

Yale Cancer Center

centerpoint

MAGAZINE



Renewed Energy in Breast Cancer Care

spring | summer 2021

contents spring–summer 2021



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Clockwise from top:
Mehra Golshan, MD, MBA;
Rachel Greenup, MD, MPH;
Meena Moran, MD; and
Maryam Lustberg, MD, MPH

Peter Baker **photographer**

yale cancer center

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Yale Cancer Center

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Yale Cancer Center and Smilow Cancer Hospital are bustling with activity and enthusiasm this summer. While we remain vigilant and cautiously optimistic, Connecticut is making considerable progress against COVID and we are hopeful. Our scientists, physicians, nurses, and staff have worked tirelessly to advance our mission in the face of unprecedented challenges this past year.

In the midst of adversity, we welcomed a new Breast Cancer leadership team to Smilow Cancer Hospital and Yale Cancer Center. The passion, expertise, and energy of Drs. Mehra Golshan, Maryam Lustberg, Rachel Greenup, and Meena Moran, combined with the experience of their entire team is unparalleled. I know they will successfully advance our research mission in breast cancer, while ensuring each patient at The Breast Center at Smilow Cancer Hospital and Network is cared for with the compassion and personalized treatment necessary.

Bill Hodovski's can-do spirit throughout his cancer journey reminds us all of the positive power that confidence, resilience, and a supportive team can have. He and his wife Johann put their trust in his care team at Smilow Cancer Hospital. Bill chose to enroll in a clinical trial to increase his likelihood of overcoming a rare form of esophageal cancer. Today, Bill is doing well following surgery and treatment and spending time at his favorite fishing holes.

Research in the laboratory of Dr. Caroline Johnson is pushing to learn more about sex-specific differences in colon cancer, specifically between left-sided and right-sided colon cancer in men and women. Dr. Johnson is looking to understand why women are diagnosed more frequently with the more dangerous right-sided colon cancer, and how to interfere sooner to achieve better outcomes.

While we work to continue to emerge stronger and more resilient from the COVID pandemic, I am continually proud of the success and progress we have achieved together in the last year. I know that Yale Cancer Center and Smilow Cancer Hospital will continue to quickly push forward with breakthrough discoveries and innovative advances in patient care.

Sincerely,



Nita Ahuja, MD, MBA

Interim Director, Yale Cancer Center
Interim Physician-in-Chief, Smilow Cancer Hospital
William H. Carmalt Professor of Surgery
Chair, Department of Surgery



A photograph of two medical professionals, a woman and a man, standing in a modern office or hospital hallway with large windows overlooking greenery. The woman, on the left, is wearing a light pink blazer, a white blouse, a long pearl necklace, and glasses. She is smiling and looking towards the man. The man, on the right, is wearing a blue suit jacket, a pink and white checkered shirt, and a blue tie. He is gesturing with his hands as if speaking. The background shows a bright, sunlit interior with large windows and lush green trees outside.


Melanie Lynch, MD, FACS
Breast Surgeon

Mehra Golshan, MD, MBA
Breast Surgeon

RENEWED ENERGY

IN BREAST CANCER CARE

Steve Kemper writer **Peter Baker** photographer



A year ago, Mehra Golshan, MD, MBA, arrived as the Deputy Chief Medical Officer for Surgical Services and the interim director of Yale Cancer Center and Smilow Cancer Hospital's Breast Cancer Program, interim chief of Breast Surgery, and quickly infused it with energy and key recruits, including a new director of The Breast Center at Smilow Cancer Hospital and new chiefs of breast surgery and medical oncology. "There's lots of change and excitement building on the exceptional work that was already happening here," said Dr. Golshan.

That's partly what drew him to Yale after 18 years as a breast cancer surgeon at Harvard's Dana-Farber Cancer Institute and Brigham and Women's Hospital. He wasn't looking to leave. Then Nita Ahuja, MD, MBA, FACS, Chief of Surgery at Yale New Haven Hospital and now Interim Director of Yale Cancer Center and Interim Physician-in-Chief for Smilow Cancer Hospital, invited him to visit Yale. The people, the culture, and the openness to new ideas altered Dr. Golshan's career path.

One of the current priorities is "next day" access for patients newly diagnosed with breast cancer. Patients can be scheduled to see a breast cancer specialist the next day at Smilow Cancer Hospital or within the Smilow Cancer Network. "Many patients with a new diagnosis are scared and worried, and they want to see someone as soon as possible," said Dr. Golshan. "We are affording them that, which is truly patient-centered care."

Dr. Golshan has worked on discontinuing traditional "wire localization," in which a radiologist inserts a thin wire into the breast as a guide on the day of surgery. "The wires can be broken, moved, or bent, and they create discomfort," explained Dr. Golshan. Now the wires are replaced with Radio Frequency Identification tags that can be inserted in advance, which lessens discomfort for the patient as well as bottlenecks in the surgery schedule.

Dr. Golshan brought his own novel research interests to Yale, which include using molecular markers with mass spectrometry and intraoperative MRIs during surgery to determine in real time whether a breast tumor has been completely removed. Surgeons and patients must often wait a week for the pathology report. If part of the tumor was missed, the patient must then return for a second operation. "My research is about making that a thing of the past," explained Dr. Golshan.

His biggest impact is likely to be the people he has helped recruit to join the current team. First, he brought in Rachel Greenup, MD, MPH, who left Duke after eight and a half years to become Chief of Breast Surgery at Yale. Dr. Greenup says that for her the "big draws" of Yale and Smilow were the people, their dedication to aligning research with clinical care, and the range of opportunities she saw to bridge evidence with patient-centered care. She is brimming with ideas and plans.

Many NCI-designated cancer centers, she notes, serve a relatively homogenous population. By contrast, Yale is committed to providing high-quality breast cancer care to an "incredibly diverse population," and makes that care locally accessible through its expanding network of breast cancer treatment centers. "Smilow provides exceptional cancer care to individuals from across many races, ethnicities, and socioeconomic backgrounds," Dr. Greenup said, "this offers a real-world view of patient experience and outcomes that can inform our continued improvements in breast cancer care delivery."

That meshes perfectly with her passion around health equity and reducing the burden of cancer care. One of breast cancer's impacts, she said, can be financial catastrophe. "We often address the medical side effects of cancer and physical toxicity of treatment," she said, "we now recognize that many of our best therapies are associated with

psychosocial consequences that impact patients both during treatment and into survivorship. These include significant financial costs, high healthcare use, and disruption to employment for patients and their families."

She is now working on improving communication with patients about the financial costs and burden of care to support shared decision-making. She believes that transparency around these contemporary challenges will improve patient-centered treatment planning, and may reduce overtreatment and the associated costs, a double win. She also hopes to embed prospective and ongoing "financial navigation" across the Smilow Network. Society often confuses more expensive and/or intensive care with better quality, she adds, and the result can be a wasteful system that is also costly for patients. Changing that through value-based care models that target more efficient and more meaningful care, is another of her research interests.

She and Maryam Lustberg, MD, MHS, the newly appointed Director of the Breast Center at Smilow and Chief of Breast Medical Oncology, are planning a specialized breast cancer program for young women whose concerns often differ from those of older women. For instance, treatment can affect a young woman's fertility and her ability to carry a pregnancy. Younger women may also need different types of psychosocial support as they juggle careers, motherhood, and cancer treatment. Additionally, there are opportunities to design individualized programs for older people with breast cancer through dedicated partnerships with the nationally recognized Yale Geriatrics Program. A focus on serving the diverse needs of the community will be facilitated by ongoing partnerships with the Equity Research and Innovation Center (ERIC) at Yale led by Dr. Marcella Nunez-Smith, as well as the Center for Community Engagement and Health Equity.

Dr. Lustberg, another of Dr. Golshan's recruits, arrived on July 1. She is nationally and internationally known for her work on survivorship and on reducing the toxicities associated with breast cancer treatments. She spent fourteen years at The Ohio State University and the James Cancer Hospital, where she was director of the Breast Cancer Survivorship Program and had no plans to leave. An invitation from Dr. Golshan and a visit to Yale changed that.

"I like to say I came for the people," she said, echoing Drs. Golshan and Greenup. "I could sense great possibilities for innovation and multidisciplinary partnerships."

She envisions the Smilow breast cancer care as a constellation of cohesive multidisciplinary services from diagnosis to the entire treatment trajectory faced by patients and caregivers. All these services need to be coordinated so patients can access them easily, locally, and without getting overwhelmed. "For instance, travel can be a huge burden," she said. "Patients prefer not to come on multiple days to multiple locations. They want a package of personalized, streamlined treatments and services targeted to their specific needs based on the latest evidence of breast cancer care."

Dr. Lustberg intends to work with the entire breast cancer team, Yale's COPPER (Cancer Outcomes, Public Policy, and Effectiveness Research) Center, and the Yale School of Management to create better models of care delivery. In addition, she plans to extensively collaborate with the preclinical scientists throughout Yale Cancer Center who are doing innovative work to understand the biologic heterogeneity of breast tumors.

"There are opportunities for great synergy here," Dr. Lustberg said. "My vision is to work collectively with these groups to improve the care for people diagnosed with breast cancer, and to make sure that for those who finish treatment, we address any acute toxicities that have developed—a particular area of



Andrea Silber, MD
Breast Oncologist

my research. I feel it's really all one thing," she added. "To deliver good care we have to find the best treatment for each patient but also deliver it in a way that's the least toxic. A good oncologist must be aware of both aspects." In addition to partnerships with scientists and clinicians, active partnerships with patients will be a key priority as The Breast Center at Smilow Cancer Hospital expands.

The fourth member of the core team was already at Yale: Meena Moran, MD, Chief of Breast Radiation Oncology. Dr. Moran is an expert in the field of breast radiation oncology and has dedicated her career to developing standards and guidelines, both nationally and internationally, and closer to home at Yale, for breast cancer patients. Over the last five years Dr. Moran has standardized breast radiation treatments across the

Smilow Cancer Hospital Network. A patient who receives radiation treatment gets the same level of expertise and state-of-the-art technology, techniques, and treatment algorithms across each site. To centralize the process, every patient with breast cancer treated with radiation therapy undergoes a peer review of their case and their treatment plan, which is conducted on a weekly basis by Dr. Moran and the Yale Therapeutic Radiology breast team. "This level of peer review and standardization across all of our sites is unique to our breast program and ensures that every patient can be confident they are receiving the same level of care and expert review, at the facility that is closest and most convenient to their home," she said.

Dr. Moran's standardization initiatives have included ensuring that all sites use certain treatment protocols, such as



Sarah Mougalian, MD
Breast Oncologist



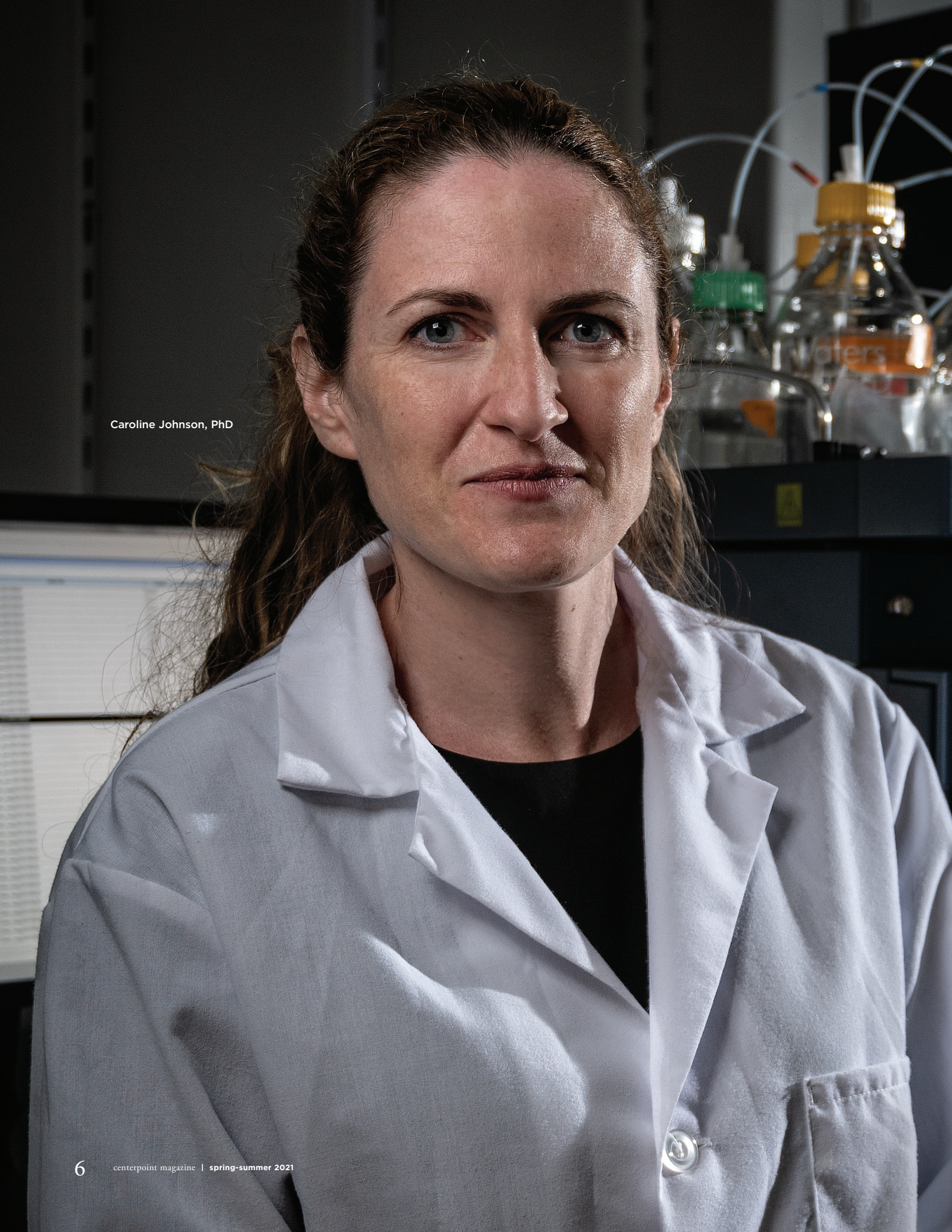
when to treat/not treat the adjacent lymph nodes, implementation of techniques such as ‘Deep Inspiration Breath Hold’ or prone breast boards (which help to protect a patient’s heart and lungs from radiation), and protocols to ensure that all patients are offered the shortest treatment duration possible. The conventional breast radiation course is typically 6-7 weeks. “The vast majority of our patients are now being treated in 3-4 weeks,” said Dr. Moran. “We have high-level data showing that the outcomes for most patients getting treated to the whole breast without lymph nodes is identical with 3-4 or 6-7 weeks, and many patients meet the criteria.” But across the country, approximately 60% of patients who are eligible for the shorter duration breast radiation are still getting longer courses. “That is where the standardization of our treatment

algorithms is a real benefit for all breast cancer patients at Smilow.” The data are equally clear about other aspects of breast cancer, such as deciding between a lumpectomy and radiation versus a mastectomy for early-stage breast cancer. There is no difference in survival with either approach, and a patient can conserve her breast without compromising her cure rate, so long as the patient also gets endocrine therapy and radiation.

Similarly, in her quest for establishing guidelines, Dr. Moran co-chaired a large initiative to settle a contentious debate: what margin of healthy tissue must exist around an excised tumor to prevent the need of a second surgery? After a meta-analysis of all available data, the answer was clear: “Because patients do so well after lumpectomy and radiation and systemic therapies afterwards, the relapse

rates are no different whether the margin is one millimeter or four millimeters. That guideline has really changed the paradigm of how margins are evaluated and has resulted in a significant decrease in the national re-excision rates. In fact, Dr. Greenup published a cost analysis estimating the millions of dollars that Medicare will save in health care costs from the decrease in re-excisions resulting from our guideline.”

Together, the breast cancer researchers and physicians across the Smilow Cancer Hospital Network are expanding breast cancer care far beyond surgery and post-surgical therapy. They are using a multidisciplinary approach to find new ways to save patients time, money, and emotional distress while maintaining excellent breast cancer outcomes. ♻️



Caroline Johnson, PhD



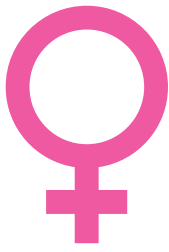
COLORECTAL CANCER & WOMEN

Steve Kemper writer Peter Baker photographer

The traditional broad categories of cancer are splintering into finer subcategories as researchers unravel the incredible complexity and variety within locational descriptors such as “breast cancer” or “lung cancer.” For instance, we now know that the general term “breast cancer” encompasses a range of heterogeneous tumors with different genetics, mechanisms, and drivers requiring different targeted therapies.

Colon cancer has been undergoing a similar subdivision. Researchers have known for years that colorectal cancer is the third most common cancer diagnosis in the United States and the second leading cause of cancer-related deaths. The National Cancer Institute estimates 149,500 new cases in 2021 and 53,000 deaths.

More recently, researchers have learned that cancers on the colon’s right-hand segment, which ascends the right side of the abdomen, differ from cancers located on the segment descending alongside the abdomen’s left. Researchers also found that these different locations led to different outcomes. People with right-sided colon cancer (RCC) had a 20 percent



These fascinating differences beg the question: why? Why do right-sided and left-sided colon cancers differ? Why are right-sided ones more dangerous? And why do women get more of them?

greater chance of dying than people with left-sided colon cancer (LCC). Subdividing further, scientists observed that left-sided cancers were split almost evenly between males and females (52 to 48 percent, respectively), but the more deadly right-sided type affected women much more—females account for 62 percent of RCCs, males just 38 percent.

These fascinating differences beg the question: why? Why do right-sided and left-sided colon cancers differ? Why are right-sided ones more dangerous? And why do women get more of them?

These questions, especially the last one, motivate Caroline Johnson, PhD, Assistant Professor of Epidemiology (Environmental Health Sciences) at Yale School of Public Health and a member of the Cancer Prevention and Control Research Program at Yale Cancer Center. Dr. Johnson began researching colorectal cancer as a research fellow at the National Cancer Institute and has continued that focus in her lab at Yale School of Public Health. Her focus is metabolites and their role in human health, particularly in colorectal cancer. Metabolites are molecules formed or used during the process of metabolism. They can be produced by diet, hormones, genetic or environmental factors, and the microbiome. The study of metabolites and their interactions is called metabolomics, Dr. Johnson's area of expertise.

"Metabolites give us information about biological processing within a sample or within a tissue," she said. "Tumors have metabolic activity and make metabolites that can produce energy for cell growth."

In the first such study ever done, she and her colleagues used metabolomics and mass spectrometry to explore the marked differences between right-sided colon cancer in males and females. The process works like this: first they extract metabolites from a tumor sample by liquefying and centrifuging it. The proteins sink, the metabolites float. The researchers run the metabolites through a mass spectrometer to get a survey of everything in the sample—perhaps 20,000 variables—which can be separated into various groups. They look for patterns and connections by putting the metabolites into a pathway analysis that reveals their links and shared networks.

"We're able to pinpoint what genes and enzymes might be altered or upregulated or downregulated in relation to the disease," said Dr. Johnson.

The researchers discovered that colorectal cancer cells on the right side generate metabolites that enable more aggressive growth in women, than in men. They also determined that the colons of males and females produce different metabolites. That insight led them to identify a distinct metabolic phenotype common among women with right-sided colon cancer.

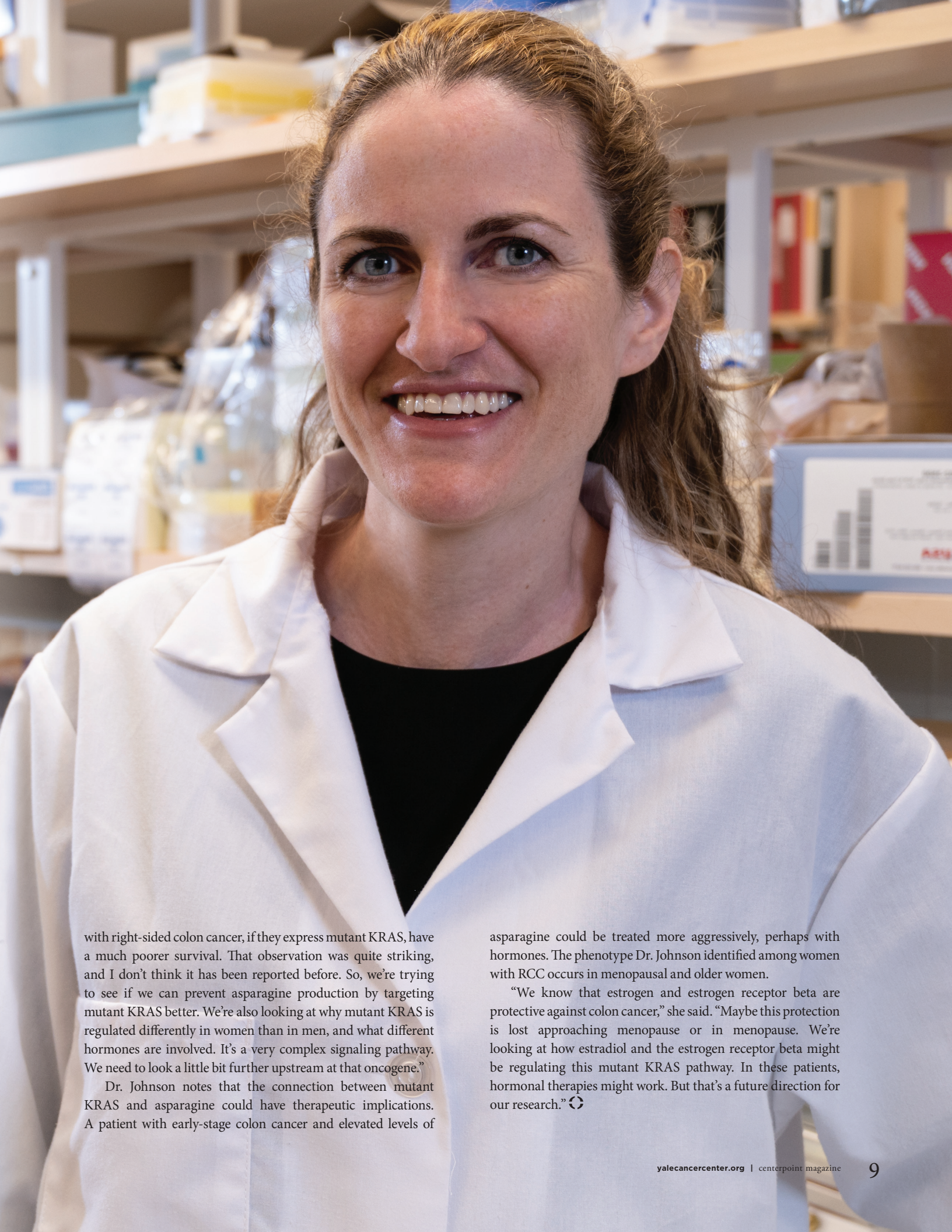
"This phenotype produces energy in a different way than happens in males," explained Dr. Johnson. The biggest difference is a large increase in asparagine, a common amino acid found in most proteins. "So, we looked at the gene that produces asparagine, which is asparagine synthetase (ASNS)," said Dr. Johnson, "and then we looked at many cancer databases to see if females with right-sided colon cancer have a higher expression of that gene and lower survival." The data showed a correlation in women but not in men. "Asparagine might be involved in tumor growth in females," said Dr. Johnson.

When right-sided colon tumors become starved for energy, they look for new sources. In women, asparagine production goes into overdrive to help the tumor increase its uptake of the amino acids and fatty acids that fuel cell growth. "It's called 'metabolic rewiring,'" said Dr. Johnson, "almost like you rewire the electricity supply in your house. The tumor suddenly switches to using different nutrients to survive in a different situation."

Dr. Johnson's discovery of asparagine's role opens therapeutic possibilities. Drugs that remove asparagine from circulating blood, depriving tumor cells of fuel, are already being used against acute lymphocytic leukemia. One of Dr. Johnson's next studies will test whether the drugs might be effective against RCCs. Using mice with colon cancer, she will remove the asparagine synthetase gene using the gene editing tool CRISPR, and then will feed the mice diets high or low in asparagine to monitor the effects on tumor growth.

She isn't sure that removing asparagine will be as effective on RCCs as it is on acute lymphocytic leukemia, since the colon is a more complex environment, including the microbiome. For that reason, she is also working on tracking the biology back toward the source before asparagine is activated. Her research indicates that mutant KRAS genes, which are implicated in several cancers including colon cancer, play a role in asparagine metabolism. That connection is now her lab's primary focus.

"We've seen that mutant KRAS could be regulating the production of asparagine," she said. "We've also seen that women



with right-sided colon cancer, if they express mutant KRAS, have a much poorer survival. That observation was quite striking, and I don't think it has been reported before. So, we're trying to see if we can prevent asparagine production by targeting mutant KRAS better. We're also looking at why mutant KRAS is regulated differently in women than in men, and what different hormones are involved. It's a very complex signaling pathway. We need to look a little bit further upstream at that oncogene."

Dr. Johnson notes that the connection between mutant KRAS and asparagine could have therapeutic implications. A patient with early-stage colon cancer and elevated levels of

asparagine could be treated more aggressively, perhaps with hormones. The phenotype Dr. Johnson identified among women with RCC occurs in menopausal and older women.

"We know that estrogen and estrogen receptor beta are protective against colon cancer," she said. "Maybe this protection is lost approaching menopause or in menopause. We're looking at how estradiol and the estrogen receptor beta might be regulating this mutant KRAS pathway. In these patients, hormonal therapies might work. But that's a future direction for our research." ↻



Finding a Sense of Normalcy

Kristin Rattini writer Peter Baker photographer



When Bill Hadovski talks about his cancer journey, he rarely uses the pronoun ‘I.’ Instead, he says, ‘we,’ for he and his wife, Johann, who together have pledged to each other that whatever health challenges come their way, they would get through them as a team.

“We’ve been together since we were teenagers,” said Mr. Hadovski, 74, a retired engineer. “We’ve had a certain number of challenges and adversities, and we’ve always dealt with them together. When Johann was diagnosed with breast cancer five years ago, we decided we would take every step of it together: all the doctor’s visits, all the therapy, everything. At the time, though, we had no idea how long that journey was going to be.”

As Johann was finishing her treatment for breast cancer, Mr. Hadovski discovered he had melanoma. And in November 2020, as they were about to move from Connecticut to Florida to start a new chapter of their lives, Mr. Hadovski was

diagnosed with esophagogastric junction adenocarcinoma.

The couple, married 53 years, renewed their vow to each other that they would face the heightened challenges of cancer treatment during pandemic times together. And they remained in Connecticut, to stay close to their trusted team of oncologists at Smilow Cancer Hospital.

A TRUSTED RESOURCE

As 2020 unfolded, Mr. Hadovski noticed he was having trouble swallowing. He brushed it off for a while; there were bigger issues to deal with between the pandemic and their much-anticipated move to the Sarasota area to be near his brothers. “We surmised that once in Florida it would take a long time to reestablish our health care providers so we decided to get all pending tests and visits taken care of before we left,” he said.

On November 18, an endoscopy

revealed that Mr. Hadovski’s swallowing problem could not be brushed off any longer. He had esophagogastric junction adenocarcinoma, a rare type of cancer in the area where the esophagus and stomach join together. One week later, he and Johann together consulted with a Smilow Cancer Hospital oncologist who knew him well.

Harriet Kluger, MD, Professor of Medicine (Medical Oncology), had treated Mr. Hadovski for melanoma and still saw him every four months for follow-up visits. She promised to put together a team of specialists who were among the best that Smilow had to offer. “Collaboration among Smilow physicians and the esprit de corps are among the best attributes of my job at Yale,” Dr. Kluger said.



TEAM HADOVSKI

The multi-modality treatment for esophagogastric junction adenocarcinoma requires a team approach. Patients like Mr. Hadovski undergo two six-week sessions of chemotherapy, the second preceded by a PET scan and paired with radiation. That's followed by surgery to remove the affected sections of the esophagus and stomach. "The treatments must be administered in a highly coordinated way," said Daniel Boffa, MD, Professor of Surgery (Thoracic) and Clinical Director of the Center for Thoracic Cancers at Smilow Cancer Hospital. "We must be in tight communication so that our patients are able to get through the entire treatment plan."

Dr. Boffa spearheaded the clinical trial at Yale Cancer Center that led to the adoption of a PET scan as a vital tool to evaluate the effectiveness of chemotherapy at its midpoint. "If the chemotherapy is working, then patients continue on for the combination therapy using the same drug,"

Dr. Boffa explained. "If it isn't working, then that provides the patient the option to try a different type of chemotherapy with their radiation."

Pamela Kunz, MD, Associate Professor of Internal Medicine (Medical Oncology) and Director of the Center for Gastrointestinal Cancers at Smilow Cancer Hospital and Yale Cancer Center, oversaw Mr. Hadovski's chemotherapy. "She was so personal, compassionate, and positive, but also down to business," Mr. Hadovski said. "She and Dr. Kluger assured me this was treatable, but we had to get it out of there as quickly as we could. So before Christmas, we were undergoing our first chemo treatment." Clinical scheduler Evelyn Corporan and social worker Laura Donnelly helped Johann coordinate the appointments to minimize their wintery 50-mile drives from Windsor, CT and connected them with The Suites at Yale for when they required an overnight stay.

At the midpoint, the PET scan showed

significant progress and Mr. Hadovski felt pretty good. Although COVID-19 restrictions prevented him from maintaining his daily gym regimen he had kept for 35 years, he and Johann walked three to five miles each day on the trails around their new apartment with their two beloved golden retrievers, Diva and Lacey.

Mr. Hadovski started daily radiation under the care of Kimberly Johung, MD, PhD, Associate Professor of Therapeutic Radiology and Chief of the Gastrointestinal Radiotherapy Program. "Swallowing becomes progressively difficult over the course of treatment, so I tell my patients that eating becomes their full-time job so they can get the nutrition they need," Dr. Johung said. "Bill was a fighter, though, and he did an excellent job."

Mr. Hadovski did feel nauseous and tired after three weeks of radiation and lost interest in food. He welcomed guidance



from dietician Vanessa Salino on how to tame the nausea and adapt his diet to get the energy he needed. Before long, he felt strong enough to return to the gym. “Dr. Boffa gave me a booklet that encourages patients to get in as good of shape as you can before surgery, so I started getting in some pretty good workouts,” he said.

In April, using minimally invasive surgery, Dr. Boffa removed two-thirds of Mr. Hadovski’s esophagus and one third of his stomach. He pulled up the remaining stomach tissue to reconstruct the area where the esophagus used to be.

Mr. Hadovski’s care team was very pleased with his outcome. “Bill is one of our many success stories,” said Dr. Johung. “He had a great response to radiation and chemotherapy. When he went to surgery, there was no residual tumor. That’s really the best we can hope for. Bill is one of those success stories that keeps you motivated, that keeps you fighting the fight with these patients.”

AN AMAZING ATTITUDE

Mr. Hadovski is still fighting the fight, too. He’s building his strength so he can focus on his hobbies of fishing and golf, and he’s adapting to the new eating regimen mandated by a smaller stomach that can only absorb a few tablespoons of food at a time. “I take the situation as a challenge,” he said, “something you’ve got to get through the best you can and find out what you can do to make it better.”














That can-do spirit continually impressed his Smilow care team throughout his treatment. “Bill had the most amazing attitude,” Dr. Kunz said. “I always wondered, ‘Where does that come from?’”

Mr. Hadovski has two answers for Dr. Kunz’s question. First: Johann. “She refused to let us do anything except concentrate on the positive.” Second: The experts at Smilow. “It was our confidence in Smilow and their team of people,” he said. “They said my cancer was treatable. We took them at their word, and we decided that we were going to charge down that path and show them that they were right.” 🔄



July 2020 – January 2021

Honors

-  **Kurt Schalper, MD, PhD**, received an **R37 Merit Award** from the National Institutes of Health (NIH) to fund his research in pathways for cancer immunotherapy over the next 7 years.
-  **Prasanna Ananth, MD, MPH**, has been awarded a **St. Baldrick's Scholar Award** from the St. Baldrick's Foundation to support her research over the next two years to better define standards of high-quality end-of-life care for children with cancer and develop interventions to provide optimal care for children with incurable cancers.
-  **Mandar Muzumdar, MD**, and **Siyuan (Steven) Wang, PhD**, have been awarded an **R33 grant** from the National Cancer Institute (NCI) for \$1.24 million to support their research on multiplexed imaging of chromatin folding and RNA profiles in cancer.
-  **John Kunstman, MD, MHS**, has received the New England Surgical Society Scholars Foundation Board **Scholars Research Grant** for his proposal "Development of an Organoid-based Model System for Intraductal Papillary Mucinous Neoplasia of the Pancreas."
-  Led by **Mandar Muzumdar, MD**, the NIH has awarded an **Exploratory Developmental Grant** to fund 3D gene imaging research at Yale Cancer Center.
-  The NIH has awarded a **Research Project Cooperative Agreement Grant** to Yale Cancer Center. The 2-year, \$1.4 million U01 award, led by **Stephanie Halene, MD, PhD**, and **Rong Fan, PhD**, will fund immuno-serological assays for monitoring COVID-19 in patients with hematologic malignancies.
-  **Marcella Nunez-Smith, MD, MHS**, was named Co-Chair of Then-President-Elect Joe Biden's Transition **COVID-19 Advisory Board**.
-  **Prajwal Boddu, MD**, was awarded a pilot grant from the NIH **NIDDK Cooperative Centers of Excellence in Hematology** to investigate mechanisms by which novel protein isoforms of Mitoferrin 1 regulate iron delivery during erythroid maturation.
-  **James Hansen, MD**, was awarded two grants to support his research, including a **Breast Cancer Research Program Breakthrough Award** from the Department of Defense for use of a modified autoantibody against breast cancer brain metastases and a NIH **NINDS R01 grant** for targeting glioblastoma with a nuclear-penetrating anti-DNA antibody.
-  **Roy S. Herbst, MD, PhD**, has been selected as the **2020 Clinical Research Award** recipient by the Association of Community Cancer Centers for significantly and positively impacting oncology patients, their families, and the broader oncology community.
-  **Jean L. Bologna, MD**, is one of six people who have been named **2020 Giants of Dermatology** by *Dermatology Times*.
-  **Luisa F. Escobar-Hoyos, PhD**, and **Mandar Muzumdar, MD**, have been selected as 2021 recipients of the **Damon Runyon-Rachleff Innovation Award**.
-  **Jun Deng, PhD, DABR, FAAPM, FInstP**, was awarded a **multi-institutional collaborative project** entitled "Dynamic Multiscale Digital Twin for a Lung Cancer Patient" from the NCI.



A Faster, Broader Pipeline for Phase I Clinical Trials

Five years after the Phase I Clinical Trial Infusion Center opened its doors at Smilow Cancer Hospital, Director Patricia LoRusso, DO, still gets a thrill reporting to her clinic every day.

The state-of-the-art facility serves as the dynamic hub of Yale Cancer Center's cutting-edge Phase I Clinical Trial Program. The program advances promising cancer therapies through the FDA approval pipeline and provides hope for patients with advanced stage cancers in need of another option beyond the standard treatment.

Under the leadership of Dr. LoRusso, Associate Cancer Center Director, Experimental Therapeutics, the program, and its dedicated highly-trained staff, have not only significantly increased the number of immune-based therapies and other treatments entering phase I trials, but also dramatically shortened the timeline for introducing those therapies to patients for whom time is of the essence.

Joseph Paul Eder, MD,
and Patricia LoRusso, DO

A CUTTING-EDGE TRIAL PORTFOLIO

Yale Cancer Center is home to some of the world's leading investigators and scientists whose breakthroughs in cancer biology, pharmacology, and drug development show great promise in the treatment of a wide range of human cancers. In particular, its reputation as an innovator in immune-based therapies provided a distinct advantage to the Phase I Clinical Trial Program from its very start.

"What distinguishes our program is that it combines both immune therapies and targeted therapies," said Joseph Paul Eder, MD, Clinical Director of the Program. "Many other cancer centers divide these approaches, so patients don't get looked at by the same set of eyes for which might be the most appropriate clinical trial for them. The fact that our patients are served by one committed team of investigators gives them broader opportunities for trials that might benefit them."

The program currently has nearly 60 active phase I trials open, and that number is growing. It's one of the most active participants nationwide in government-sponsored cancer clinical trials through the National Cancer Institute's Cancer Therapy Evaluation Program (CTEP). "We've opened 27 new trials since July 2020, just to keep our portfolio fresh and stay on the cutting edge of what novel therapies are out there that could benefit our patients," said Nicole Sinclair, phase I clinical trials team manager.

Among the most exciting trials underway are five using "checkpoint inhibitor" immunotherapies that activate the immune system and shrink tumors. These trials target melanoma, kidney cancer, and lung cancer, among others.

"A lot of the drugs are now more selective for specific tumor types,"

explained Dr. LoRusso. "So we have to have a large portfolio to be able to service a large number of patients with different tumor types and different scenarios. If you have a drug in your early pipeline that targets a specific mutation, it offers patients another therapeutic option that potentially could be as good if not better than the typical standard of care."

CATERING TO PATIENTS' NEEDS

A phase I trial, by its very nature, has a lot of unknowns. Its primary goal is to establish the maximum tolerated dose of a drug that is safe to use in humans. It might be the first time a particular drug has been given to a patient. As a result, patients often spend long days at the infusion center, so that the nurses can conduct special labs and tests before, during, and after the infusion and closely monitor for any reactions to the novel medication.

The infusion center was designed with the comfort of the patients, and their families, in mind. "It's a warm, welcoming place," Dr. LoRusso described. "We have an amazing staff that really focus on our patients. We recognize how frightening it can be for patients to go on a novel treatment; to enter this new environment and new unknown. Our patients are our heroes. We try to make it as comfortable as possible for them."

Behind the scenes, clinical trial team managers, such as Ms. Sinclair, orchestrate the incredibly complex process of ushering a phase I trial through to completion. She coordinates with industry sponsors and pharmacists, nurses and data managers, regulatory and research teams to make sure that every step of a trial goes seamlessly. "We're the glue that holds all of the pieces together," she said.

With five years of industry-leading experience to draw on, the team

continually evaluates its processes to improve the patient experience and patient outcomes. For example, Ms. Sinclair spearheaded a phase I pilot that reduced the average launch time for trials from 250 days down to around 120 days, with an end target of 90 days. "Our goal is to have an even greater variety of trials open more quickly for our patients," she said.

Those extra months are precious for patients who are in advanced stages of cancer. "Doing early phase trials is intense, but it's also exciting," Dr. LoRusso said. "If a new therapy can get a patient through their daughter's graduation, son's wedding, the birth of their grandchild, or beyond, it's so rewarding."

"We recognize how frightening it can be for patients to go on a novel treatment; to enter this new environment and new unknown. Our patients are our heroes."

-Dr. Patricia LoRusso



PETER BAKER

Smilow Cancer Hospital Care Center at Orange

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Johanna LaSala, MD
Kelsey Martin, MD

“Our team at the Smilow Cancer Hospital Care Center in Orange brings innovative Smilow cancer care to our patients in a small, intimate setting where our patients personally know each team member. We’re proud to provide our patients with access to a National Cancer Institute- designated Comprehensive Cancer Center and its clinical trials and advances. Our physicians coordinate with our colleagues in New Haven to ensure all treatment options are reviewed through multidisciplinary tumor boards, and each patient receives personalized cancer care.”

— Dr. Johanna LaSala, Medical Director



meet the physician

Harriet Kluger, MD

Professor of Medicine (Medical Oncology)
Deputy Section Chief of Medical Oncology
Director of Yale SPORE in Skin Cancer
Associate Cancer Center Director for Education,
Training, and Faculty Development

You've helped transform the treatment of melanoma and renal cell carcinoma over the last decade with the introduction of immunotherapy treatment. How has the tremendous growth in treatment options and success impacted your patients' options?

It has been an absolute privilege to be a part of the current revolution in cancer care. Together, our scientists and physicians have all played a pivotal role in taking cancer care a huge step forward. But, we're not done—until we can cure 100% of our patients with little to no toxicities, there is still work to do. Despite the significant progress in FDA-approved treatments, patients should be considered for trials and physicians should be very motivated to offer our patients innovative therapies. While survival has increased dramatically, I am determined to see further progress in the next decade.

What areas are the Yale SPORE in Skin Cancer focused on?

Our SPORE (Specialized Programs of Research Excellence) grant is in its 13th year of funding from the National Cancer Institute and currently has four primary areas of research. The first, led by Michael Girardi, MD, W. Mark Saltzman, PhD, and

Douglas Brash, PhD, is focused on the creation of a morning-after sunscreen to help reverse the intracellular processes that continue to cause sun damage after exposure. Dr. David Hafler's lab is working with my research team on developing blood tests to measure activity of the immune cells that come from a tumor to predict response to immunotherapy. Qin Yan, PhD, Marcus Bosenberg, MD, PhD, and Mario Sznol, MD, are working together to study KDM5 enzymes and their link to immunotherapy resistance in melanoma. And lastly, I am working with Dr. Bosenberg and Susan Kaech, PhD, to study co-activation of the innate and adaptive immune systems using novel drugs that affect both of these arms of the immune system.

In your role as Associate Cancer Center Director for Education, Training, and Faculty Development, what are some of the priorities in mentorship and training at Yale Cancer Center?

The past five years have seen a striking increase in training program opportunities at Yale Cancer Center. We have worked diligently to build programs across the spectrum, from high school students to junior faculty, and across disciplines, including basic, translational, clinical, and outcomes research. We are fortunate to have received training grants to allow our trainees to have protected research time and the capacity to participate in workshops and new courses. These new programs have increased our ability to attract stellar scholars, and the additional generous support of Yale Cancer Center has enabled us to recruit diverse trainees.

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