singleton, an educator, human rights activist, multi-disciplinary artist, and death doula, was one of these collaborators. In the Fall 2023 issue of Fine Arts, Fine Arts Museums of San Francisco's membership journal, Singleton wrote an article titled "Interpreting Kehinde Wiley" about the interpretation work's importance in "using the word 'Black' as a main identifier and the word 'people' in lieu of 'bodies," and how much the language we use to discuss Wiley's work matters. He went on to compare the models' positions in repose to his own experience with cancer: "Wiley's subjects lying down are no different than I was when I was lying down getting chemotherapy. The opportunity to shift words about the meaning of art is the sacred

healing part of this experience, and it feels like we are healing in real time."

While the figures portrayed in this exhibition glowed with what at first glance seems to be health and youth, accompanying written materials—and even the exhibition's title—indicated otherwise and ensured viewers would take pause, possibly view the figures as martyrs, but definitely feel the reverberations of how, more often than otherwise, the images our culture holds up of Black people are those in similar poses after an untimely death. Wiley's work continues to be as impeccably executed as ever, but the importance has shifted away from re-visioning famous works; the way a model is presented is what is fascinating, and the de Young exhibited as many sculptures as paintings. It is clear that the way viewers interact with Wiley's work is personal, independent from references to art history.

In recent years, too, producing fewer paintings that might be directly connected to a specific Old Masters' work (even the painters of the Grand Manner style) could be due to that historical reference having been transcended, the essence of art history now more part of Wiley's painterly muscle memory than the overarching or overriding purpose. His 2023 painting, Portrait of Ya Fatu Conteh, is one such work. As Wiley has done with re-visioning Old Masters' paintings, he also re-visions designs and patterns housed in museums and museum archives. Portrait of Ya Fatu Contehuses a 1850's A.H. Lee & Sons design pattern ("Hollyhock," in the archives at the Victoria and Albert Museum), the model's body interacting with the design as if it has come to life, somehow, while still remaining two-dimensional.

Wiley "casts" his models by introducing himself to people on the streets of cities he lives in and visits; he believes if someone is alive in the world, they already have something quite grand going for them, so painting strangers who strike him is a notion that makes sense. The 96x72" oil on canvas is of a woman he met in London while prepping for a 2020 exhibition at William Morris Gallery. Some viewers have seen this painting as a nod to Degas' dancers, but since Wiley has been mum about the painting beyond where he met the model and when, there is no guarantee that any reference to Degas was intentional.

One painting that was quite intentional in re-visioning is his A Portrait of a Young Gentleman, commissioned by the Huntington Library to celebrate 100 years of the aforementioned Thomas Gainsborough's painting, The Blue Boy, being part of the Huntington collection. The Gainsborough painting first exhibited in the U.K. as A Portrait of a Young Gentleman in 1770 and was purchased by Henry and Arabella Huntington in 1921. The collection it is part of formally became the Huntington in 1928 after his death. They undertook a major restoration of The Blue Boyin 2018 in preparation for their 100-year celebration. Melinda McCurdy, the Huntington's Curator of British Art, said that although Wiley is an American rather than European painter, "Our minds went to Kehinde because of his longstanding comments about how he visited the Huntington as a child and how the collection helped inspire him to become an artist, specifically to work with figural art in the Grand Manner format." Since The Blue Boy is such a pivotal part of their collection, they wanted to do something that not only celebrated the work, but also, McCurdy said, "We wanted to make it relevant for audiences today. Collections of historical European art don't often have images of people of color. This is a factor of that type of collection, so we will use the work of a contemporary artist to help rectify that as much as we can." They worked with Julie Roberts of Roberts Projects Los Angeles to commission Wiley.





McCurdy told me, "His body of work, the way he takes historical examples of portraiture and other compositions and retools them with contemporary figures, that was a really interesting approach for us to be able to make connections across our portrait collection with contemporary practice and the way he diversifies his sitters, his models, and it was important for us to bring in people who look different from the portraits that are on our wall." Indeed, while the model's pose is similar to the original, there is a more contemporary spin with both stance and attire of our time, the pose activated by being less formal and direct-facing. The two figures, by not being identical in pose or even mirror images, interact as two confident young men in conversation.

Wiley had intended to cast his model in Los Angeles since the Huntington is local and because he grew up in Los Angeles—but when the pandemic-era lockdowns took effect, he was working in his studio in Senegal. The young Senegalese man he chose is rumored to be a surfer, but again, Wiley has not confirmed this, and ultimately it is the young man's presence and portrayal that is important. Experiencing how the two paintings interact is remarkable and has further ensured the art world's shift toward normalizing Black people being portrayed and celebrated in public art collections.

Wiley's *A Portrait of a Young Gentleman* first debuted in October 2021 and continues to exhibit directly across from *The Blue Boy* in the Thornton Portrait Gallery. McCurdy told me that she encourages all to visit to view the works in person. She said, "I think it has just transformed the Portrait Gallery at the Huntington, and it's enlivened it in a way that we were hoping for, but we didn't quite expect how powerful the connection across the gallery would be between the historic painting of *The Blue Boy* and Kehinde's new version of it, which is something that really comes through in person." While she doesn't track the numbers of visitors, she has heard anecdotally that a larger, younger audience have been visiting. She hopes that at some point they will have enough data to be able to share metrics about the broader, more diverse audiences visiting directly corresponding to the addition of Wiley's painting to the collection.

Kehinde Wiley's paintings of Black men and women are vital to conversations about Black history and the current reality Black people face. But Wiley's paintings are also beautiful. What draws the viewer to his work is that he, as the Grand Manner artists he admired in his youth had hundreds of years prior, is painting beautiful people with exquisite skill in brilliant tones. \Box

For more information on Kehinde Wiley or to inquire about available work, please contact his gallery, Roberts Projects, at www.robertsprojectsla.com or 323-549-0223.

Kehinde Wiley, *A Portrait of a Young Gentleman*, 2021. Oil on linen. Canvas: 70 $1/2 \times 49 1/8$ in. (179.1 \times 124.8 cm.) frame: 87 \times $64 \times 5 1/4$ in. (221 \times 162.6 \times 13.3 cm.) © Kehinde Wiley. Collection of The Huntington Library, Art Museum, and Botanical Gardens; Commissioned through Roberts Projects, Los Angeles; Gift of Anne F. Rothenberg, Terry Perucca and Annette Serrurier, and the Philip and Muriel Berman Foundation. Additional support was provided by Laura and Carlton Seaver, Kent Belden and Dr. Louis Re, and Faye and Robert Davidson.

Thomas Gainsborough (British, 1727-1788), *The Blue Boy*, 1770. Oil on canvas, 70 $5/8 \times 48 \ 3/4 \times 1$ in. The Huntington Library, Art Museum, and Botanical Gardens.

Kehinde Wiley, *Portrait of Ya Fatu Conteh*, 2024. Oil on canvas. Canvas: 96 x 72 in (243.8 x 182.9 cm) frame: 107 x 83 x 5 in (271.8 x 210.8 x 12.7 cm). Courtesy of the Artist and Roberts Projects, Los Angeles. Photo: Paul Salveson

Contributed by: Ciara Shuttleworth

Ciara Shuttleworth is an alumnus of the prestigious San Francisco Art Institute. She has worked for three prominent San Francisco fine art galleries. Additionally, she has provided art consulting for private and corporate collections, including Google. She is also a published writer with works in the *Norton Introduction to Literature* and *The New Yorker*. Her most recent book is the poetry collection, *Rabbit Heart*.



HIGH-DOSE RADIOTHERAPY WITH CHEMOTHERAPY EFFECTIVE IN TREATING PEOPLE WITH NON-SMALL CELL LUNG CANCER

UCLA-led study finds delivering high doses of radiation with chemotherapy for locally advanced lung cancer is safe and effective when integrating a novel adaptive boost.

A new study led by researchers from the UCLA Health Jonsson Comprehensive Cancer Center shows that using high doses of radiation while integrating an ablative radiotherapy technique called stereotactic ablative radiotherapy (SABR) concurrently with chemotherapy is safe and effective in treating people with locally advanced non-small cell lung cancer that is not suitable for surgery.

Based on mid-treatment response, researchers found the combination treatment, which involves a second radiation plan to personalize a boost for the last third of radiation treatments, is a viable and promising option that helps reduce the risk of toxic side effects and having the cancer return within the chest.

The findings were published in the journal *JAMA Oncology*.

"This treatment method explores uncharted territory," said Dr. Trudy Wu, a radiation oncology resident at UCLA and first author of the study. "Our field has been moving towards hypofractionation across many disease sites; however, it is particularly challenging in locally advanced lung cancer due to the close vicinity of tumor to sensitive structures such as the airways and esophagus. This treatment is also typically delivered with chemotherapy which magnifies treatment-related toxicity. Using a novel adaptive boost technique personalized to an individual's treatment response after the first two thirds of radiation treatment allows for a tighter conformal radiation boost plan and reduction of healthy tissue receiving radiation."

In the past, the prognosis for those with unresectable, locally advanced non-small cell lung cancer has been poor, with low survival rates despite treatment with a combination of chemotherapy and radiation. Current standard of care for this group of patients consists of 30 treatments spanning over six weeks, which can be logistically challenging for many patients. While outcomes have improved with the help of modern treatment advances, like immunotherapy, a portion of patients still develop disease relapse in the chest.

One potential way to prevent cancer from returning within the chest after local therapy is to deliver radiation with a higher dose per single treatment in a more intense, or ablative, fashion.

To find the highest personalized boost dose that could be given safely in combination with chemotherapy, 28 patients at UCLA with stage II or III non-small cell lung cancer were enrolled between May 2011 and May 2018 on an early phase dose escalation trial.



All patients first received a base radiation dose of 4 Gy \times 10 fractions followed by an adaptive SABR boost to target any remaining metabolically active cancer. The first ten patients received a boost dose of 25 Gy (low, 5 Gy \times 5 fractions). If this was deemed safe within a specified follow-up period, patients proceeded to receive a higher boost dose of 30 Gy (intermediate, 6 Gy \times 5 fractions), followed by 35 Gy (high, 7 Gy \times 5 fractions), all with concurrent weekly chemotherapy.

Along with determining the maximum tolerated dose of this novel and personalized approach, the researchers aimed to improve progressionfree survival and shorten the overall duration of treatment for locally advanced non-small cell lung cancer.

The investigators observed the most promising results in the intermediate-dose cohort, where patients received a total of 70 Gy in 15 fractions, inclusive of a 30 Gy boost. This dosage showed a favorable balance between side effects while being a very effective treatment.

Rates of two-year local control, which is when the cancer does not grow back, were 74.1%, 85.7%, and 100.0% for the low-, intermediate-, and high-dose cohorts. Two-year overall survival was 30.0%, 76.2%, and 55.6% for the low-, intermediate-, and high-dose cohorts.

There were no severe toxic effects observed in the intermediate-dose boost cohort. Most patients experienced some degree of mild side effects which included fatigue, and inflammation of the esophagus or lungs resulting in sore throat or cough, respectively. The high dose regimen led to severe treatment-related side effects in two cases.

"Our data shows patients may benefit from targeted, high-dose radiation with chemotherapy

if it's done thoughtfully with adaptive radiation," said Dr. Beth Neilsen, a study author and radiation oncology resident at UCLA. "For the intermediate dose regimen, the incidence of severe side effects was relatively low and showed potential for better local control of the cancer."

The authors note this approach could be explored further in future trials with the addition of consolidation immunotherapy, which is now standard of care in this setting.

"This study contributes to ongoing efforts to improve the treatment of lung cancer, a leading cause of cancer-related death," said Dr. Michael Steinberg, professor and chair of radiation oncology at the David Geffen School of Medicine, director of Clinical Affairs at the UCLA Health Jonsson Comprehensive Cancer Center and one of the senior authors on the study. "The integration of adaptive radiation with chemotherapy offers a novel approach that shows promise in terms of safety, effectiveness and improved patient outcomes, paving the way for more effective and personalized treatments."

The investigators also noted the study has limitations, including a small sample size and need for longer follow-up to assess late side effects.

The study's senior author is Dr. Percy Lee, who was a professor of radiation oncology at UCLA when the research was conducted and is now a practicing radiation oncologist at City of Hope. Other involved UCLA researchers include Dr. Jonathan Goldman, Dr. Edward Garon, Dr. Jay Lee, Carol Felix, Minsong Cao, Stephen Tenn and Daniel Low. □

Contributed by: Denise Heady

Denise Heady is a science communications and media relations manager at UCLA Health. She covers the clinical cancer program along with basic and clinical translational research for the UCLA Health Jonsson Comprehensive Cancer Center.



THE IMPORTANCE OF HUMAN CONNECTIONS

"To uncover, in a sense that is revealing some deeper truth."

NICK FLYNN

ould you believe me if I told you that hope and joy are currencies worth trading in? What if we remained curious enough to attempt to provide those around us with as much hope and joy as we'd like to receive in return? While hope could be said to be expectations based on our own desires, true joy is unadulterated, is simply taking in or sharing pleasure. Or, as the poet Ross Gay said in an episode of *This American Life* podcast about delight, "Come gasp with me." The human condition is a constantly shifting dichotomy: striving for or thriving off moments of successfully attaining joy, walking as many muddy deer trails as paved sidewalks.

One of the loveliest things about poets is how open to and curious about the world they are. Nick Flynn encapsulates this in his approach to collages and poems, and despite notability for his memoirs as well as his poems, he remains ardentheartedly human and filled with wonder for the world around him. (If you've never read his work, you probably know him from the Robert DeNiro-Julianne Moore film, *Being Flynn*, which was adapted from his memoir, *Another Bullshit Night in Suck City*, on the set of which he played a small role opposite his wife, the actress Lili Taylor.)

Low, Flynn's sixth book of poems with Graywolf Press, springs from collages he creates, often with his daughter. Collage is an artform he took to in his teens, and, in the style of Rauschenberg or Dadaera collagists, the medium allows him to combine found materials into images that help make sense of the world, much in the way his poems do in their exploration, and in the case of Low, combining. "When I go through the world, I see an image that somehow hooks on my subconscious," he says, "and I keep it, I bring it back and live with it for a while. And then I find another. It's slow; it takes a long time to make one. Sometimes it takes a year to create one."

Many of the poems in *Low* were drafted during several 30-day poem-a-day practices he undertook when Covid lockdowns occurred and he and his family "left Brooklyn to hunker down upstate." He'd taken stacks of his collages with him, and for each of those 30-day stints, he would choose one at random, look at it for 30 seconds, meditate on it for seven minutes, and then spend ten minutes



free-writing anything he could remember from the collage and the reactions he had during the meditation.

"Sacred Trash" directly addresses a collage of the same title: "My daughter scribbles out / a stranger's face in the news- // paper-maybe // she saw something in his eyes, / something she didn't want // to see." And yet he goes on to examine how "... no one knew what // was worth saving, or whose hand / made anything // sacred," before admitting that, "Nothing // has changed. My daughter / draws a picture of the two of us, // side-by-side, our arms wide-- / this is what I'll remember, // I tell myself." How do we know what to hold onto, what to let go of? What is the meaning of a collage and how will that meaning change over time? With no owner's manual, no one way to live a life, we are left to count on each other remaining open, remaining curious.

"Having a daughter was a very good thing, and I hate to sort of think I'm using my daughter for some sort of enlightenment, but I really feel that. Right when she was born, I had a friend about ten years younger than me, Ben Wizner, who was having a party, and my wife was out of town. And so I took my infant daughter with me and had her on my lap. Ben asked, 'What do you miss most now that you have a kid?' and it was such an odd question because I was sitting there with this crazybeautiful child in my lap. It changed instantly-that was my life." As a long-time reader, I have been privy to the adventures Flynn has undertaken with his now-16-year-old daughter. He says he feels lucky that she shares so much with him and his wife about her life, wants to engage with theirs.

In many of the poems, Flynn directly addresses words, their origins, and their iterations, transformations, and transmogrifications. In "Notes on a Monument to Ether," he focuses on words including "anesthesia" and "revelation," with "...when it comes to pain, you can either feel it or you can numb it. / You spend too long in that realm, wrestling with whatever it is you / hope to numb yourself from feeling, & soon enough very little else / will matter," is followed three stanzas later by, "To uncover, in the sense that it is revealing some deeper truth." The poem is a deep dive into his past, when "I / anesthetized myself daily with whatever I could find," when he worked in a shelter helping others whose afflictions were worse than his own. His fascination with *The History of English* podcast is not uncommon in his line of work, but his exploration of words in *Low* deep-dive into his own encounters with how they help him better understand both people and random connections.

But this poem is also teaching the reader how to enter Low, how to walk or drive beside Flynn as he asks us to look with him, to question with him. In "The Day the Earth Stood Still," he asks of us, "Look // into the night, there must be / millions like you, each looking back // at us. Maybe we are all speaking to each / other, maybe we are showing vou how // we want to be held." It is seeking human connection that drives many to finding community in a bar, as in "OOOO," when he is in bar picking up takeout, a woman, "runs a finger / along my shoulder & says, I like your infinity shirt," before showing him her double-infinity tattoo. "What does it mean / to have twice as much of what is already terrifying?" he wonders. What if he had still been in bars to drink rather than simply to get food? And so this book also hosts an undercurrent of Flynn's long-term sobriety, his having found community and human connection without seeking the numbing he unpacks in poems such as the aforementioned "Notes on a Monument to Ether." The poems in Low exhibit the in-the-present awareness of someone who has overcome his need for exiting the world through substances, who embraces the wonder each moment might have to offer. But, too, Flynn has been sober for so long that his experience with the world has altered... not in his desire to care for others and be part of a community, but in his lack of need to find black and white answers.

In both "Notes on Want" and "Notes on a Calendar Found in a Stranger's Apartment," Flynn imagines scenarios for strangers, poses possible narratives for the unanswerability of what he witnesses. He is at once inquisitive about what he is witnessing and protective of the secrets he will never be privy to, allowing the unknown to remain exactly that. Flynn says, "That comes from my non-fiction work…our job is simply to observe. I may drift into fairytale or speculation, but trust what people say. Someone's inner life is sacred, and it's up to them to reveal what they want to reveal."

And so, I leave you with "Unbroken," his unpacking of the metaphor of a horse as the past, a horse/ the past as broken. Flynn shared a story from the Dodge Festival a few years ago: "It's one of the pleasures one has as a poet. You get to imagine a collective unconscious. Whether it exists or not, I'm sure is up for debate, but as far as I'm concerned there it is in how poems speak to each other across centuries." He goes on to recollect a quote from Brenda Hillman, "(Her hands tracking down her body as she spoke.) 'A poem starts in a seemingly autobiographical,' (her hands around her head) 'and as you keep working on it, it transforms to the universal,' (her hands went moving down her torso) 'but in order for it to become a poem, it has to cross the threshold into the mystery,' (her hands now at her hips). She was tracking her body into the whole experience. The process of writing a poem is a journey into a deeper mystery. That's what I look for in art, that mystery."

The human connection is evident from page one, experiences as universal, nothing as precious... and yet, all as worthy of experiencing. This 100+ page book of poems may seem long, but there is no poem that should have been cut. There isn't a single poem that isn't vital to *Low*. \Box

For more information on Nick Flynn, his books, and his collages, please visit https://nickflynn.org

Contributed by: Ciara Shuttleworth

Ciara Shuttleworth is an alumnus of the prestigious San Francisco Art Institute. She has worked for three prominent San Francisco fine art galleries. Additionally, she has provided art consulting for private and corporate collections, including Google. She is also a published writer with works in the *Norton Introduction to Literature* and *The New Yorker*. Her most recent book is the poetry collection, *Rabbit Heart*.



Unbroken

By Nick Flynn

As if the past were riding up to meet you as if the past could ride a horse

as if the past were a horse wandering riderless along a dusty road

as if the horse had never been ridden

/

They say a horse is broken when the rider can stay on

they say the past is broken when you can let go of it

I have broken with the past, she says

I have erased it from my phone I have blindered my eyes from her eyes

```
/
```

I didn't know the past was made of horses I didn't even call it a horse until now

I didn't even call it strange until I looked back on it

the past was a horse crossing a desert a body draped over it

this is how we get the beloved home

/

Stranger now to never hear a horse upon waking or when out in the field

I didn't know the past would come for me I didn't even call it the past until now

sometimes one gallops past but no one else ever sees it

Nick Flynn, "Unbroken" from <u>Low</u> Available on <u>Amazon</u> Copyright © 2023 Nick Flynn Reprinted by permission of Nick Flynn



TIVATING HAPPINESSICON

DR. LAURIE SANTOS

DR. LAURIE SANTOS

UCLA Radiation Oncology's Dr. Ann Raldow and Kathleen Mier, LCSW recently caught up with Dr. Laurie Santos to talk happiness and how to cultivate more of it in 2024.

Dr. Laurie Santos is an expert on human cognition and the cognitive biases that impede better choices. Her course, "Psychology and the Good Life," teaches students what the science of psychology says about how to make wiser choices and live a life that's happier and more fulfilling. The class is Yale's most popular course in over 300 years and has been adapted into a free Coursera program that has been taken by over 3.3 million people to date.

Dr. Santos has been featured in numerous news outlets including the *The New York Times, NBC Nightly News, The Today Show, CBS This Morning, NPR, GQ Magazine, Slate, CNN and O, The Oprah Magazine.*

Dr. Santos is a winner of numerous awards both for her science and teaching from institutions such as Yale and the American Psychological Association. She has been featured as one of *Popular Science's* "Brilliant 10" young minds and was named *TIME Magazine's* "Leading Campus Celebrity."

Dr. Laurie Santos is also the podcast host for *The Happiness Lab*, which launched in 2019 and has over 100 million downloads.

A / K: Before Yale and your historic happiness course, what sparks drew you to cognitive science and psychology?

L: I was always interested in how people think and how the mind works. My initial research was on the question of what makes people unique, and I studied that question by exploring cognition and thinking in non-human animals, specifically monkeys and dogs. I wound up switching to the study of the science of happiness when I saw the mental health crisis that my students were facing in my role as a Head of College on campus.

A / K: Our patients often face significant change in a short period of time due to their diagnoses. What specific practices or exercises have you found most effective in fostering happiness and resilience among individuals facing health challenges?

L: One strategy is to find ways to acknowledge and allow negative emotions. All too often we assume that the right way to deal with negative feelings is to suppress them or to push them away. But research shows we're better off finding ways to allow our tough emotions. One of my favorite strategies for doing this comes from a practice popularized by the meditation teacher Tara Brach, known as R.A.I.N (https:// www.tarabrach.com/rain/) in which you recognize and allow tough feelings. Another suggestion is to approach these tough times with self-compassion (see https:// self-compassion.org/), specifically mindfully recognizing your own struggles and treating yourself with kindness.

A / K: How can we foster meaningful social connection in a major city where we exist in buffered zones (commuting in our cars by ourselves versus NYC public transport, behind our phones/headphones, ordering groceries/food for delivery versus shopping/dining, etc.)?

L: First, we need to prioritizing spending time with the people we do care about— find time to call a friend or schedule an in-person meet up. Second, I think we need to find more opportunities to talk to strangers. Even a quick conversation with the barista at a coffee shop or a stranger standing near you in line can improve our mood. The key is that we ourselves need to prioritize these interactions in real life. A / K: Sadly, burnout in medicine became commonplace during and post pandemic. How can we apply your work on happiness and the work of Dr. Amy Wrzesniewski on "job crafting" to reset the lens of how we experience and perceive our jobs?

L: Job crafting is the practice of making sure that you're using your strengths and values at work. To make sure you're doing that more effectively, I'd suggest first finding out what your signature strengths are, which you can do by taking this VIA Character Strengths survey: https:// www.viacharacter.org/. Once you know your own personal signature strengths, you should creatively find ways to bring more of these values into your day-to-day work.

A / K: Your instruction on crafting gratitude letters was one of the greatest takeaway gifts from your course. And, as awkward as it can initially feel, doing it in-person with someone you love or care about has been profound. What is a gratitude letter and how can our patients, their families, and our practitioners create and share one today?

L: A gratitude letter is a letter of thanks that you send to someone who

has helped you but who you never properly thanked. Anyone can write a gratitude letter— you just grab a pen and piece of paper and write out why you're so grateful for the impact that someone had on your life. Research shows that writing these gratitude letters can significantly improve your well-being even for several weeks.

A / K: Where can we find you, your work, and your iconic happiness course in 2024?

L: You should check out my podcast, *The Happiness Lab*, anywhere you get your podcasts. And you can learn more about my free online course here: https://www.coursera.org/learn/ the-science-of-well-being. □

For more information on Dr. Laurie Santos, her work, course, or podcast please visit www.drlauriesantos.com





NAVIGATING NEW WAYS TO TREAT CANCER: How MRI-Guided Radiation Therapy (MRGRT) is changing healthcare

In this review article, UCLA physicians from the Department of Radiation Oncology provide a comprehensive overview of the potential benefits, challenges, and economic considerations associated with MRgRT. Unlike traditional methods, MRgRT uses real-time imaging from magnetic resonance imaging (MRI) to guide and adapt radiation therapy, allowing for more precise and effective treatments. While the technology has the potential to revolutionize the field and may even change the standard process of treatment planning and delivery, the authors note that careful evaluation from a healthcare economic and policy perspective is required for its successful implementation, as incorporation of any type of new technology requires that it demonstrates value within the healthcare system. Current evidence suggests that while MRgRT may involve higher initial costs, its advantages in terms of improved outcomes and streamlined processes could ultimately make it cost-effective. Clinical trials, such as the MIRAGE trial, indicate potential benefits of MRgRT, including a reduction in acute genitourinary and gastrointestinal toxicities compared to CT-guided radiation therapy. While the MIRAGE trial demonstrated the toxicity benefits that MRgRT can provide, the SMART trial further demonstrated the potential advantages of MRgRT by incorporating adaptive planning with MRgRT for pancreatic cancer. This review highlighted the capability for on-table adaptive radiation therapy in real-time, which allows for target dose escalation while reducing the risk of injury to surrounding tissues. While the advantage of MRgRT with respect to cancer outcomes make it appealing from the value perspective, the authors emphasize the need for additional evidence, including cost-effectiveness analyses and patient-reported outcomes, to support the widespread adoption of MRgRT. The review's first author is Dr. Travis Courtney, a Radiation Oncology Resident at UCLA. The senior author is Dr. Michael Steinberg, Professor and Chair of Radiation Oncology at the David Geffen School of Medicine. \Box

Contributed by: Denise Heady

Denise Heady is a science communications and media relations manager at UCLA Health. She covers the clinical cancer program along with basic and clinical translational research for the UCLA Health Jonsson Comprehensive Cancer Center.

MRI-GUIDED RADIATION THERAPY An Emerging and disruptive process of care: Healthcare economic and policy considerations

MRI-guided radiation therapy (MRgRT) is an emerging, innovative technology that provides opportunities to transform and improve the current clinical care process in radiation oncology. As with many new technologies in radiation oncology, careful evaluation from a healthcare economic and policy perspective is required for its successful implementation. In this review article, we describe the current evidence surrounding MRgRT, framing it within the context of value within the healthcare system. Additionally, we highlight areas in which MRgRT may disrupt the current process of care, and discuss the evidence thresholds and timeline required for the widespread adoption of this promising technology.

Introduction

Radiation oncology is a field constantly seeking to improve patient outcomes by bringing novel and sophisticated treatment paradigms into the standard of care. Technological innovation in radiation oncology often emphasizes enhancing precision and accuracy in planning and treatment delivery by developing processes that widen the therapeutic ratio by allowing for dose-escalation to tumor tissues while simultaneously reducing dose to surrounding normal tissues. MRI-guided radiation therapy (MRgRT) is a rapidly emerging technology that seeks to achieve these goals through a variety of mechanisms, including taking advantage of superior soft-tissue contrast compared with the current standard of care CT-guided radiation therapy (CTgRT). ¹ MRgRT further leverages MRI capabilities to observe motion and deformation of tumor targets and organs at risk in real-time. This not only allows for beam-on gating, whereby radiation is only delivered to the target structure when it falls within a predefined gating margin, ² but also the innovative and paradigm-shifting possibility of real-time, on-table adaptive treatment delivery ³ which can be augmented through integration of advanced imaging techniques such as functional imaging. ⁴

Given the clinical promise of MRgRT, there has been significant work verifying and validating the use of MRgRT in the United States, Europe, and Asia in recent years. ^{5, 6} Although still early in its development, MRgRT appears to be capable of significantly disrupting the current process of care in

radiation oncology which has been relatively stable for decades. More than just a linear accelerator combined with an MRI device, this technology has been acknowledged to offer more than the sum of its parts, largely due to the real-time imaging features, adaptive planning possibilities of MRgRT, and functional imaging serving as a real-time biomarker for treatment response. In total, MRgRT allows radiation oncologists to operate more akin to surgeons who observe, modify and actively manage their treatments with real-time feedback. The rapidly developing and transformative treatment delivery modality of MRgRT thus invites several important health policy and healthcare economic considerations which will be discussed herein.

The Value Proposition of MRgRT

When a new medical technology emerges that disrupts the routine process of care, it is incumbent for stakeholders to evaluate how the new technology will fit into the existing system from the perspective of delivery of care and value. Incorporation of a new technology, in this case MRgRT, requires that it demonstrates value within the healthcare system. This is particularly true in radiation oncology, which has often been historically singled out for scrutiny given the typically high upfront costs in spite of eventually proving to be high-value care. ^{7,8} As proposed by Steinberg et al.,⁹ value within the field of radiation oncology is influenced by 4 key components: cost, outcomes, structure, and process. Cost and outcomes represent recognizable and intuitive components of value,¹⁰ while the other components of structure and process derive from a separate yet related model for assessing quality in healthcare.¹¹ Structure refers to the larger organization of care delivery as well as the facilities where medical care is being provided, including the equipment, staff, and institutions, and emphasizes technologically current and safe environments. Structure can also extend to include insurance coverage and reimbursement models.¹² Process, on the other hand, relates to the components of healthcare delivery that originate from the patient perspective, emphasizing patient-centered care as well as the technical delivery of care including factors such as physician expertise and physics quality assurance methods. This model can be summarized and expressed as an equation which includes all 4 components, in which value = (outcomes + structure + process)/cost, and where the numerator can also be considered as "quality." Through this equation, there are multiple ways in which value can be enhanced, such as by increasing the numerator of quality and/or decreasing the denominator of cost. However, it is worth noting that value can also be enhanced even in the context of increasing costs through proportionally greater increases in quality, and it is ultimately the overall ratio of quality/cost that is of importance when evaluating value. Thus, a new treatment or technology, in this case MRgRT, can still demonstrate value in radiation oncology despite potentially increased costs, by offsetting these costs with substantial improvements in the structure, process, and outcomes of care.

Cost

As described above, cost is a key component in determining the value of a treatment or technology. In addition, both provider and patient perspectives on cost are important. While this is true for all new treatments, it is of particular importance in radiation oncology where upfront technology costs can be significant.¹³ Such is the case for MRgRT, where the device cost is typically higher than state of the art CT-based treatment delivery devices, and there are supplemental construction costs associated with installing MRI shielding.¹⁴ Moreover, setting in place the additional care delivery infrastructure such as increased medical physics oversight and staffing cost required for these devices, which may have lower throughput compared to standard CT-based treatment devices, all need to be taken into

consideration.¹⁵ However, these apparent expenditures are perhaps less impactful than initially anticipated when one considers other cost savings and increased utility that can be associated with MRgRT. For example, when compared with CTgRT delivery in time-driven activity-based costing analyses, it was estimated that MRgRT was only incrementally more expensive for the delivery of stereotactic body radiation therapy (SBRT) for hepatocellular carcinoma¹⁴ and in absolute dollars, just \$1,497 (in 2021 United States Dollars) more expensive per course of SBRT for prostate cancer16 from thehealth system perspective. Furthermore, while the upfront device costs seem expensive on the surface, the machine costs are amortized over time, and much of the long-term costs associated with MRgRT actually derive from associated staffing and personnel needs.^{17, 18} Ultimately though, cost associated with new technology is often ephemeral in nature, and there are multiple advantages of MRgRT that may actually invite cost-savings and improve value, as will be discussed. Given the upfront investment required to implement MRgRT programs, early acquisition and use of MRgRT remains primarily in larger, well-resourced medical facilities, and widespread adoption may initially be limited by the inability of smaller facilities to acquire the necessary equipment and infrastructure.^{19, 20, 21} At the same time, MRgRT has also demonstrated its ability to successfully integrate into the workflows of some varied US healthcare practice settings-ranging from large academic centers²² to community practices²³ to universal access healthcare systems such as the Veterans Health Administration.²⁴ This suggests that even the high upfront costs are surmountable in a number of practice environments.

Early economic analyses of MRgRT, which mainly examine prostate cancer and focus on cost from the provider perspective, highlight a few important points regarding the economic implications of this technology.¹⁵ As it currently stands and as noted above, MRgRT is associated with incrementally increased costs compared with CTgRT. However, these studies identify multiple practicable ways by

		Change in CTgRT costs Change in MRgRT costs
Model input (baseline assumption)	Decrease in cost	Increase in cost
No. of fractions (5)	-\$554 -\$908	<u>\$564</u>
Expected minutes per year LINAC is expected available (106,448)	<mark>-\$430</mark> -\$750	\$645\$1,124
Price of LINAC (\$4.7M for CTgRT; \$7.8M for MRgRT)	-\$182 -\$433	5182 5433
Useful life for equipment (10 years)	-\$152 -\$361	\$228 \$541
Annual LINAC maintenance costs (\$417.5K for CTgRT; \$550K for MRgRT)		<u>\$160</u> \$305
Capacity cost rate for radiation therapist (\$1.95/minute)	_\$186 _\$270	<u>5186</u> 5270
Duty cycle (60%)	<mark>-\$103</mark> -\$212	<u>5154</u> 5318
Beam-on time per fraction, without gating (5 minutes for CTgRT; 8.2 minutes for MRgRT)	<mark>-\$123</mark> -\$255	5123 5255
Capacity cost rate for radiation oncologist (\$4.75/minute)	<mark>-\$201</mark> -\$216	<u>\$201</u> \$216
Capacity cost rate for dosimetrist (\$2.08/minute)	<mark>-\$127</mark> -\$133	5127 5133
Capacity cost rate for interventional radiologist (\$4.23/minute)	<mark>-589</mark> \$0	589 \$0
Capacity cost rate for nurse (\$2.23/minute)	579 \$48	\$79 \$48

Figure 1. Sensitivity analysis of various costs within the MRI-guided radiation therapy (MRgRT) and CT-guided radiation therapy (CTgRT) processes for stereotactic body radiation therapy (SBRT) in localized unresectable hepatocellular carcinoma. Reproduced with permission from: Parikh, NP, Lee PP, Raman SS, et al. Time-driven activity-based costing comparison of CT-guided versus MR-guided SBRT. JCO Oncol Pract. 16:e1378–1385. https://ascopubs.org/doi/full/10.1200/JOP.19.00605. No changes were made to this figure from the original publication.

A valid concern is that, in its current rendition, treatment times are relatively long with MRgRT, vielding decreased patient throughput with this technology.²⁵ This phenomenon holds true even when not performing real-time on-table adaptive treatment and is thought to be related to issues of machine functionality and capability, such as the intensity modulated radiation therapy (IMRT) treatment delivery modality being a step-and-shoot technique rather than the more efficient volumetric arc therapy technique,¹⁴ as well as the need to further optimize adaptive workflows. Longer treatment times and workflow inefficiency thus impact the value proposition for MRgRT at this point in time. It should be pointed out, however, that full implementation of a MRgRT-only workflow (ie, MRI simulation only) is likely to be associated with reduced cost and improved efficiency over the current process of care.^{26, 27} In the current fee-for-service model, included in the value equation is the number of fractions per treatment course. To the extent that MRgRT enhances our ability to safely deliver ultra-hypofractionated treatments, further cost savings from wide MRgRT implementation are likely to ensue. While some published studies found MRgRT 5 fraction SBRT to be more costly than CTbased treatment,¹⁵ further reducing the number of fractions delivered is another possible method for improving its cost-effectiveness.¹⁴ Such fraction-reducing treatment paradigms are currently under prospective evaluation in prostate cancer ^{28, 29} as well as other disease sites.^{30, 31, 32, 33} The underlying rationale for studies such as these is sound, given that MRgRT has already demonstrated incremental improvements in both patient-and physician-reported toxicity profiles of ultra-hypofractionated radiation therapy.³⁴ Moreover, ultra-hypofractionated treatment courses may mitigate patient financial toxicity through less missed work, reduced caregiver burden, and fewer travel-related expenses, among other components, 35, 36, 37, 38 and shorter treatment courses may even have positive environmental impacts as well.^{39, 40} Furthermore, there are factors specific to the CTgRT process, such as the need for the procedural insertion of fiducial markers for certain disease sites,⁴¹ which are not required with MRgRT, thereby creating additional opportunities for cost savings and improvements in patient outcomes. Finally, MRgRT most often requires both CT and MRI simulations for planning in its current state.⁴² When the treatment planning process can omit CT simulation, which is potentially the case with synthetic CTs,^{16, 43, 44, 45} the costs of MRgRT can be improved even further.

Also fundamental to a treatment's value is how it is incorporated into healthcare insurance coverage and reimbursement policies, and indeed, changes in our billing and coding paradigms are critical for making MRgRT cost-effective as well. Such an undertaking must balance the often-competing interests of payers, patients, the centers investing in MRgRT capabilities, as well as the healthcare system overall. Despite the significant innovations offered by MRgRT, the current billing and coding nomenclature neither distinguishes nor does it differentially reimburse for MRgRT or the process by which it is used in adaptive treatment delivery.^{46, 47} The reflex may be to simply plug these novel treatment delivery processes into the pre-existing adaptive billing lexicon. However, the current coding structure for adaptive radiation therapy is based on legacy adaptive radiation planning and thus does not sufficiently account for the radically different processes utilized in MRgRT adaptive planning. This is especially important to consider under the proposed radiation oncology-alternative payment model (RO-APM),⁴⁸ where adaptive MRgRT may be susceptible to reduced reimbursement relative to its infrastructure costs in the setting of bundled payments.⁴⁹ Continued thought and discussions are needed on how to best account for the different processes introduced by MRgRT in the billing and coding nomenclature in order to maximize the benefit of this technology for all financial stakeholders.

Outcomes

The ability of a treatment or technology to improve oncologic outcomes, such as toxicity or disease control, is a crucial component of value in radiation oncology and healthcare as a whole. Multiple studies have started to report on the clinical outcomes of MRgRT in a variety of cancer sites.⁵⁰ While these data are mostly retrospective in nature, there exist some high-quality prospective studies which begin to confirm the theoretical benefits of MRgRT with respect to cancer outcomes.

The recently published MIRAGE clinical trial³⁴ randomized men with clinically localized prostate cancer to either CTgRT or MRgRT and sought to evaluate whether reductions in isotropic planning target volume (PTV) margins from 4 mm to 2 mm, enabled by MRgRT, would reduce the risk of acute genitourinary (GU) and gastrointestinal (GI) toxicity from SBRT. Indeed, the incidence of physicianreported acute GU (24.4% versus 43.4%, 56.2% relative reduction) and GI (0.0% versus 10.5%, 100% relative reduction) toxicities were improved in the MRgRT arm, as were patient-reported toxicity outcomes. In the economic analyses discussed above, relative reductions in toxicity of 7-54% were needed for MRgRT to become cost-effective compared with CTgRT,^{51, 52} a threshold which was met and indeed exceeded by the results of this trial. Additionally in this trial, patients in the CTgRT arm required fiducial placement whereas those in the MRgRT arm did not, adding further cost savings to the healthcare system otherwise unaccounted for with MRgRT. However, this trial also demonstrated some of the economic concerns with MRgRT, including the need for 2 simulation scans (CT and MRI) in the healthcare system where this single institution study was carried out and increased postimaging treatment delivery times with MRI versus CT guidance (median 1133 seconds versus 232 seconds). Nevertheless, a rigorously demonstrated decrease in radiation-associated toxicity should not be overlooked as it not only improves patient health-related quality of life, but it also reduces acute hospital encounters related to treatment toxicity which can be associated with high costs, procedures, and overall burden for patients, providers, and the healthcare system. Drawing parallels between MRgRT and other historical innovations in radiation oncology, namely IMRT, recall that the widespread adoption of this novel technology was primarily spurred by its associated improvements in normal tissue sparing and toxicity,^{53, 54, 55} and perhaps an analogous implementation threshold would be worthwhile for MRgRT.

While the MIRAGE trial demonstrated the toxicity benefits that MRgRT can provide without daily adaptation, the SMART trial further demonstrated the potential advantages of MRgRT by incorporating adaptive planning.⁵⁶ In this multi-center, single-arm phase II trial of MRgRT in borderline resectable or locally advanced pancreatic cancer, patients were treated to an unprecedented dose of 50 Gy in 5 fractions, and on-table adaptive re-planning was used if the original radiation plans recomputed onto the daily anatomy would not meet treatment constraints. This resulted in adaptive planning being performed in 93.1% of fractions. Overall, there were low rates of acute grade 3 or higher GI toxicity probably (2.2%) and definitely (0%) related to radiation therapy at the augmented dose. Furthermore, this study also reported noteworthy oncologic outcomes including 1 year local control (82.9%), distant progression free survival (50.6%), and overall survival (65.0%). Previous research of MRgRT in inoperable pancreatic cancer found that dose-escalation above a biologically effective dose 10 (BED10) of 70 Gy, which was primarily achievable by adaptive MRgRT, was associated with improved overall survival without an increase in toxicity.⁵⁷ In fact, patients treated with dose-escalated adaptive MRgRT experienced less toxicity than patients treated at a lower BED10 without adaptive radiation therapy. The

SMART trial dosing regimen equates to a BED10 of 100 Gy, further highlighting the clinical advantage of on-table adaptive planning enabled by MRgRT in this study. Importantly, the primary study objective of demonstrating <15.8% acute grade 3 or higher GI toxicity definitely related to radiation therapy was met, indicating that additional prospective evaluation of this technique should be performed.

The SMART trial highlights a unique and important strength of MRgRT compared with the current radiation treatment process—notably, the capability for on-table adaptive radiation therapy in realtime, which allows for target dose escalation while minimizing the risk of injury to surrounding normal tissues. The increased use of MRgRT in recent years has been accompanied by an increase in the percentage of on-table adapted fractions with this technology.^{5, 6} The logistics of this process has been described in multiple studies,^{2, 3, 50, 56} and implementation of this multifaceted workflow is important to consider (Fig. 2). What should also be considered is the amount of time required to complete adaptive treatments, as this has been identified as a cost concern for MRgRT.^{3, 14, 16} The economic evaluations described above did not include adaptive planning in their total treatment time, which has been documented to range from 50-100 min,^{3, 25} although one did note that that this would increase healthcare system costs by only \$529 per adaptive treatment.¹⁴ Additionally, increased staffing and resources are needed for this process, as are technologies and systems for ensuring sufficient plan evaluation and safe treatment delivery.58 However, mechanisms to improve protracted treatment times and inefficiencies are being actively studied, such as through the deployment of artificial intelligence and auto-segmentation^{59, 60} and deep learning.⁶¹



Online Adaptive Planning Workflow
UCLA RADIATION ONCOLOGY JOURNAL

Moving forward, the use of MRgRT and real-time adaptive planning is currently being studied and implemented in a variety of disease sites and clinical situations, including central nervous system tumors,^{50, 62} head and neck cancers,⁵⁰ and breast and lung neoplasms^{50, 62, 63} as well as re-irradiation64 and single fraction metastatic cases,^{65, 66} and may even be expanded to other situations where real-time, high-resolution soft tissue imaging is crucial, such as palliative celiac plexus irradiation^{67, 68, 69} (Fig. 3). Additionally, MRgRT capabilities will continue to progress as well. Beyond motion management and adaptive planning, MRI-specific functional imaging represents a future method through which MRgRT can continue to demonstrate its value.^{62, 70, 71} For example, diffusion-weighted imaging has been identified as a potential biomarker for treatment response and could be incorporated into the MRgRT treatment process for dose escalation of non-responsive disease or dose de-escalation of rapidly responding disease.⁴ The expansion of MRgRT to additional clinical situations and the continued development and improvement of the adaptive treatment process will further support the economic justification of this promising technology.



Figure 3. Utilization of MRI-guided radiation therapy (MRgRT) technology in a variety of disease sites and scenarios. Reproduced with permission from: Fischer-Valuck BW, Henke L, Green O, et al. Two-and-a-half-year clinical experience with the world's first magnetic resonance image guided radiation therapy system. Adv Radiat Oncol, 2:485–493. Copyright Elsevier (2017). No changes were made to this figure from the original publication.

As an emerging technology, a sufficient body of evidence demonstrating the benefit of MRgRT is needed to successfully argue for its incorporation into standard of care of radiation paradigms. A recent survey investigation highlighted the potential challenges associated with widespread adoption of MRgRT based on interviews of personnel involved with MRgRT, revealing that lack of current evidence of clinical benefit was a primary concern surrounding its implementation.¹⁹ Certainly, additional evidence, including not only traditional objective oncologic outcomes but also more thorough cost-effectiveness analyses^{72, 73} and subjective measures like patient-reported outcomes,⁷⁴ would help to further support the MRgRT value proposition. However, emerging technology also frequently outpaces the evidence supporting its use, and thus our field is in the position where we must consider and respect the need for evidence prior to widespread implementation of MRgRT while simultaneously respecting the drive to enable our patients to experience the intuitive but untested benefits of MRgRT. Additionally, it should be acknowledged that technology trials are challenging to conduct,⁷⁵ and it is often infeasible to

perform a randomized controlled trial for every new treatment paradigm. While some endpoints require robust prospective data and extended time periods to measure, such as disease-specific and overall survival, there are other relevant endpoints, such as acute toxicity, which can be determined in a shorter timeframe. Thus, the widespread use of MRgRT need not be delayed until longer-term endpoints are met, similar to the intuition around and the adoption of IMRT.^{76,77} It should also be noted that level I evidence is similarly not reasonable nor a required threshold for the creation of a new Current Procedural Terminology (CPT) code to, for example, capture the work and practice expense of MR-guided adaptive radiation therapy. Therefore, we must carefully consider the evidence threshold required for widespread adoption of MRgRT and associated processes of care. Fortunately, efforts are already ongoing to ensure the appropriate accumulation of data for the introduction of MRgRT.⁷⁸

Additional Opportunities for Value with Disruptive Workflows

While the advantages of MRgRT with respect to cancer outcomes make it appealing from the value perspective, additional value may come from the disruptive workflows inherent to MRI simulation and adaptive processes of care. These aspects relate to the structure and process components of the value equation describe above. Regarding the MRgRT simulation process, being able to omit CT simulation improves value from the patient and system perspectives through reduced appointments, radiation exposure, and overall healthcare congestion, among other factors. Instrumental to this process is the use of synthetic CTs, in which MRI simulation images are converted to synthetic CT data (eg, Hounsfield Units) necessary for dose calculation and treatment planning, which are actively being studied and validated.^{43, 44, 45} Additionally, use of both CT and MRI simulations for treatment planning, which is increasingly the case for disease sites where soft tissue resolution is paramount such as central nervous system, head and neck, and gastrointestinal tumors,⁴² can introduce errors during the image registration process,⁷⁹ introducing yet another opportunity for improvement in outcomes with MRI-only workflows.

However, there are multiple potential advantages of MRI simulation in and of itself compared with CT simulation, which invite additional opportunities for innovation and improving value. For example, the superior soft tissue visualization with MRI allows for improved target delineation such that MRI simulation-based target delineation notably results in smaller clinical target volumes (CTVs) in prostate⁸⁰ and cervical cancer.⁸¹ Furthermore, when combined with online adaptive planning in lung cancer, MRI-based planning resulted in smaller PTVs than would have been generated from an internal target volume (ITV) approach.⁸² Additionally, a recent small retrospective study found that the use of MRI simulation was associated with improved local control in nasopharyngeal cancer, particularly in stage T4 disease, compared with PET/CT simulation, which was proposed to be the result of full visualization of disease extent with MRI.⁸³ MRI-only workflows have been developed^{84, 85} (Fig. 4), and the feasibility and safety of a same-day MRI-only simulation with an adaptive MRgRT workflow was recently demonstrated in palliative radiotherapy cases with encouraging results.⁸⁶ The improved value to the patient provided by this accelerated process is apparent in the palliative setting, where symptom control and minimizing treatment length are emphasized, though this expedited workflow would certainly benefit all patients, especially those receiving a single fraction of radiation or travelling from great distances. Further in the future, with the real-time motion management and plan adaptation capabilities of MRgRT, the concept of the PTV may be rendered obsolete, and future treatments might be planned based solely on the gross tumor volume (GTV) or CTV, which would allow for further

UCLA RADIATION ONCOLOGY JOURNAL

reduction in dose delivered to organs at risk. Beyond the standard anatomic considerations at the time of treatment planning, MRI simulation also unlocks functional tumor-specific considerations as well, which can be interrogated with MRI-based functional imaging, as noted previously. Given the rapidly increased use of MRI-simulation in recent years, the American Association of Physicists in Medicine (AAPM) have published a task group report providing recommendations on the safe and optimal use of MRI simulation,⁸⁷ which is a key aspect of the structure component in the value framework described above. These advantages, as well as the more complicated process of care, validate the notion that MRI-only simulation should not just be conflated with standard simulation nomenclature. Instead, its work and practice expense should be valued for what are already established equipment costs and process of care differences.



Figure 4. Example workflow diagram of an MRI-only prostate radiation therapy process. Permission to reproduce this figure was obtained through the Creative **Commons Attribution 4.0** International License (https:// creativecommons.org/licenses/ by/4.0/). Reproduced with permission from: Persson E, Gustafsson CJ, Ambolt P, et al. MR-PROTECT: Clinical feasibility of a prostate MRIonly radiotherapy treatment workflow and investigation of acceptance criteria. Radiat Oncol, 15:77. Copyright BMC (Part of Springer Nature (2020). No changes were made to this figure from the original publication.

Also crucial to this discussion of incorporating MRgRT into the standard of care in radiation oncology is the realization that the process of care for MRI-based radiation therapy, particularly MRI adaptive radiation therapy, is fundamentally a very different radiation treatment delivery process than that currently utilized for CT-based radiation therapy. The ability for on-table adaptive planning and re-planning with MRgRT represents the most unique aspects of this technology.⁸⁸ While adaptive radiation treatment is not a new concept in radiation oncology,⁸⁹ it historically has been limited due to the logistics of CTgRT. Specifically, legacy approaches to adaptive radiation therapy have not been performed on-table in real-time.⁵⁰ Instead, they are done off-line prior to the next treatment, and they cannot address target or organ at risk deformation. MRgRT, in contrast, allows for a feasible and superior mechanism for performing adaptive radiation therapy, specifically while the patient is on the treatment table, and can be repeated daily. While the data supporting adaptive radiation therapy continue to accumulate, our field must remain open to the plasticity that may accompany the radical shifts in the process of care that MRgRT affords.

Peering into the future, one might imagine a treatment process where simulation as we have come to know it is not performed at all, and treatment is simply delivered de novo based on the daily anatomy. A simulation-free radiation treatment process has been explored in palliative cases, though this process relied on diagnostic images for planning.⁹⁰ In the future, we might be able to rely on treatment machine-generated MRI images alone. These images will require adequate soft-tissue contrast during the on-table acquisition period, which is currently under evaluation.⁹¹ Omission of traditional simulation scans might thus represent a potential avenue to enhance accuracy and quality of care, particularly from the patient perspective as this would reduce appointments, costs, and time from consult to treatment, which might be of particular benefit for patients experiencing symptoms from their tumor such as pain or bleeding.reduction in dose delivered to organs at risk. Beyond the standard anatomic considerations at the time of treatment planning, MRI simulation also unlocks functional tumor-specific considerations as well, which can be interrogated with MRI-based functional imaging, as noted previously. Given the rapidly increased use of MRI-simulation in recent years, the American Association of Physicists in Medicine (AAPM) have published a task group report providing recommendations on the safe and optimal use of MRI simulation,⁸⁷ which is a key aspect of the structure component in the value framework described above. These advantages, as well as the more complicated process of care, validate the notion that MRI-only simulation should not just be conflated with standard simulation nomenclature. Instead, its work and practice expense should be valued for what are already established equipment costs and process of care differences.

Conclusion

MRgRT has already disrupted the process of care as it pertains to radiation treatment delivery and is well on its way to disrupting the current process of care as it pertains to simulation and treatment planning. With disruption comes new opportunities to evaluate value. While key randomized and non-randomized prospective studies have begun to support the value of MRgRT, this work will be further supplemented by formal cost-effectiveness analyses as more and more robust toxicity and efficacy data emerge. In addition, many prospective clinical trials are currently underway or in development. Ultimately, we postulate that, similar to other disruptive technology in our field (eg, 3D planning, IMRT, image-guided radiation therapy, etc.), the value of MRgRT will be borne out in due course. MRgRT represents more than just another more accurate treatment modality but is a potential departure from

the current radiation therapy planning and treatment process in which on-table daily adaptive radiation therapy is the norm, and perhaps even without a separate simulation. As such, aggressive study in this

space followed by rapid evidence-based implementation is warranted. \Box

References

1. JJW Lagendijk, BW Raaymakers, CAT Van Den Berg, et al. *MR guidance in radiotherapy. Phys Med Biol*, 59 (21 (2014), 10.1088/0031-9155/59/21/R349

2. S Klüter. *Technical design and concept of a 0.35 T MR-Linac. Clin Transl Radiat Oncol*, 18 (2019), 10.1016/j. ctro.2019.04.007

3. J Lamb, M Cao, A Kishan, et al. *Online adaptive radiation therapy: Implementation of a new process of care. Cureus*, 9 (8) (2017), 10.7759/cureus.1618

4. N Shaverdian, Y Yang, P Hu, et al. *Feasibility evaluation of diffusion-weighted imaging using an integrated MRI-radiotherapy system for response assessment to neoadjuvant therapy in rectal cancer. Br J Radiol*, 90 (1071) (2017), Article 20160739, 10.1259/bjr.20160739

5. MD Chuong, MA Clark, LE Henke, et al. *Patterns of utilization and clinical adoption of 0.35 MR-guided radiation therapy in the United States—understanding the transition to adaptive, ultra-hypofractionated treatments. Int J Radiat Oncol Biol Phys,* 111 (3) (2021), pp. 161-168, 10.1016/j.ijrobp.2021.07.1400

6. BJ Slotman, MA Clark, E Özyar, et al. *Clinical adoption patterns of 0.35 Tesla MR-guided radiation therapy in Europe and Asia. Radiat Oncol,* 17 (1) (2022), p. 146, 10.1186/s13014-022-02114-2

7. Y Lievens, M Pijls-Johannesma. *Health economic controversy and cost-effectiveness of proton therapy. Semin Radiat Oncol*, 23 (2) (2013), pp. 134-141, 10.1016/j.semradonc.2012.11.005

8. PE Wallner, ML Steinberg, AA Konski. *Controversies in the adoption of new healthcare technologies. Front Radiat Ther Oncol*, 43 (2011), pp. 60-78, 10.1159/000322401

9. S Teckie, SA McCloskey, ML Steinberg. Value: A framework for radiation oncology. J Clin Oncol, 32 (2014), pp. 2864-2870, 10.1200/JCO.2014.55.1150

10. ME Porter. What is value in health care?. N Engl J Med, 363 (26) (2010), pp. 2477-2481, 10.1056/NEJMp1011024

11. A Donabedian. *Evaluating the quality of medical care. Milbank Q*, 83 (4) (2005), pp. 691-729, 10.1111/j.1468-0009.2005.00397

12. AC Raldow, EM Chang and ML Steinberg, *Healthcare economics and health policy, In: EC Halperin, DE Wazer, CA Perez and LW Brady, Perez and Brady's Principles and Practice of Radiation Oncology*, ed 7, Wolters Kluwer; Philadelphia, PA

13. TR Bortfeld, JS Loeffler. *Three ways to make proton therapy affordable. Nature*, 549 (7673) (2017), pp. 451-453, 10.1038/549451a

14. NR Parikh, PP Lee, SS Raman, et al. *Time-driven activity-based costing comparison of CT-guided versus MR-guided SBRT. JCO Oncol Pract*, 16 (11) (2020), pp. e1378-e1385, 10.1200/jop.19.00605

15. A Castelluccia, P Mincarone, MR Tumolo, et al. *Economic evaluations of magnetic resonance image-guided radiotherapy (MRIgRT): A systematic review. Int J Environ Res Public Health*, 19 (17) (2022), p. 10800, 10.3390/ ijerph191710800

16. NR Parikh, MA Clark, P Patel, et al. *Time-driven activity-based costing of CT-guided vs MR-guided prostate SBRT. Appl Radiat Oncol*, 10 (3) (2021), pp. 33-40

17. M van Herk, A McWilliam, M Dubec, et al. *Magnetic resonance imaging-guided radiation therapy: A short strengths, weaknesses, opportunities, and threats analysis. Int J Radiat Oncol Biol Phys*, 101 (5) (2018), pp. 1057-1060, 10.1016/j.ijrobp.2017.11.009

18. C Hehakaya, AM Sharma, JRN van der Voort Van Zijp, et al. *Implementation of magnetic resonance imaging-guided radiation therapy in routine care: Opportunities and challenges in the United States. Adv Radiat Oncol,* 7 (5) (2022), Article 100953, 10.1016/j.adro.2022.100953

19. C Hehakaya, JR van der Voort van Zyp, JJW Lagendijk, et al. *Problems and promises of introducing the magnetic resonance imaging linear accelerator into routine care: The case of prostate cancer. Front Oncol*, 10 (2020), p. 1741, 10.3389/fonc.2020.01741

20. Treatment Centers. Accessed March 29, 2023. https://www.elekta.com/patients/treatment-centers/

21. MRIdian Treatment Centers. Accessed March 29, 2023. https://viewray.com/mridian-treatment-centers/

22. Davis RL. *Department of radiation oncology to install MRIdian Linac system*. 2017. Accessed March 29, 2023. https://radonc.wustl.edu/department-of-radiation-oncology-to-install-new-mridian-linac-system/

23. Hoag Family Cancer Institute. *Hoag is revolutionizing cancer therapy.*, 2021. Accessed March 29, 2023. https://www.hoag.org/hoag-for-life/hoag-is-revolutionizing-cancer-therapy/

24. ViewRay Inc. Louis Stokes Cleveland VA Medical Center Purchases ViewRay's MRIdian Linac for MRI-guided radiation therapy. 2020. Accessed March 29, 2023.https://investors.viewray.com/news-releases/news-release-details/louis-stokes-cleveland-va-medical-center-purchases-viewrays

25. JW Randall, N Rammohan, IJ Das, et al. *Towards accurate and precise image-guided radiotherapy: Clinical applications of the MR-Linac. J Clin Med*, 11 (14) (2022), p. 4044, 10.3390/jcm11144044

26. J Keyriläinen, O Sjöblom, S Turnbull-Smith, et al. *Clinical experience and cost evaluation of magnetic resonance imaging -only workflow in radiation therapy planning of prostate cancer. Phys Imaging Radiat Oncol*, 19 (2021), 10.1016/j.phro.2021.07.004

27. E Persson, N Svanberg, J Scherman, et al. *MRI-only radiotherapy from an economic perspective: Can new techniques in prostate cancer treatment be cost saving?*. Clin Transl Radiat Oncol, 38 (2023), pp. 183-187, 10.1016/j.ctro.2022.11.012

28. C Greco, O Pares, N Pimentel, et al. *Safety and efficacy of virtual prostatectomy with single-dose radiotherapy in patients with intermediate-risk prostate cancer: Results from the PROSINT phase 2 randomized clinical trial. JAMA Oncol,* 7 (5) (2021), pp. 700-708, 10.1001/jamaoncol.2021.0039

29. Y Alayed, P Cheung, W Chu, et al. *Two StereoTactic ablative radiotherapy treatments for localized prostate cancer (2STAR): Results from a prospective clinical trial. Radiother Oncol*, 135 (2019), pp. 86-90, 10.1016/j. radonc.2019.03.002

30. SL Wang, H Fang, YW Song, et al. *Hypofractionated versus conventional fractionated postmastectomy radiotherapy for patients with high-risk breast cancer: A randomised, non-inferiority, open-label, phase 3 trial. Lancet Oncol,* 20 (3) (2019), pp. 352-360, 10.1016/S1470-2045(18)30813-1

31 Chin R. *Stereotactic body radiation therapy using HyperArc in treating patients with recurrent head and neck cancer.* Accessed March 29, 2023. https://clinicaltrials.gov/ct2/show/NCT03892720

32 RR Bahadoer, EA Dijkstra, B van Etten, et al. *Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): A randomised, open-label, phase 3 trial. Lancet Oncol, 22 (1) (2021), pp. 29-42, 10.1016/S1470-2045(20)30555-6*

33. A Kalbasi, M Kamrava, FI Chu, et al. *A phase II trial of 5-day neoadjuvant radiotherapy for patients with highrisk primary soft tissue sarcoma. Clin Cancer Res*, 26 (8) (2020), pp. 1829-1836, 10.1158/1078-0432.CCR-19-3524

34. AU Kishan, J Lamb, M Casado, et al. *Magnetic resonance imaging-guided versus computed tomography-guided stereotactic body radiotherapy for prostate cancer (MIRAGE): Interim analysis of a phase III randomized trial. J Clin Oncol*, 40 (6 suppl) (2022), pp. 365-373, 10.1200/jco.2022.40.6_suppl.255

35. TN Sholklapper, ML Creswell, AT Payne, et al. *Patient-reported financial burden following stereotactic body radiation therapy for localized prostate cancer. Front Oncol*, 12 (2022), Article 852844, 10.3389/fonc.2022.852844

36. S McClelland, EE Harris, DE Spratt, et al. *Navigator-assisted hypofractionation (NAVAH) to address radiation therapy access disparities facing African-Americans with breast cancer. Rep Pract Oncol Radiother*, 27 (3) (2022), pp. 583-588, 10.5603/RPOR.a2022.0064

37. LA Gharzai, R Jagsi. *Incorporating financial toxicity considerations into clinical trial design to facilitate patient-centered decision-making in oncology. Cancer*, 129 (8) (2023), pp. 1143-1148, 10.1002/cncr.34677

38. SY Zafar, AP Abernethy. *Financial toxicity, Part I: A new name for a growing problem. Oncology* (Williston Park), 27 (2) (2013), pp. 80-81

39. D Larios, SA Dunn, JH Li, et al. *The carbon footprint of radiation oncology on climate change: A model in early-stage breast cancer. Int J Radiat Oncol Biol Phys*, 114 (3, Supplement) (2022), p. S129

40. NJ Coombs, JM Coombs, UJ Vaidya, et al. *Environmental and social benefits of the targeted intraoperative radiotherapy for breast cancer: Data from UK TARGIT-A trial centres and two UK NHS hospitals offering TARGIT IORT. BMJ Open*, 6 (5) (2016), Article e010703, 10.1136/bmjopen-2015-010703

41. N Scher, M Bollet, G Bouilhol, et al. *Safety and efficacy of fiducial marker implantation for robotic stereotactic body radiation therapy with fiducial tracking. Radiat Oncol*, 14 (1) (2019), p. 167, 10.1186/s13014-019-1373-2

42. D Moore-Palhares, L Ho, L Lu, et al. *Clinical implementation of magnetic resonance imaging simulation for radiation oncology planning: 5 year experience. Radiat Oncol*, 18 (1) (2023), p. 27, 10.1186/s13014-023-02209-4

43. M Lerner, J Medin, C Jamtheim Gustafsson, et al. *Clinical validation of a commercially available deep learning software for synthetic CT generation for brain. Radiation Oncology*, 16 (1) (2021), 10.1186/s13014-021-01794-6

44. E Palmér, A Karlsson, F Nordström, et al. *Synthetic computed tomography data allows for accurate absorbed dose calculations in a magnetic resonance imaging only workflow for head and neck radiotherapy. Phys Imaging Radiat Oncol*, 17 (2021), p. 36-42, 10.1016/j.phro.2020.12.007

45. SH Hsu, Z Han, JE Leeman, et al. *Synthetic CT generation for MRI-guided adaptive radiotherapy in prostate cancer. Front Oncol*, 12 (2022), Article 969463, 10.3389/fonc.2022.969463

46. Centers for Medicare & Medicaid Services. *Billing and coding guidelines for radiation oncology including. intensity modulated radiation therapy (IMRT)*. Accessed December 2, 2023.https://downloads.cms.gov/medicarecoverage-database/lcd_attachments/34652_13/L34652_RAD014_BCG.pdf

47. American Society for Radiation Oncology (ASTRO). *Basics of coding*. Accessed December 2, 2023. https://www astro.org/Daily-Practice/Reimbursement/Practice-Management-Resources/Basics-of-Coding

48. Centers for Medicare & Medicaid Services. *Radiation oncology model*. Accessed March 29, 2023. https://innovation.cms.gov/innovation-models/radiation-oncology-model

49. RF Palm, KG Eicher, AJ Sim, et al. *Assessment of mri-linac economics under the ro-apm. J Clin Med*, 10 (20) (2021), p. 4706, 10.3390/jcm10204706

50. WA Hall, E Paulson, XA Li, et al. *Magnetic resonance linear accelerator technology and adaptive radiation therapy: An overview for clinicians. CA Cancer J Clin*, 72 (1) (2022), 10.3322/caac.21707

51. C Hehakaya, JRN van der Voort van Zyp, BGL Vanneste, et al. *Early health economic analysis of 1.5 T MRIguided radiotherapy for localized prostate cancer: Decision analytic modeling. Radiother Oncol*, 161 (2021), pp. 74-82, 10.1016/j.radonc.2021.05.022

52. LED Schumacher, AD Pra, SE Hoffe, et al. *Toxicity reduction required for MRI-guided radiotherapy to be cost-effective in the treatment of localized prostate cancer. Brit J Radiol*, 93 (1114) (2020), Article 20200028, 10.1259/ bjr.20200028

53. DA Shumway, KA Griffith, LJ Pierce, et al. *Wide variation in the diffusion of a new technology: Practice-based trends in intensity-modulated radiation therapy (IMRT) use in the state of michigan, with implications for IMRT use nationally. J Oncol Pract, 11 (3) (2015), pp. e373-e379, 10.1200/JOP.2014.002568*

54. A Eisbruch, J Harris, AS Garden, et al. *Multi-institutional trial of accelerated hypofractionated intensity-modulated radiation therapy for early-stage oropharyngeal cancer (RTOG 00-22). Int J Radiat Oncol Biol Phys,* 76 (5) (2010), pp. 1333-1338, 10.1016/j.ijrobp.2009.04.011

55. CM Nutting, JP Morden, KJ Harrington, et al. *Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): A phase 3 multicentre randomised controlled trial. Lancet Oncol*, 12 (2) (2011), pp. 127-136, 10.1016/S1470-2045(10)70290-4

56. PJ Parikh, P Lee, D Low, et al. *Stereotactic MR-guided on-table adaptive radiation therapy (SMART) for patients with borderline or locally advanced pancreatic cancer: Primary endpoint outcomes of a prospective phase II multi-center international trial. Int J Radiat Oncol Biol Phys,* 114 (5) (2022), pp. 1062-1063, 10.1016/j. ijrobp.2022.09.010

57. S Rudra, N Jiang, SA Rosenberg, et al. *Using adaptive magnetic resonance image-guided radiation therapy for treatment of inoperable pancreatic cancer. Cancer Med*, 8 (5) (2019), pp. 2123-2132, 10.1002/cam4.2100

58. JE van Timmeren, M Chamberlain, J Krayenbuehl, et al. *Treatment plan quality during online adaptive replanning. Radiat Oncol*, 15 (1) (2020), p. 203, 10.1186/s13014-020-01641-0

59. EB Van Dieren, LGM Zwart, A Bhawanie, et al. *Adaptive radiotherapy can be applied routinely, using an artificial intelligence solution, to treat prostate cancer patients. Int J Radiat Oncol Biol Phys*, 108 (3) (2020), pp. E274-E275, 10.1016/j.ijrobp.2020.07.658

60. D Cusumano, L Boldrini, J Dhont, et al. *Artificial Intelligence in magnetic resonance guided Radiotherapy: Medical and physical considerations on state of art and future perspectives. Phys Med*, 85 (2021), pp. 175-191, 10.1016/j.ejmp.2021.05.010

61. OJ Gurney-Champion, G Landry, KR Redalen, et al. *Potential of deep learning in quantitative magnetic resonance imaging for personalized radiotherapy. Semin Radiat Oncol*, 32 (4) (2022), pp. 377-388, 10.1016/j. semradonc.2022.06.007

62. J Ng, F Gregucci, RT Pennell, et al. *MRI-LINAC: A transformative technology in radiation oncology. Front Oncol*, 13 (2023), Article 1117874, 10.3389/fonc.2023.1117874

63. T Finazzi, MA Palacios, CJA Haasbeek, et al. *Stereotactic MR-guided adaptive radiation therapy for peripheral lung tumors. Radiother. Oncol.*, 144 (2020), pp. 46-52, 10.1016/j.radonc.2019.10.013

64. AM Chen, M Cao, S Hsu, et al. *Magnetic resonance imaging guided reirradiation of recurrent and second primary head and neck cancer. Adv Radiat Oncol*, 2 (2) (2017), pp. 167-175, 10.1016/j.adro.2017.02.002

65. S Lee, P Yadav, AJ van der Kogel, et al. *In silico single-fraction stereotactic ablative radiation therapy for the treatment of thoracic and abdominal oligometastatic disease with online adaptive magnetic resonance guidance. Adv Radiat Oncol*, 6 (3) (2021), Article 100652, 10.1016/j.adro.2021.100652

66. Chuong M. *Stereotactic MRI-guided adaptive radiation therapy (SMART) in one fraction (SMART ONE).* Accessed March 29, 2023. https://clinicaltrials.gov/ct2/show/NCT04939246

67. S Liu, W Fu, Z Liu, et al. *MRI-guided celiac plexus neurolysis for pancreatic cancer pain: Efficacy and safety. J Magn Reson Imaging*, 44 (4) (2016), pp. 923-928, 10.1002/jmri.25246

68. G Jacobson, R Fluss, A Dany-BenShushan, et al. *Coeliac plexus radiosurgery for pain management in patients with advanced cancer: Study protocol for a phase II clinical trial. BMJ Open*, 12 (3) (2022), Article e050169, 10.1136/bmjopen-2021-050169

69. L Hammer, D Hausner, M Ben-Ayun, et al. *Single-fraction celiac plexus radiosurgery: A preliminary proof-of-concept phase 2 clinical trial. Int J Radiat Oncol Biol Phys*, 113 (3) (2022), pp. 588-593, 10.1016/j.ijrobp.2022.02.038

70. PJ van Houdt, Y Yang, UA van der Heide. *Quantitative magnetic resonance imaging for biological imageguided adaptive radiotherapy. Front Oncol*, 10 (2021), Article 615643, 10.3389/fonc.2020.615643

71. MR Tomaszewski, K Latifi, E Boyer, et al. *Delta radiomics analysis of magnetic resonance guided radiotherapy imaging data can enable treatment response prediction in pancreatic cancer. Radiat Oncol*, 16 (1) (2021), p. 237, 10.1186/s13014-021-01957-5

72. GD Sanders, PJ Neumann, A Basu, et al. *Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: Second panel on cost-effectiveness in health and medicine. JAMA*, 316 (10) (2016), pp. 1093-1103, 10.1001/jama.2016.12195

73. SD Ramsey, RJ Willke, H Glick, et al. *Cost-effectiveness analysis alongside clinical trials II-An ISPOR good research practices task force report. Value Health.*, 18 (2) (2015), pp. 161-172, 10.1016/j.jval.2015.02.001

74. E Basch, AP Abernethy, CD Mullins, et al. *Recommendations for incorporating patient-reported outcomes into clinical comparative effectiveness research in adult oncology. J Clin Oncol*, 30 (34) (2012), pp. 4249-4255, 10.1200/JCO.2012.42.5967

75. S Siva, P Ost, M Ali. *The MIRAGE trial-optical illusion or the future of prostate stereotactic radiotherapy?*. *JAMA Oncol*, 9 (3) (2023), pp. 373-375, 10.1001/jamaoncol.2022.6334

76. TS Hong, MA Ritter, WA Tomé, et al. *Intensity-modulated radiation therapy: Emerging cancer treatment technology. Br J Cancer*, 92 (10) (2005), pp. 1819-1824, 10.1038/sj.bjc.6602577

77. R Young, B Snyder. *IMRT (intensity modulated radiation therapy): Progress in technology and reimbursement. Radiol Manage*, 23 (6) (2001), pp. 20-26

78. LGW Kerkmeijer, CD Fuller, HM Verkooijen, et al. *The MRI-linear accelerator consortium: Evidence-based clinical introduction of an innovation in radiation oncology connecting researchers, methodology, data collection, quality assurance, and technical development. Front Oncol,* 6 (2016), p. 215, 10.3389/fonc.2016.00215

79. J Jonsson, T Nyholm, K Söderkvist. *The rationale for MR-only treatment planning for external radiotherapy. Clin Transl Radiat Oncol*, 18 (2019), pp. 60-65, 10.1016/j.ctro.2019.03.005. View PDFView articleView in

80. A Gunnlaugsson, E Persson, C Gustafsson, et al. *Target definition in radiotherapy of prostate cancer using magnetic resonance imaging only workflow. Phys Imaging Radiat Oncol*, 9 (2019), pp. 89-91, 10.1016/j. phro.2019.03.004

81 J Veera, K Lim, JA Dowling, et al. *Dedicated MRI simulation for cervical cancer radiation treatment planning: Assessing the impact on clinical target volume delineation. J Med Imaging Radiat Oncol*, 63 (2) (2019), pp. 236-243, 10.1111/1754-9485.12831

82. T Finazzi, MA Palacios, CJA Haasbeek, et al. *Stereotactic MR-guided adaptive radiation therapy for peripheral lung tumors. Radiother Oncol*, 144 (2020), pp. 46-62, 10.1016/j.radonc.2019.10.013

83. M Gundog, H Basaran, S Dogan, et al. *MR-guided simulation is superior than FDG/PET-guided simulation for local control in nasopharyngeal cancer patients treated with intensity-modulated radiotherapy. Asia Pac J Clin Oncol*, 17 (1) (2021), pp. 43-51, 10.1111/ajco.13400

84. E Persson, C Jamtheim Gustafsson, P Ambolt, et al. *MR-PROTECT: Clinical feasibility of a prostate MRI-only radiotherapy treatment workflow and investigation of acceptance criteria. Radiat Oncol*, 15 (1) (2020), p. 77, 10.1186/s13014-020-01513-7

85. M Lerner, J Medin, C Jamtheim Gustafsson, et al. *Prospective clinical feasibility study for MRI-only brain radiotherapy. Front Oncol*, 11 (2022), Article 812643, 10.3389/fonc.2021.812643

86. JP Schiff, B Maraghechi, RI Chin, et al. *A pilot study of same-day MRI-only simulation and treatment with MR-guided adaptive palliative radiotherapy (MAP-RT). Clin Transl Radiat Oncol*, 39 (2023), Article 100561, 10.1016/j. ctro.2022.100561

87. CK Glide-Hurst, ES Paulson, K McGee, et al. *Task group 284 report: Magnetic resonance imaging simulation in radiotherapy: Considerations for clinical implementation, optimization, and quality assurance. Med Phys*, 48 (7) (2021), pp. e636-e670, 10.1002/mp.14695

88. KK Brock. Adaptive radiotherapy: Moving into the future. Semin Radiat Oncol, 29 (3) (2019), pp. 181-184, 10.1016/j.semradonc.2019.02.011

89. D Yan, F Vicini, J Wong, et al. *Adaptive radiation therapy. Phys Med Biol*, 42 (1) (1997), pp. 123-132, 10.1088/0031-9155/42/1/008

90. JP Schiff, T Zhao, Y Huang, et al. *Simulation-free radiation therapy: An emerging form of treatment planning to expedite plan generation for patients receiving palliative radiation therapy. Adv Radiat Oncol*, 8 (1) (2023), Article 101091, 10.1016/j.adro.2022.101091

91. JS Ginn, D O'Connell, DH Thomas, et al. *Model-interpolated gating for magnetic resonance image-guided radiation therapy. Int J Radiat Oncol Biol Phys*, 102 (4) (2018), pp. 885-894, 10.1016/j.ijrobp.2018.05.012

Authors

P. Travis Courtney 1, Luca F. Valle 1, Ann C. Raldow, Michael L. Steinberg Department of Radiation Oncology, University of California, Los Angeles, CA

Originally published by *Seminars in Radiation Oncology* in Volume 34, Issue 1, January 2024, Pages 4-13. This publication can be accessed online at: https://www.sciencedirect.com/science/article/pii/S1053429623000693?via%3Dihub

Cited by (0) Conflict of interest: none. 1 Author contributed equally as first authors.

Reprinted under Fair Use. © 2023 Elsevier Inc. All rights reserved.



E X P L O R I N G T H E S C I E N T I F I C C O N N E C T I O N B E T W E E N N U T R I T I O N A N D M E N T A L H E A L T H W I T H

DR. UMA NAIDO



DR. UMA NAIDOO

UCLA Radiation Oncology's Registered Dietitian, Lydia Chau, MS, RDN, CNSC, recently caught up with Dr. Uma Naidoo, a Harvard trained nutritional psychiatrist, professional chef, nutritional biologist, and author of *Calm your Mind with Food*, as well as national and international bestseller, *This Is Your Brain on Food*.

Michelin-starred chef David Bouley described Dr. Uma Naidoo as the world's first "triple threat" in the food and medicine space: a Harvard trained psychiatrist, professional chef graduating with her culinary school's most coveted award, and a trained Nutrition Specialist. Her nexus of interests have found their niche in Nutritional Psychiatry.

Dr. Naidoo founded and directs the first hospital-based Nutritional Psychiatry Service in the United States. She is the Director of Nutritional and Lifestyle Psychiatry at Massachusetts General Hospital (MGH) & Director of Nutritional Psychiatry at MGH Academy while serving on the faculty at Harvard Medical School. She was considered Harvard's "Mood Food" expert and has been featured in the *The Wall Street Journal*.

Dr. Naidoo is also the national bestselling author of *This Is Your Brain On Food*. In her book, she shows the cutting-edge science explaining the ways in which food contributes to our mental health and how a diet can help treat and prevent a wide range of psychological and cognitive health issues, from ADHD to anxiety, depression, OCD, and others.

The United States is facing an unprecedented anxiety crisis. At the same time, scientific and medical knowledge about these conditions is rapidly increasing, with massive strides being made in our understanding of the complex relationship between the mind and the gut.

Through her work, Dr. Uma Naidoo presents cutting-edge research about the ways anxiety is rooted in the brain, gut, immune system, and metabolism. Drawing on the latest science on the connection between diet and anxiety, Dr. Naidoo shows us how to effectively use food and nutrition as essential tools for calming the mind.

L: What is nutritional psychiatry and how does it differ from widely practiced defensive medicine?

U: Nutritional psychiatry is the practice of utilizing the power of diet and the food we eat to boost mental health and fend off mental health symptoms. Nutritional psychiatry incorporates principles from both nutrition science and psychiatry to develop personalized dietary interventions aimed at improving mental health outcomes. These interventions may involve dietary changes, nutritional supplements, and lifestyle modifications tailored to individual needs.

The key difference between nutritional psychiatry and defensive medicine lies in their primary focus and approach. While nutritional psychiatry aims to address underlying causes of mental health issues through dietary interventions, defensive medicine prioritizes the symptoms rather than preventing the underlying cause. Often there are unnecessary medical interventions and integrated or holistic approaches to health and wellness are ignored. Nutritional psychiatry helps individuals be proactive by taking charge of their mental health and building long-term habits to sustain overall well-being. Of note when someone is acutely mentally ill such as experiencing suicidal ideation, or manic or psychotic

symptoms--nutrition is important but may not be the first step as they usually require more urgent medical care.

L: How did you arrive at this intersection? What life experiences inspired you?

U: I am honored to pioneer the field of Nutritional, Lifestyle, and Metabolic Psychiatry, making dietary recommendations, a form of a food "prescription," which are highly personalized and based on an individual's unique makeup. This is a precision medicine model due to the uniqueness of the gut microbiome. I learned to cook later in life and discovered it to become a calming space where I could be my most creative. This passion led me to pursue training as a professional chef inspired by my food hero Julia Child.

Since childhood, I had been learning about healthy eating--having spent much time with my grandparents while my mom was at medical school. So during the day, I'd help pick fresh vegetables from the garden and sit down to a delicious meal with my grandparents. They also taught me yoga and meditation. I also experienced Ayurvedic medicine from members of my extended family. When I began working with patients in mental health and studying complex medications and their side effects, I felt strongly that counseling patients about nutrition and lifestyle was key to helping them cope with this. I have always been fascinated with the nutritional value of food. I found that diet and mental health are inextricably linked, and the connection between them goes both ways. After I graduated from culinary school, I completed a program in nutritional science to augment my knowledge of nutrition and confidence in integrating dietary advice into my clinical practice. Armed with my knowledge of psychiatry, nutrition, and the culinary arts, I continued to blend my clinical work with nutritional, lifestyle, and metabolic health techniques.

I honed my own holistic and integrated approach to psychiatry. That method has become the blueprint for my work, culminating in the founding of the Nutritional, Lifestyle, and Metabolic Psychiatry program at Massachusetts General Hospital, the first clinic of its kind in the United States.

L: What is the microbiome and how does it communicate with our brain? How can one improve their microbiome?

U: The microbiome is composed of trillions of bacteria(and other types of microscopic organisms like fungi and protozoa) that inhabit each and every person's gut. In fact, the total microbial population in the human body outnumbers our own human cells 10 to 1 and is composed of thousands of different species! Gut microbiota help us break down nutrients in food, and produce vitamins and other nutrients. The primary reason gut bacteria have such a profound effect on mental health is that they are responsible for making many brain chemicals through which they modulate the nervous system and hormone responses. If healthy gut bacteria are not present, the production of neurotransmitters such as dopamine, serotonin, glutamate, and

gamma-aminobutyric acid (GABA)—all critically important for the regulation of mood, memory, and attention—is impacted, and healthy communication with our brain is disrupted.

As it turns out, the food you eat has a major influence on the balance of your microbiota, because your diet is also your microbiome's diet. Different types of bacteria thrive on different kinds of nutrients, and changes in the foods you eat can vastly vary in bacterial composition in the gut. Thus, it is crucial to feed your microbiome in a way that promotes the growth of helpful bacteria and discourages harmful ones. To improve your microbiome, I always recommend eating the rainbow and more fiber! That is, to eat a diverse array of whole plant-based foods, colorful vegetables, fruits, herbs, nuts, seeds, whole grains, and beans. When gut bacteria feed on these fiberrich foods, they produce anti-inflammatory compounds and promote better digestion and microbiome growth. I also believe in a balanced diet including healthy fats(e.g. avocado or olive oil, nuts and seeds), clean proteins (lentils, legumes, organic non-GMO tofu or pasture-raised chicken, or grass-fed beef for example), and complex carbs (broccoli, greens, and cauliflower).

L: What are the "six pillars" and how can we start applying them today?

U: The six pillars of nutritional psychiatry will help you understand how to utilize food to support your mental health. **1. Be Whole, Eat Whole:** More than 80% of your diet should consist of whole, real, unprocessed, and fiber-rich foods that support the development of a healthy mind and gut.

2. Eat The Rainbow: Different colored plant foods contain different brain-boosting nutrients. So to optimize the nutrient quality of your diet, be sure to eat the rainbow! With every meal strive to fill 75% of your plate with whole, fiber-rich, low-glycemic vegetables such as leafy greens, cucumbers, radishes, eggplant, mushrooms, and tomatoes.

3. The Greener, The Better: Greens are amazing for the mind! Leafy greens encompass a variety of options such as spinach, Swiss chard, collard greens, arugula, romaine, and dandelion greens. These greens are rich in folate, a vital vitamin essential for neurotransmitter function. Studies have linked folate consumption to reduced depressive symptoms and enhanced cognition.

4. Tap Into Your Body Intelligence: An important aspect of mental well-being is mindfulness and the capacity to acknowledge how things make you feel, food included, and act accordingly. Pay attention to your mental health symptoms in response to various foods and use this body intelligence to guide you.

5. Consistency and Balance are the Keys!: Sustainable dietary change requires balance and short-term miracle diets or quick fixes will not help your brain in the long term. To optimize your mental health in a lasting way, follow the 80/20 rule. **6. Avoid Anxiety Triggering Foods:** Embrace the beneficial alterations you've implemented in your diet and how you approach food while removing items that may hinder your progress. Foods with inflammatory properties and those known to induce anxiety, such as added and refined sugars, industrial seed oils (like soy, corn, and grapeseed), as well and processed foods, and meats containing nitrates, aren't conducive to mental well-being.

L: Can one eat to reduce and/or eliminate anxiety? Poor sleep? Memory loss? If yes, what does that look like? Do you have any recipes you're willing to share?

U: Regarding anxiety, the impact of our diet on our levels of worry and distress is remarkably significant. As a practitioner in Nutritional Psychiatry, I advocate for prioritizing whole foods to manage anxiety and enhance mental well-being. Below are my top five foods that have consistently shown clinical benefits in my patients, supported by scientific evidence. Increasing consumption of these foods while decreasing intake of sugary and processed foods can effectively alleviate symptoms of anxiety, leading to an improved sense of calm.

1. Prebiotic Fiber: veggies are rich in prebiotic fibers that feed and help maintain an abundance of healthy bacteria in the gut which is associated with reduced neuroinflammation and stress. Prebiotic foods include asparagus, garlic, onions, leafy greens, artichokes, legumes, mushrooms, and apples, amongst others. I recommend including a variety of these veggies in the diet to ensure a diversity of brain-boosting vitamins and minerals along with fiber.

2. Berries: loaded with fiber, antioxidants, and vitamins, berries support a healthy microbiome and can reduce inflammation. Blueberries specifically contain one of the highest concentrations of anxiety-reducing anthocyanin, a powerful antioxidant that supports brain health by fighting off oxidative stress. Wild blueberries even have twice the antioxidant power of regular blueberries! However, raspberries, blackberries, and strawberries are all great fruits to reach for when feeling anxious. I love having a quarter cup of blueberries daily as part of a brainhealthy breakfast or snack!

3. Omega-3 Fatty Acids: omega-3 fatty acids are an incredibly powerful tool in reducing inflammation in the gut and brain. They can be found abundantly in wild-caught fish like salmon, anchovies, tuna, mackerel, and sardines, as well as in nuts and seeds like walnuts and chia seeds. Omega-3 consumption is associated with reduced anxiety, brain fog, and cognitive decline, as well as improved mood.

4. Spices: spices like turmeric with a pinch of black pepper, cinnamon, saffron, rosemary, and ginger not only boost the flavor and color of our meals but are also rich in antioxidants, micronutrients and anti-inflammatory compounds for improved mental fitness. Enjoying my turmeric latte each morning is one of my go-to practices for reduced stress and good energy throughout the day!

5. Fermented Foods: a healthy microbiome

is dependent on a healthy presence of good bacteria in the gut and an effective way to replenish these populations of good bacteria is through eating fermented foods! Naturally rich in live cultures, foods like sauerkraut, kimchi, kefir, miso, and plain yogurts are excellent for mental fitness. Consuming fermented foods in conjunction with the above-mentioned fiberrich veggies is key for maintaining a healthy microbiome and defending against chronic inflammation.

On my website blog *umanaidoomd.com*, you can find several recipes that offer practical ways to help you integrate these foods into your diet and feel more comfortable in your kitchen! My two books, *This is Your Brain on Food*, as well as *Calm Your Mind With Food*, also offer detailed menus for combating anxiety, depression, OCD, and improving calm and focus!

L: You are a survivor of cancer. When you were diagnosed, did you implement any aspects of your research into your life? If yes, what? What was your lived experience of their efficacy?

U: After I was diagnosed with breast cancer, I strongly believe my research into nutritional psychiatry is what saved me and helped me push through to become a survivor. While I was used to making nutritional recommendations as a clinician, this time I had become the patient, and it allowed me the opportunity to firsthand critically reflect on the impact of food on my body and mental health, while also experiencing the benefits of eating whole foods after I implemented my advice.

Throughout my treatment journey, I resolved to take care of my mind and body by eating healthy food—no matter what the cancer threw at me. Because of how I ate, I was never nauseous after chemotherapy. My appetite increased and decreased as a side effect of medications, which made my weight fluctuate. However, I continued to eat food I loved, even when medication changed its flavor. Through all of this oncologic assault on my body, I felt surprisingly healthy. The food I ate helped me maintain energy, even though I should have been drained from the constant round of treatments.

It was admittedly a greater challenge to stay on top of my mental health, but once again, the food I ate was crucial to keeping an even keel and positive emotional outlook.

I was careful to make smart food choices that were not loaded with unhealthy calories. Fatigue prevented me from working out, so I chose to take brisk walks regularly. These walks also uplifted my mood (exercise does raise endorphins).

L: What are you currently working on? What's next for the field?

Currently, I am continuing to promote my new book *Calm Your Mind with Food* while also exploring how we can leverage health technology to further personalize nutritional psychiatry recommendations. I am releasing my new podcast later this year and am very excited to share more soon. I am hopeful to dive into further research to determine optimal dosing and duration of nutritional recommendations for specific concerns and conditions. □

For more information on Dr. Uma Naidoo, her work, recipies, and books please visit: https:// umanaidoomd.com

Amazon: https://www.amazon.com/stores/Uma-Naidoo-MD/author/B08D3HXP9H?ref=ap_rdr& isDramIntegrated=true&shoppingPortalEnable d=true

DR. THOMAS E. MCWILLIAMS

ONE PATIENT'S CAREWITH UCLA Health RADIATION ONCOLOGY

s a retired physician and former medical school Dean, I feel comfortable in evaluating the quality of medical care. Since one in every 7-8 men will eventually have prostate cancer, I thought it might be useful to comment on my recent experiences at the UCLA health care system. Most of my practice era colleagues are now retired and I relied on my youngest son for a recommendation. He is now the Section Chief for Interventional Radiology at UCLA and he referred me to Dr. Wayne Brisbane (Urology), Dr. Albert Chang (Fiduciary and OAR spacer placement), and Dr. Amar Kishan (Radiation Oncology - Stereotactic Body Radiation Therapy) at UCLA. I found the care by these physicians and their entire team to be exceptional. The equipment at UCLA is top notch, and I would highly recommend consideration of this facility to anyone needing evaluation and management of this condition. It was certainly worth traveling to CA. Dr. Kishan has a number of presentations available on YouTube that I found helpful in making decisions regarding care. The evaluation and management of prostate cancer has changed dramatically since I was in active practice. I would like to formally express my appreciation to the professionals at UCLA--they have a highly developed system for providing comprehensive and responsive health care. " - Thomas E. McWilliams, D.O., FACOFP





THERE'S POWER IN WHERE YO



U PUT YOURSELF IN A SPACE

Within a building designed by the late Mexican architect Luis Barragán, Grattan's living room drips with light. On the previous page, a custom console is topped in marble and faced in in velvet. Grattan added mirrors to the space to bounce light and cast back the park just beyond the windows.

ON MARTING.

UCLA RADIATION ONCOLOGY JOURNAL

GRATTAN

Our Editor-in-Chief recently caught up with Mark Grattan, a multi-disciplinary designer who works between New York, Mexico, and Brazil to delve into well-being and "the power of where you put yourself in a space."

Grattan's work, unabashedly eclectic yet cohesive, is a dialogue in color and texture. His singular furnishings and interiors are steeped in Tropical Modernism, modern contemporary Italian design, and Art Deco.

His studio is known for made-to-order collectible furniture, interior architecture, interior design, and design consulting. Ohio raised and Pratt Institute trained, Grattan has been a master woodworker for nearly two decades. He is the winner of HBO Max's *Ellen's Next Great Designer* and a pioneer and activist for the establishment of black bodies in design. Grattan designed the New York home of sports superstars, Sue Bird and Megan Rapinoe. And Solange Knowles has sourced Grattan to helm product development for her design studio and creative agency, Saint Heron. In 2021 *Elle Deco*r wrote that Grattan was a "designer about to take flight." In 2024 I'd argue he's soaring—has become a designer with staying power.



"I would advocate, but I would not insist, repetition and order are directly linked to well-being and peace of mind."

E: Richard Neutra, who left an imprint on the landscape of Los Angeles, believed spatiophenomenological stimuli could elicit a physiological response from the body. The first time I heard you speak, you expressed a similar sentiment—that there's "power in where you put yourself in a space. How you live in a space. What you wake up to and go to bed to every night." Can you elaborate on this? What connections can be drawn between how we live and our well-being?

M: I put this in the same category as healthy eating and exercise. You can't fully understand the benefits unless you are in the practice. You can't really understand the difference unless you have something to compare with those habits, patterns, routines, or experiences. My health and what I surround myself with are the only two things I can control. In some cases, my health and home are the only things that help me cope with a world that feels so harsh and unpredictable at times. My home grounds me, reminds me of how far I've come, helps me set goals. My home helps me remember who I am; it helps me set peace, feel inspired. And it helps me feel well rested and, overall, in a desirous, curious state of mind. In a more specific physical context, I am deeply influenced by visual noise (or the lack thereof) and lighting. For example, clearing visual noise or putting things away, I've learned whether that be in the work studio or in the home, helps me think more clearly and promotes an overall productive lifestyle where I'm ready to problem solve (keyword).

E: How did your upbringing and life experience inform your trajectory and sensibilities as a multi-disciplinary designer?

M: Both of my parents worked for the City of Cleveland. And both were ambitious in their own rebellious ways. We were a rebellious Black family in a place where we were meant to be one way, my sister included. The Grattan Family consistently upset the status quo, my mother in particular. This state of mind helped guide me through challenges of feeling alone, unsupported, and undesirable in an industry that most of the time bores me with its point of view. The protest in my work comes from my mother and the creativity comes from my father, who was a woodworker in his free time.

E: Repetition is visually apparent in much of your work, including your singular furniture. How does this concept lend itself to a sensation of order and well-being? How can we apply this concept to our own lives?

M: Repetition makes me feel comfort. A series of shapes or a familiarity in what is to come could be another explanation. It surely must be a psychological request for contentment, that might feel ritualistic, nature of habit. While some thrive on order, many others can thrive off spontaneity and disarray. I would advocate, but I would not insist, repetition and order are directly linked to well-being and peace of mind.

E: Many who reside in major cities do not own. What is your advice for improving a rental making it a refuge?

M: This is a dangerous question to be asking me. I treat every rental like it's my own. Haha! I do not own yet, and I cannot wait for the day I have full freedom. However, my advice would be to ask yourself a few questions before you sign a lease agreement: How is the natural light and where does the sun rise and set? What is the quality of the existing finishes on floors? How much storage do I have? And what about this layout—is there a flow? Does it look like the landlord cares about the property? Working with great bones or foundation leaves a lot less work for you in the end. Choose a rental carefully based on a few dealbreakers, like natural light. Settling on something because "it's just a rental, I won't be here that long" is one reason why most people feel uncomfortable and miserable in their own homes.

E: When fast manufacturing and furnishing is so prevalent, what is your advice for thoughtfully curating a space where we will feel our best? In an editorial in *Sight Unseen*, you said it took you nearly fourteen months to furnish your apartment in Mexico. What were you doing, germinating on, observing during that time? What foundational pieces should one focus on in a new space that will provide the highest quality of life? And, for those of us who are already established in our spaces, what can we do to improve upon them?

M: I disagree with the idea of "now." Build on something with time. Furnishing a home is a slow journey and accelerating that journey can leave you feeling regretful. Enjoy the process of discovering what you love about furniture, lighting, textile, shape, and color in regard to your own personality and what resonates with your aesthetic. Fill your home with larger objects that occupy a space rather than a clutter of smaller furnishings. Less sometimes is more. Instead of pushing everything up against a wall, create dynamics by placing objects in the center of a space and give pieces room to breathe—give your eye room to breathe. Have a place for things. Don't be a hoarder. Throw shit away. You don't need that basket of seashells from your family vacation in 2012.

E: Are you a minimalist? What does minimalism mean to you? Is it, in itself, a form of self-care? In an ever-shifting design landscape, will minimalism always have a place?

M: My home is filled with only the things of value to me and my life. I must be discerning and critical. I am not a collector of things and I habitually purge. There's a peace I feel knowing that when it's time to get up and go, it won't be too overwhelming. Minimalism isn't a movement to me. It's a lifestyle. It can be the concept of learning how to be more grateful for what you have. I would describe my work as a designer maximal. A bit difficult to explain, but I believe my work has a foundation in maximalism, but is stripped back. I can be a minimalist and a maximalist in the same breath. □

For more information on Mark Grattan, his work, and furnishings, please visit: https:// markgrattan.com Grattan's noble Himalayan reclines on a custom bed imagined and crafted by Grattan. On the previous page—details of the handcrafted frame.

P

1

A sculptural side table by Grattan's design studio.

1

111



The open-plan kitchen Grattan designed for Sue Bird and Megan Rapinoe. The countertops and backsplash are Brazilian quartzite in Crystal Tiffany.

A

1

NE TO

60⁵⁰

A NOVEL APPROACH TO METASTATIC PROSTATE

Novel treatment approach combines potent hormone therapy with metastasisdirected stereotactic body radiation therapy to treat metastatic prostate cancer

A team of UCLA Health Jonsson Comprehensive Cancer Center investigators has shown the combination of a short course of powerful and intense hormonal therapy with targeted radiation is safe and effective in treating people with prostate cancer that has come back and has spread to other parts of the body.

In the small study, researchers found that 50% of the patients who were treated with the combination therapy had no signs of the cancer and remained free of recurrence six months after their treatment, with less than a quarter experiencing severe side effects from the treatment.

"In contrast, without this combined treatment approach, we would expect approximately 1% of patients to have no evidence of disease at the six month stage," said Dr. Amar Kishan, professor of radiation oncology at the David Geffen School of Medicine at UCLA and senior author of the study. "These results suggest a substantial improvement and strongly suggest there can be a meaningful impact —namely, delaying the need for hormonal therapy and thus without the significant side effects of it— by attacking metastatic prostate cancer early."

The results were published in the journal of *European Urology*.

Nearly all men who are diagnosed with metastatic hormone-sensitive prostate cancer are treated with androgen deprivation therapy, a type of hormonal therapy that aims to lower the levels of male hormones called androgens that can stimulate the growth of prostate cancer cells.

Hormonal therapy can have very significant side effects, like weight gain and loss of libido, and many end up choosing intermittent androgen deprivation therapy. This approach works by periodically stopping and then resuming therapy to better manage side effects of the treatment. And while intermittent androgen deprivation therapy offers better quality of life for patients compared to receiving the treatment continuously, nearly all men in this setting see their cancer return within six months.

One way to prolong the use of hormonal therapy while controlling PSA levels is to leverage a combination of therapies, including stereotactic body radiation therapy (SBRT), which delivers highly focused and intense doses of radiation to the tumor while minimizing exposure to surrounding healthy tissues in short duration.

The UCLA team conducted a single-arm phase 2 trial to evaluate whether the addition of metastasis-directed SBRT and dual androgen

receptor pathway inhibitors, a more potent but shorter course of hormonal therapy, to intermittent androgen deprivation therapy improves the recurrence rates for men.

To find participants for the trial, the team used prostate-specific membrane antigen (PSMA) PET/CT scanning, a new, sensitive imaging test, to identify men with a limited burden of disease and who may be most likely to be helped by this combination approach.

The team enrolled 28 patients with recurrence of the disease following radical prostatectomy. Overall, the researchers found that the treatment was well tolerated, 93% of participants completed the treatment regimen, and only 21% experienced severe drug-related side effects.

"We found that the majority of patients tolerated this treatment without significant side effects. This is important because we are always taking into account how our treatments affect patients' short-term and long-term quality of life," said Dr. John Nikitas, a radiation oncology resident at UCLA Health and first author of the study.

At six months after testosterone recovery, which occurs when testosterone returns to normal levels after hormone therapy is stopped, the investigators found 50% of patients remained recurrence-free.

The team also found that patients with no prior hormonal therapy were less likely to experience recurrence.

"This study marks a crucial step forward in managing recurrent metastatic prostate cancer," said Kishan. "The combination of highly potent systemic therapy and targeted radiation has shown impressive results in maintaining low PSA levels after testosterone recovery, offering hope for improved outcomes in these patients, but further studies are still needed to determine the best regimen."

The investigators also noted the study's limitations, including a small sample size from a single institution and the need for longer follow-up. □

Other authors of the study, all from UCLA, include Dr. Matthew Rettig, Dr. John Shen, Dr. Robert Reiter, Dr. Alan Lee, Dr. Michael Steinberg, Dr. Luca Valle, Ankush Sachdeva, Tahmineh Romero, Dr. Jeremie Calais, Dr. Johannes Czernin, and Dr. Nicholas Nickols.

The study was funded by Janssen Scientific Affairs.as funded by Janssen Scientific Affairs.

Contributed by: Denise Heady

Denise Heady is a science communications and media relations manager at UCLA Health. She covers the clinical cancer program along with basic and clinical translational research for the UCLA Health Jonsson Comprehensive Cancer Center.



RECENT WINS FROM THE UCLA DEPARTMENT OF RADIATION ONCOLOGY

1

. 8.,

RESIDENT WINS

Eulanca Liu, MD / PGY-3 ABR Holman Research Pathway

Awarded the UCLA Clinical and Translational Science Institute (CTSI) TL1 Translational Science Fellowship for Postdoctoral Trainees

Awarded the UCLA JCCC Trainee Travel Award (JCCC Trainee Travel Award for the 2024 Multidisciplinary Head and Neck Conference taking place Feb 29-March 2 in Phoenix, AZ

Had a poster presentation at the 2024 Multidisciplinary Head and Neck Conference (Feb 29-March 2, 2024 in Phoenix, AZ)

Had a poster presentation at the 2024 ACRO Summit (March 13 – 17, 2024 in Orlando, FL)

Created an ACRO Narrative Medicine webinar recording with Dr. Matt Farrell and Dr. Puja Venkat (https://www.youtube. com/watch?v=ELvthp7qbg4&ab_channel=AmericanCollege ofRadiationOncology), which was followed by live seminar workshop on March 14 at ACRO Summit in Orlando, FL

Co-led EDU-MD150.03--Narrative Medicine Writing Workshop for 4th year medical students with Matt Farrell and Puja Venkat (01/22/2024 - 02/09/2024)





John Nikitas, MD / PGY-4

Awarded the Conquer Cancer Merit Award for the 2024 ASCO GU Symposium

Awarded the Best of Clinical Member in Training Award at the 2024 RSS Scientific Meeting

Dr. Nikitas had the following recent publication: Nikitas J, Ong WL, Carrier N, et al. *Prostate-Specific Antigen Response* to Androgen Deprivation Therapy in the Neoadjuvant Setting for High-Risk Prostate Adenocarcinoma (PIRANHA): Pooled Analysis of Two Randomized Clinical Trials. Int J Radiat Oncol Biol Phys. Published online December 25, 2023. doi:10.1016/j.ijrobp.2023.12.022.

UCLA RADIATION ONCOLOGY JOURNAL



Travis Courtney, MD, MS / PGY-3

Dr. Courtney had the following recent publication:

Courtney T, Valle LF, Raldow AC, Steinberg ML. MRI-Guided Radiation Therapy-An Emerging and Disruptive Process of Care: Healthcare Economic and Policy Considerations. PMID: 38105092 DOI: 10.1016/j. semradonc.2023.10.014.

He had two ASTRO 2023 Abstracts:

1. Association of Provider Zip Code Sociodemographic Characteristics with Radiation Therapy Modality Use in the Medicare Population

2. Use of Postoperative PET/CT in Altering Management in Adjuvant Head and Neck Radiation Therapy

Dr. Courtney also presented an abstract at the 2024 Multidisciplinary Head and Neck Symposium, which should be published in the coming weeks, Introduction of Routine Postoperative PET/CT prior to Adjuvant Head and Neck Radiation Therapy.

Jesus Juarez, MD / PGY-3

Dr. Juarez, a UCLA Medical Preceptorship Medical Student turned UCLA Radiation Oncology Resident, has been selected to be the third Christian W. Schiepers Fellow working with the Department of Radiation Oncology and the Division of Nuclear Medicine at UCLA. He will be the Fellow from July 1, 2024 to June 30, 2025.



Michelle Ann Eala, MD / PGY-2

Dr. Eala had the following five recent publications:

Ginsburg O, Vanderpuye V, Beddoe AM, Bhoo-Pathy N, Bray F, Caduff C, Florez N, Fadhil I, Hammad N, Heidari S, Kataria I, Kumar S, Liebermann E, Moodley J, Mutebi M, Mukherji D, Nugent R, So WKW, Soto-Perez-de-Celis E, Unger-Saldaña K, Allman G, Bhimani J, Bourlon MT, Eala MAB, Hovmand PS, Kong YC, Menon S, Taylor CD, Soerjomataram I. *Women, power, and cancer: a Lancet Commission. Lancet.* 2023 Dec 2;402(10417):2113-2166. doi: 10.1016/S0140-6736(23)01701-4. Epub 2023 Sep 26. PMID: 37774725.

Dee EC, Eala MAB, Robredo JPG, Ramiah D, Hubbard A, Ho FDV, Sullivan R, Aggarwal A, Booth CM, Legaspi GD, Nguyen PL, Pramesh CS, Grover S. *Leveraging national and global political determinants of health to promote equity in cancer care. J Natl Cancer Inst.* 2023 Oct 9;115(10):1157-1163. doi: 10.1093/jnci/djad123. PMID: 37402623; PMCID: PMC10560599.

Feliciano EJG, Ho FDV, Yee K, Paguio JA, Eala MAB, Robredo JPG, Ng K, Lim J, Pyone KT, Peralta CA, Flores JA, Yao JS, Santos PMG, Ang CDU, Lasco G, Chan JSK, Tse G, Tangco ED, Kingham TP, Chitapanarux I, Bhoo-Pathy N, Legaspi GD, Dee EC. *Cancer disparities in Southeast Asia: intersectionality and a call to action. Lancet Reg Health West Pac.* 2023 Nov 18;41:100971. doi: 10.1016/j.lanwpc.2023.100971. PMID: 38053740; PMCID: PMC10694578.

Arevalo MVPN, Maslog EAS, Manlongat KD, Ornos EDB, Chitapanarux I, Eala MAB, Dee EC. *Social determinants of sex disparities in cancer in Southeast Asia. iScience.* 2023 Jun 14;26(7):107110. doi: 10.1016/j.isci.2023.107110. PMID: 37456827; PMCID: PMC10339016.

Co LMB, Puno FLMA, Ong EP, Ho FDV, Eala MAB, Dee EC, Maslog EAS, Barroso RT; PAHPBS Philippine Association of Hepatopancreatobiliary Surgeons; Kingham TP, Ang SD, Ang CDU. Access to surgical treatment for hepatopancreaticobiliary cancer in the Philippines. Surgery. 2024 Feb;175(2):561-563. doi: 10.1016/j.surg.2023.09.051. Epub 2023 Nov 11. PMID: 37953137.





Trudy Wu, MD / PGY-5

Dr. Wu had the following nine recent publications:

Wu TC, Stube A, Felix C, Oseguera D, Romero T, Goldman J, Garon EB, Lee JM, Glaspy J, Lisberg AE, Rusthoven CG, Camidge DR, Siva S, Solomon B, Lee A, Tenn SE, Shaverdian N, Steinberg ML, Raldow AC, Lee P. Safety and Efficacy Results from iSABR, a Phase I Study of Stereotactic Ablative Radiotherapy (SABR) in Combination with Durvalumab for Early-Stage Medically Inoperable Non-Small Cell Lung Cancer (NSCLC). Int J Radiat Oncol Biol Phys. 2023 Apr 4:S0360-3016(23)00325-5. doi: 10.1016/j.ijrobp.2023.03.069. Epub ahead of print. PMID: 37023987.

Wu TC*, No HJ*, Rahimy E, Kishan AU, Steinberg ML, Raldow AC, Beadle BM. *Performance Analysis of a Radiation Oncology Educational Podcast. J Am Coll Radiol.* 2023 Jul 27:S1546-1440(23)00533-1. doi: 10.1016/j.jacr.2023.06.026. Epub ahead of print. PMID: 37516159.

Morris E, Chin R, Wu T, Smith C, Nejad-Davarani S, Cao M. *ASSET: Auto-Segmentation of the Seventeen SEgments for Ventricular Tachycardia Ablation in Radiation Therapy. Cancers (Basel).* 2023 Aug 11;15(16):4062. doi: 10.3390/ cancers15164062. PMID: 37627090; PMCID: PMC10452457

Miller ED, Wu T, McKinley G, Slivnick J, Guha A, Mo X, Prasad R, Yildiz V, Diaz D, Merritt RE, Perry KA, Jin N, Hodge D, Poliner M, Chen S, Gambril J, Stock J, Wilbur J, Pierre-Charles J, Ghazi SM, Williams TM, Bazan JG, Addison D. *Incident Atrial Fibrillation and Survival Outcomes in Esophageal Cancer following Radiotherapy*. 2023 August 12; In press at IJROBP. https://doi.org/10.1016/j. ijrobp.2023.08.011. Online ahead of print. PMID: 37574171

Wu TC, Smith CP, Li JS, Burton J, Jackson NJ, Tao R, Ludmir EB, Raldow AC. *A Systematic Review and Meta-analysis of Pathologic Complete Response Rates for Patients with Unresectable Cholangiocarcinoma treated on Orthotopic Liver Transplant Protocols. J Surg Oncol.* 2023 Nov 20. doi: 10.1002/jso.27511. Epub ahead of print. PMID: 37986552

Wu TC, Deng J, Chu F, Sadeghi S, Finn R, Agopian VG, Lee P, Raldow AC. *A Single Center Experience Using Stereotactic Body Radiation Therapy (SBRT) on Orthotopic Liver Transplant Protocol for Unresectable Cholangiocarcinoma. HPB (Oxford).* 2023 Dec 10:S1365-182X(23)02011-7. doi: 10.1016/j. hpb.2023.12.004. Epub ahead of print. PMID: 38142182

Wu TC, Farrell MJ, Karimi-Mostowfi N, Chaballout BS, Akingbemi WO, Grogan T, Raldow AC Evaluating the Impact of Race and Ethnicity on Health-Related Quality of Life Disparities in Patients with Esophageal Cancer: A SEER-MHOS National Database Study. Cancer Epidemiol Biomarkers Prev. 2023 Nov 28. doi: 10.1158/1055-9965.EPI-23-0789. Epub ahead of print. PMID: 38015776

Wu TC, Smith LM, Woolf D, Faivre-Finn C, Lee P. Exploring the Advantages and Challenges of MR-guided Radiotherapy in Non-Small Cell Lung Cancer: Who are the optimal candidates? Semin Radiat Oncol. 2024 Jan;34(1):56-63. doi: 10.1016/j. semradonc.2023.10.007. PMID: 38105094

Wu TC*, Luterstein E*, Neilsen BK, Goldman J, Garon EB, Lee JM, Felix C, Cao M, Tenn SE, Low DA, Kupelian PA, Steinberg MLS, Lee P. Accelerated Hypofractionated Chemoradiation Followed by Stereotactic Ablative Radiotherapy Boost (HyCRT-SABR) for Locally Advanced Unresectable Non-Small Lung Cancer: A Prospective Phase 2 Radiation Dose-Escalation Study. JAMA Oncol. 2024 Jan 11:e236033. doi: 10.1001/jamaoncol.2023.6033. Epub ahead of print. PMID: 38206614
FACULTY WINS



Amar Kishan, MD

Dr. Kishan was promoted to Professor in the Department of Radiation Oncology at UCLA.

He was also named one of *L.A. Business Journal's* Top Doctors.

Tania Kaprealian, MD, MBA

Dr. Kaprealian was elected as Chief of Staff Elect for Ronald Reagan UCLA Medical Center, Los Angeles. Her term starts in July and will run for two years, followed by two years as Chief of Staff.

Dr. Kaprealian will also be Chair of the Credentialing Committee for the Medical Staff starting in July.





Nzhde Agazaryan, PhD, DABR, FAAPM

Dr. Nzhde Agazaryan will serve as Chair of the ClinCAP Academic Senate Committee, a standing committee of the Council on Academic Personnel (CAP), for the 2024–25 academic year. ClinCAP reviews personnel actions from faculty in the Health Sciences Clinical Professor (HSCP) Series. ClinCAP reviews the following actions in the HSCP series: Appointments to Associate or Full; Fourth-Year Appraisals, Promotions to Associate or Full; and Merit Advancements to Step VI. ClinCAP also reviews proposals to change departments, split appointments, and change series to HSCP.

Dr. Agazaryan was one of the Scientific Directors of the Novalis Circle International Conference 2023, Munich, Germany and also a Session Chair.

Dr. Nzhde Agazaryan and Dr. Tania Kaprealian had invited presentations and Dr. John Hegde attended and participated as well.

Jack Neylon, PhD, DABR

Dr. Neylon had the following recent publication:

Neylon J, Ma TM, Savjani R, Low DA, Steinberg ML, Lamb JM, Nickols NG, Kishan AU, Cao M. Quantifying Intrafraction Motion and the Impact of Gating for Magnetic Resonance Imaging-Guided Stereotactic Radiation Therapy for Prostate Cancer: Analysis of the Magnetic Resonance Imaging Arm From the MIRAGE Phase 3 Randomized Trial. Int J Radiat Oncol Biol Phys. 2023 Dec 30:S0360-3016(23)08309-8. doi: 10.1016/j.ijrobp.2023.12.035. Epub ahead of print. PMID: 38160916.





Sharon Qi, PhD, DABR

Dr. Sharon X. Qi had the following recent publication:

Rong Y, Chen Q, Fu Y, Benedict S, Buchsbaum J, Qi X. NRG Oncology Assessment of Artificial Intelligence Deep Learning–Based Autosegmentation for Radiation Therapy: Current Developments, Clinical Considerations, and Future Directions. 2023, November 13. DOI:https://doi.org/10.1016/j.ijrobp.2023.10.033.

John V. Hegde, MD

Dr. John Hegde was selected as one of three RO-ILS 2023 Safety Stars





Luca Faustino Valle, MD

Dr. Luca Faustino Valle's proposal, *Elucidating Circulating Tumor and Immunological Phenotypes Following Treatment with SBRT +/- 177Lu-PNT2002 in Men with Oligometastatic Recurrent Prostate Cancer*, was chosen by the Mike Slive Foundation for their pilot Prostate Cancer Research Grant Program. Dr. Faustino Valle will be awarded \$50,000 for the 2023-2024 cycle. Dr. Valle is currently a Winn CDA Scholar.

Daniel Low, PhD, FAAPM, FASTRO Jack Neylon, PhD, DABR James Lamb, PhD

Through the efforts of Dr. Low, Dr. Neylon, and Dr. Lamb, the VA has developed a plan to upload the past ten years of radiation therapy treatment planning data to a common database to allow big data analytics for exploring how treatments impact patient outcomes. The process of collecting and curating these data from the 41 VA clinics that have radiation therapy departments is challenged by the different treatment planning systems and the different versions of those systems used throughout the clinics and years. UCLA was awarded a contract to a) develop the technology for automatically and semi-automatically upload and curate the treatment planning and delivery data, b) apply this to 4 VA clinics as proof-of-concept, testing, and collecting the first four of the 41 clinical datasets. This contract has a term of one year, and a new 4-year contract is expected to be developed to gather the remaining clinic's data.



James Lamb, PhD

Dr. Lamb's research group had three papers accepted for publication:

Charters J, Luximon D, Petragallo R, Neylon J, Low D, Lamb JM. Automated detection of vertebral body misalignments in orthogonal kV and MV guided radiotherapy: application to a comprehensive retrospective dataset. Accepted at Biomedical Physics & Engineering Express.

Petragallo R, Luximon D, Neylon J, Bardach N, Ritter T, Lamb JM. *Clinical Physicists' Perceptions* of the Shifting Weekly Chart Check Paradigm Assessed by Structured Interviews. Accepted at Journal of Applied Clinical Medical Physics.

Luximon D, Neylon J, Ritter T, Agazaryan N, Hegde J, Steinberg ML, Low D, Lamb JM. *Results* of an AI-Based Image Review System to Detect Patient Misalignment Errors in a Multi-Institutional Database of CBCT-Guided Radiotherapy. Accepted at International Journal of Radiation Oncology*Biology*Physics.

ADDITIONAL DEPARTMENT WINS

Ling He, PhD (The Pajonk Lab at UCLA)

Dr. Ling He, a Project Scientist The Pajonk Lab at UCLA, recieved an impact score of 20 on her NIH R03 application on mini brains and radiation.

CONTACT US / REFER A PATIENT

WESTWOOD

UCLA DEPARTMENT OF RADIATION ONCOLOGY 200 UCLA MEDICAL PLAZA, SUITE B265, LOS ANGELES, CA 90095

TEL: (310) 825-9775 FAX: (310) 794-9795

SANTA CLARITA

UCLA DEPARTMENT OF RADIATION ONCOLOGY 27235 TOURNEY ROAD, SUITE 1400, SANTA CLARITA, CA 91355

TEL: (661) 287-0010

FAX: (661-)287-0030

SANTA MONICA

UCLA DEPARTMENT OF RADIATION ONCOLOGY 1223 16TH STREET, SUITE 1100, SANTA MONICA, CA 90404

> TEL: (424) 259-8777 FAX: (424) 259-8796

DOWNTOWN / DTLA

UCLA DEPARTMENT OF

RADIATION ONCOLOGY

1338 S. HOPE ST. A (LOWER LEVEL) LOS ANGELES, CA 90015

TEL: (213) 744-1460

FIND US ONLINE / CLICK BELOW TO VISIT OUR SITE



UCLA RADIATION ONCOLOGY JOURNAL



UCLA Health



The UCLA Department of Radiation Oncology pushes back the boundaries that limit ordinary clinical cancer treatment through the application of thoughtful discovery-based novel treatment strategies.