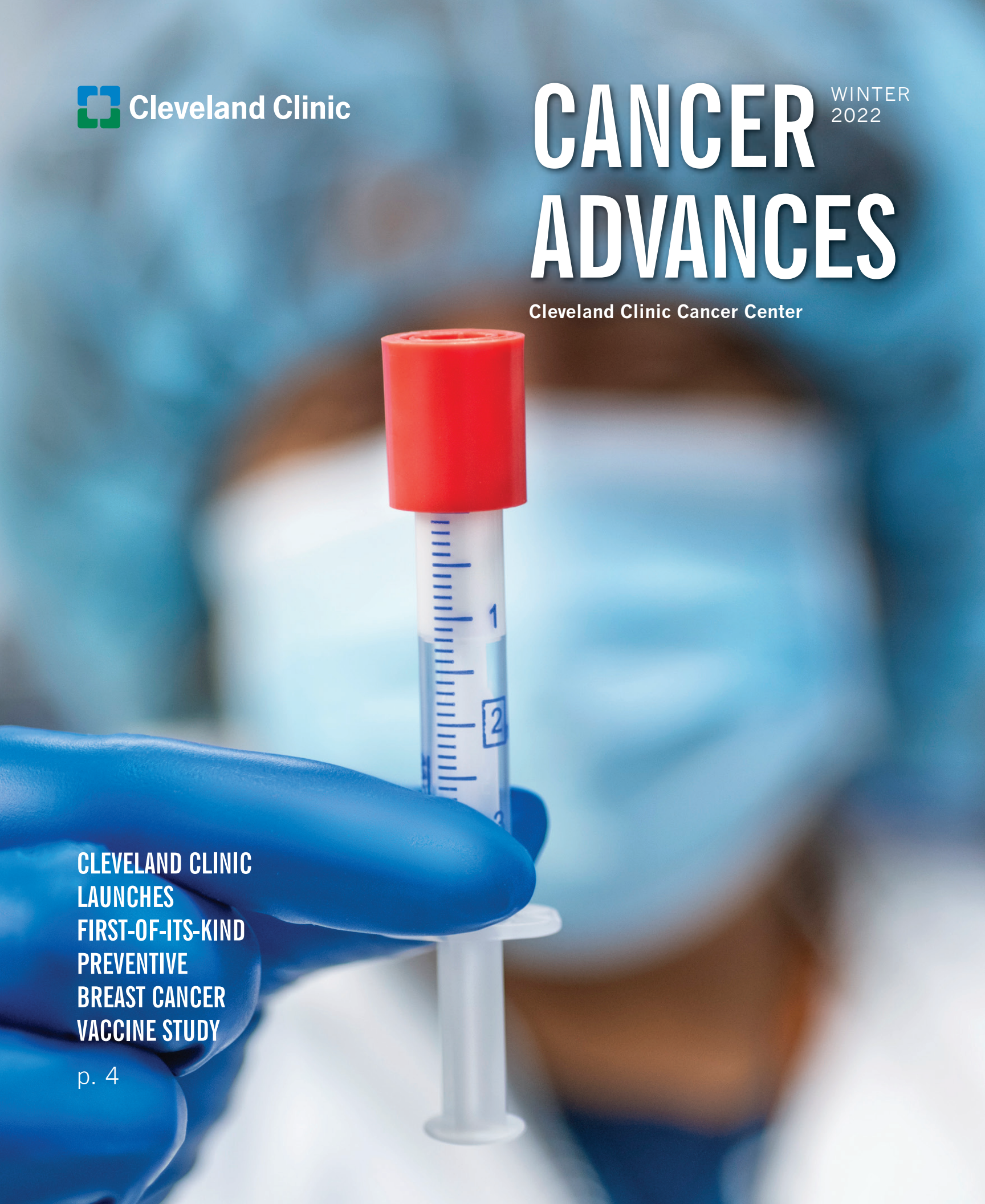


CANCER ADVANCES

WINTER
2022

Cleveland Clinic Cancer Center

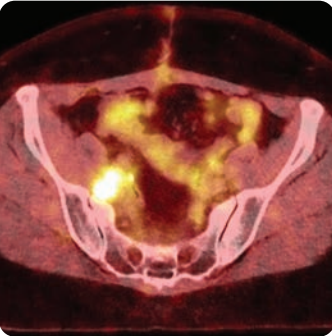
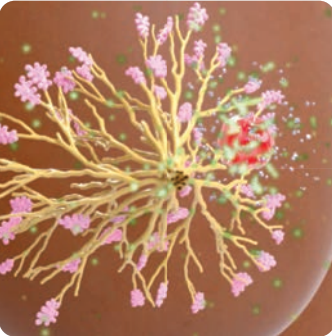


**CLEVELAND CLINIC
LAUNCHES
FIRST-OF-ITS-KIND
PREVENTIVE
BREAST CANCER
VACCINE STUDY**

p. 4

Cleveland Clinic Cancer Center provides complete cancer care enhanced by innovative basic, genetic and translational research. It offers the most effective techniques to achieve long-term survival and improve patients’ quality of life. The Cancer Center’s more than 700 physicians, researchers, nurses and technicians care for thousands of patients each year and provide access to a wide range of clinical trials. Cleveland Clinic Cancer Center unites clinicians and researchers based in Taussig Cancer Institute and in Cleveland Clinic’s 20 other patient-centered institutes, as well as cancer specialists at our regional hospitals, health centers and Cleveland Clinic Florida. Cleveland Clinic is a nonprofit, multispecialty academic medical center with more than 4,500 staff physicians and researchers who integrate outpatient and hospital care with research and education for better patient outcomes and experience. Cleveland Clinic is currently ranked as one of the nation’s top hospitals by *U.S. News & World Report*.

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ON THE COVER — Clinical testing has begun on a novel vaccine designed to combat triple-negative breast cancer by priming high-risk patients to mount an immune response against a “retired” lactation protein expressed only in cancer cells.

DEAR COLLEAGUES,

It is with great pleasure that we present the latest edition of *Cancer Advances*. This issue not only showcases the diversity and great promise of our clinical and translational research, it also highlights the dedication and remarkable skill of the clinicians and scientists who help our program thrive.



As Cleveland Clinic’s centennial year draws to a close, it is inspiring to reflect on the extraordinary achievements that have positioned the Taussig Cancer Institute as one of the greatest centers for oncology research and clinical care in the world.

Although the cancer field continues to evolve at a dizzying pace, our core beliefs remain as fixed and focused as they were when our program was established more than three decades ago. Serving patients remains our greatest privilege, and we are committed to providing compassionate, comprehensive care informed by the most advanced research available.

When I think about all we’ve accomplished this year, I’m filled with gratitude for our entire cancer team and for colleagues like you, whose invaluable support continues to invigorate us.

On behalf of our Cleveland Clinic caregivers, I wish you a happy and healthy 2022!

Sincerely,

Jame Abraham

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CLEVELAND CLINIC LAUNCHES FIRST-OF-ITS-KIND PREVENTIVE BREAST CANCER VACCINE STUDY

Retired-protein strategy represents new approach to immunization



Vincent Tuohy, PhD



G. Thomas Budd, MD

Cleveland Clinic has begun clinical testing of a novel vaccine designed ultimately to prevent triple-negative breast cancer (TNBC) by priming high-risk women to mount an immune response against a “retired” lactation protein expressed only in cancer cells.

TNBC is so-named because patients’ cancer cells test negative for estrogen and progesterone receptors and the human epidermal growth factor receptor 2 (HER2) protein, making hormone therapy and HER2-targeted drugs ineffective. It accounts for 12-15% of all breast cancers and is the most aggressive and lethal subtype. Nearly one-quarter of all TNBC patients die within five years of diagnosis; five-year survival in patients with distant metastases is only 12%. TNBC disproportionately affects Black women and women with germline *BRCA1* gene mutations. The only effective prophylaxis currently available to women at high risk for TNBC is bilateral mastectomy.

The prototype Cleveland Clinic vaccine represents a potential new way to combat breast cancer. It is the result of nearly two decades of research by immunologist Vincent Tuohy, PhD, of the Lerner Research Institute’s Department of Inflammation and Immunity. Dr. Tuohy persevered despite others’ skepticism about his unusual approach and the difficulty of obtaining funding to support years of basic science work to determine the vaccine’s feasibility.

“There was a lot of resistance to these kinds of new ideas,” he says. “It took a long time for people to think that this vaccine wasn’t just pie in the sky — that it was based on good science and was doable.”

Dr. Tuohy is the primary inventor of the vaccine technology, which Cleveland Clinic has licensed to Anixa Biosciences, Inc. He will receive a portion of commercialization revenues received by Cleveland Clinic for this technology and also holds personal equity in the company.

The U.S. Food and Drug Administration recently approved an investigational new drug application for the vaccine, allowing the clinical trial to move forward. The study is funded by the U.S. Department of Defense.

[Taking aim at primary prevention](#)

Most breast cancer vaccines presently in development are meant to treat patients with existing tumors or to prevent recurrence in cancer survivors. Current data indicate that therapeutic vaccines have limited efficacy, at least in part because they employ target antigens that fail to induce a clinically relevant immune response and adjuvants that don’t adequately enhance the response.

Dr. Tuohy’s experimental vaccine is aimed at primary prevention – stopping cancer before tumors develop.

“We know from the childhood vaccine program that vaccines are to prevent disease,” he says. “You don’t wait to get polio or measles and then vaccinate. But the entire field of cancer vaccination was using vaccines to treat. And I

LEFT — Cleveland Clinic researchers aim to create a true preventive vaccine capable of stopping the development of triple-negative breast cancer in healthy women.

“It took a long time for people to think that this vaccine wasn’t just pie in the sky — that it was based on good science and was doable.” — VINCENT TUOHY, PhD

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“[Study participants] are patients who may have microscopic cancer cells present in their body, so a vaccination when the disease is microscopic could provide some benefit.” — G. THOMAS BUDD, MD

didn't think that was right. As a standalone, therapeutic cancer vaccines have not worked well,” primarily because of the tumors’ substantial head start in growth, the onset of clinical symptoms, the establishment of tumor defenses against the immune response, and the potential for local and distant metastasis.

The retired-protein hypothesis

Potential tumor antigens are variations of normal self-generated molecules. A prophylactic cancer vaccine targeting such antigens likely would trigger profound, systemic autoimmune complications.

To avoid this problem, Dr. Tuohy sought to target tissue-specific proteins that were no longer expressed in normal tissues because of the aging process but were expressed in tumors that emerge from these specific tissues with age, such as breast, ovarian and prostate cancers. He called this idea the ‘retired protein hypothesis.’

Dr. Tuohy and his research team chose the breast-specific lactation protein α -lactalbumin as their target vaccine autoantigen because it is no longer found in detectable amounts in normal, aging breast tissues but is expressed at high levels in more than 70% of TNBCs. The selection of the adjuvant component for the preventive vaccine was critical, both in terms of its ability to activate the aggressive proinflammatory T-cell response needed for effective tumor immunity, and to pass regulatory scrutiny. Adjuvants are necessary to activate the innate immune response for orchestrating the adaptive immune response and conferring immunological memory.

“The adjuvant is the irritant,” Dr. Tuohy says. “It provides the danger signal. So now the immune system sees α -lactalbumin in

the context of a danger signal and activates the entire cascade of innate and adaptive immunity.”

Details of the clinical trial

The phase I dose-escalation trial will enroll approximately 24 women who are within three years of TNBC diagnosis and currently have stable disease with high risk of recurrence.

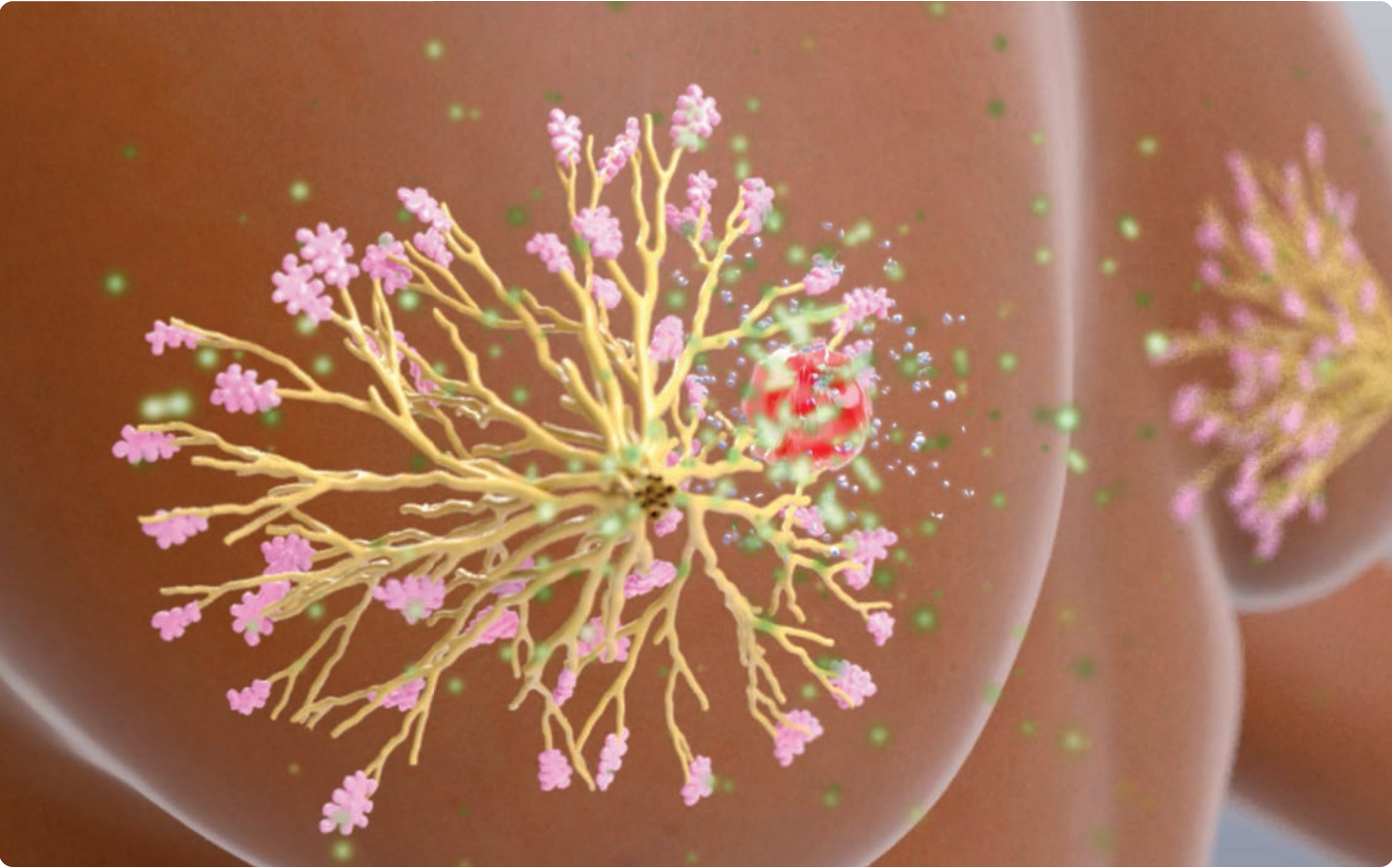
“These are patients who may have microscopic cancer cells present in their body, so a vaccination when the disease is microscopic could provide some benefit,” says Cleveland Clinic oncologist G. Thomas Budd, MD, the trial’s principal investigator. “Long-term, we are hoping that this can be a true preventive vaccine that would be administered to healthy women to prevent them from developing triple-negative breast cancer, the form of breast cancer for which we have the least effective treatments.”

In the current trial, participants will receive up to three vaccinations, each two weeks apart, to determine the optimal immunologic dose and the maximum tolerated dose. The women will be closely monitored for side effects and immune response, the latter assessed by blood tests to detect a pro-inflammatory T-cell response consistent with tumor protection. The study is expected to be complete in September 2022.

Attempting to prevent other cancer types

Dr. Tuohy is hopeful the retired-protein strategy will enable vaccines that prevent other types of cancers in addition to TNBC.

BELOW — The result of nearly two decades of research, the prototype Cleveland Clinic vaccine represents a potential new way to combat breast cancer.



He is developing an ovarian cancer vaccine that targets the extracellular domain of anti-Müllerian hormone receptor II (AMHR2-ED), an ovary-specific self-protein.

“There is a great need for a 21st-century vaccine program that protects us from diseases we confront with age, in the same way that 20th-century vaccines protected us from childhood infectious diseases,” Dr. Tuohy says. “I envision our efforts at Cleveland Clinic being the beginning of that. This is the first step of many, many steps. I won’t be around for all of them, but we’re not done until we eliminate all of these different cancers.”

This trial includes only a small number of patients. Participants have all been identified, and we are no longer accepting new patients for the study. Additional Cleveland Clinic cancer clinical trials are available at clevelandclinic.org/cancerclinicaltrials.

For more details, visit ccf.org/CA22.

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NATIONAL EWING’S SARCOMA TUMOR BOARD CONNECTS EXPERTS, FACILITATES DISCUSSION

How to get involved



Matteo Trucco, MD

Physicians treating patients with Ewing’s sarcoma will get a chance to discuss challenging cases with experts from Cleveland Clinic and other leading cancer centers throughout the country in a new National Ewing’s Sarcoma Tumor Board.

The board brings together a multidisciplinary group of specialists to review and discuss cases once a month. Its goal is to support physicians in rural or smaller hospitals by giving them access to expertise and resources from some of the nation’s foremost Ewing’s sarcoma specialists.

“We have a very strong sarcoma team and provide a large number of second opinions formally,” says pediatric oncologist Matteo Trucco, MD, who is leading the tumor board. “This is a way to informally educate clinicians who do not have as much experience with this rare tumor.”

How it started

The project, which started with inspiration and support from foundations focused on Ewing’s sarcoma, motivated Cleveland Clinic to establish a more specialized Ewing’s sarcoma tumor board. Cleveland Clinic Cancer Center and Cleveland Clinic Children’s will be leading the effort, with experts from MD Anderson Cancer Center, Dana Farber Cancer Institute and other major cancer centers joining the panel. It’s the first tumor board of its kind in the United States.

Research shows that patients who are treated by specialists at sarcoma centers tend to have better outcomes, but many cases are handled by oncologists at smaller regional or community hospitals. The tumor board is intended to help those physicians and patients, Dr. Trucco explains.

How it works

Dr. Trucco says that patients who have relapsed multiple times or have medical complications that make them difficult to treat with the standard regimen would be good candidates for review by the board. The board will have a secure portal through which the physician can submit an intake form describing the case. The board will review approximately four cases per month.

Adult and pediatric medical oncologists, radiation oncologists, surgical oncologists, orthopaedic tumor surgeons and anyone else in the medical community with an interest in Ewing’s sarcoma is invited to attend. To protect patients’ privacy, meetings will not be open to patients or families of patients with Ewing’s sarcoma.

“Nothing is formal; no one will have seen the patient or reviewed the complete medical record, but we can offer some suggestions. ‘Have you thought about this? Have you looked at that?’ ‘Maybe reach out to this person who has a clinical trial nearby,’” Dr. Trucco says.

The Cleveland Clinic Cancer Center is a leader in treating Ewing’s sarcoma, with some of the country’s top specialists in medical oncology, pediatric oncology, radiation oncology, orthopaedic surgery and thoracic surgery, as well as one of the top pathology departments in the country for sarcomas.

BELOW — Pediatric oncologist Dr. Matteo Trucco has found a novel way to informally educate clinicians who have not had much experience with Ewing’s sarcoma.



For more information about the National Ewing Sarcoma Tumor Board or to submit a case for review, visit [Clevelandclinic.org/NEWSBoard](https://clevelandclinic.org/NEWSBoard).

Editor’s note: This forum is for educational discussions only; it does not obviate the need for a second opinion or clinical consultation, and the presenting physician is solely responsible for the patient’s treatment plan.

For more details, visit ccf.org/CA22.

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CASE REPORT: MULTIDISCIPLINARY APPROACH TO METASTATIC COLORECTAL CANCER IN YOUNG PATIENT

Case highlights importance of early screening, multimodal treatment



Suneel Kamath, MD



Emre Gorgun, MD

In October 2020, a 39-year-old woman presented to Cleveland Clinic Cancer Center with a recurrence of advanced rectal adenocarcinoma. The year before, her disease was diagnosed at another institution as stage III (T3N2M0); it was treated with chemotherapy, chemoradiation and surgery, but unfortunately the cancer recurred very quickly.

The patient's first treatment regimen included eight cycles of FOLFOX (folinic acid, 5-fluorouracil [5-FU] and oxaliplatin) plus chemoradiation with capecitabine. That was followed by an abdominopelvic resection with end colostomy, right pelvic lymph node dissection and right lateral pelvic lymph node dissection.

Three months later, still at the outside institution, the woman was found to have stage IV metastatic disease in a soft-tissue tumor in her right pelvic side wall and right common iliac lymph node. Her right ureter also was entrapped by the pelvic side wall tumor. She then was treated with FOLFIRI (folinic acid, 5-FU and irinotecan) plus bevacizumab.

"Disease in the pelvic sidewall is difficult to treat, and the patient wanted to explore all her options," explains Cleveland Clinic oncologist Suneel Kamath, MD. "She reached out via our Virtual Second Opinion program, which provided her access to a team of medical experts that offered a multimodal approach."

Dr. Kamath's first recommendation was to intensify the patient's chemotherapy to FOLFOXIRI (folinic acid, 5-FU, oxaliplatin and irinotecan) with bevacizumab. She received that regimen for four months before undergoing stereotactic body radiation therapy (SBRT). A

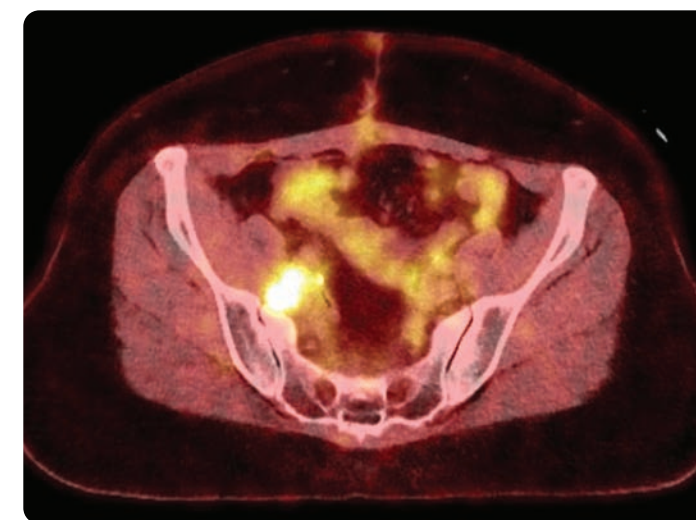
total of 40 Gy was delivered in five fractions over a five-day period.

Operative solution

The patient underwent multidisciplinary surgery at Cleveland Clinic in May 2021, led by colorectal surgeon Emre Gorgun, MD, who performed an exploratory laparotomy with excision of the soft-tissue tumor, right salpingo-oophorectomy and deep lateral pelvic lymph node dissection. The surgery also included (1) mobilization of the right ureter by urologist Hadley Wood, MD; (2) complex en bloc ligation of the right external iliac vein and internal iliac artery and ligation of the right epigastric artery by vascular surgeon Lee Kirksey, MD; and (3) intraoperative radiation therapy (15 Gy x 1 fraction) delivered by radiation oncologist Ehsan Balagamwala, MD.

"The number of surgical specialties represented in the operating room was amazing, as was the complexity of the procedures performed," says Dr. Kamath. "This patient might not have been considered a candidate for surgery at another institution, but we achieved full resection of the tumor and reconstruction of several important structures."

During the surgery, the team noted that the preoperative radiation the woman had undergone had eradicated her tumor. She had no major



LEFT — PET scan reveals a soft-tissue tumor (bright yellow) in the patient's right pelvic side wall and right common iliac artery.

complications following the surgery and has required no additional treatment. Computed tomography scans of her chest, abdomen and pelvis, done in September, and magnetic resonance imaging of her pelvis, done in October, show no evidence of disease. Although the patient is at high risk of recurrence and will need to be monitored closely, she is free of cancer.

Lessons for the future

"This case is unusual, not only because of the multimodal approach but also the age of the patient," explains Dr. Kamath. "It underscores the unfortunate rise of young-onset colorectal cancer. Thirty years ago, the median age at onset of colorectal cancer was 72 years. It has fallen to 66 years, and we are seeing more cases in patients in their 20s and 30s."

The take-home message for clinicians, according to Dr. Kamath, is to never assume that hemorrhoids are the sole cause of rectal bleeding in a young person. "If a patient has classic symptoms, do a colonoscopy instead of simply prescribing stool softeners or a change in diet," he says. "It's far better to perform a potentially unnecessary diagnostic test than delay the diagnosis of a potentially deadly disease."

According to the National Cancer Institute, cases of colorectal cancer in patients under age 50 have grown by more than 50% since the 1990s.

Cleveland Clinic recently established a Center for Young-Onset Colorectal Cancer, which is dedicated to the management and

research of cases like this one. Younger patients often have diagnostic and treatment considerations that are specific to their age. A colorectal cancer diagnosis can interrupt their most productive years. The specialized center, which provides a comprehensive personalized care plan for each patient, features a multidisciplinary team that includes specialists in surgery, oncology, radiation therapy, genetics, gastroenterology, fertility, psychology and lifestyle medicine.

For more details, visit ccf.org/CA22.

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ADDITION OF DARATUMUMAB TO TREATMENT REGIMEN MAY IMPROVE OUTCOMES IN PATIENTS WITH IMMUNOGLOBULIN LIGHT-CHAIN AMYLOIDOSIS

Study associates human CD38-targeting antibody with few complications



Jason Valent, MD

The anti-cancer drug daratumumab appears to reduce the risk of major organ deterioration and hematologic disease progression in patients with immunoglobulin light-chain (AL) amyloidosis, a protein disorder that most commonly affects the heart and kidneys.

According to a new study recently published in the *New England Journal of Medicine*, daratumumab may offer significant benefits — including a promising safety profile — when used in combination with bortezomib, cyclophosphamide and dexamethasone, a three-drug regimen frequently used to treat multiple myeloma.

AL amyloidosis is commonly managed with bortezomib-based chemotherapy, but there is certainly room for improvement in the survival of these patients. Researchers in the multicenter phase III ANDROMEDA clinical trial evaluated whether the addition of daratumumab, a fully humanized CD38-targeting antibody, could improve outcomes in patients with the disease, which is characterized by the deposition of amyloid fibrils of light chains produced by clonal CD38+ plasma cells.

Clinical implications

The outlook for patients with AL amyloidosis has improved in recent years thanks to novel chemotherapy treatments and better patient selection for high-dose melphalan and hematopoietic autologous stem cell transplantation. However, the disease has remained particularly challenging to diagnose and manage, and outcomes have historically been bleak.

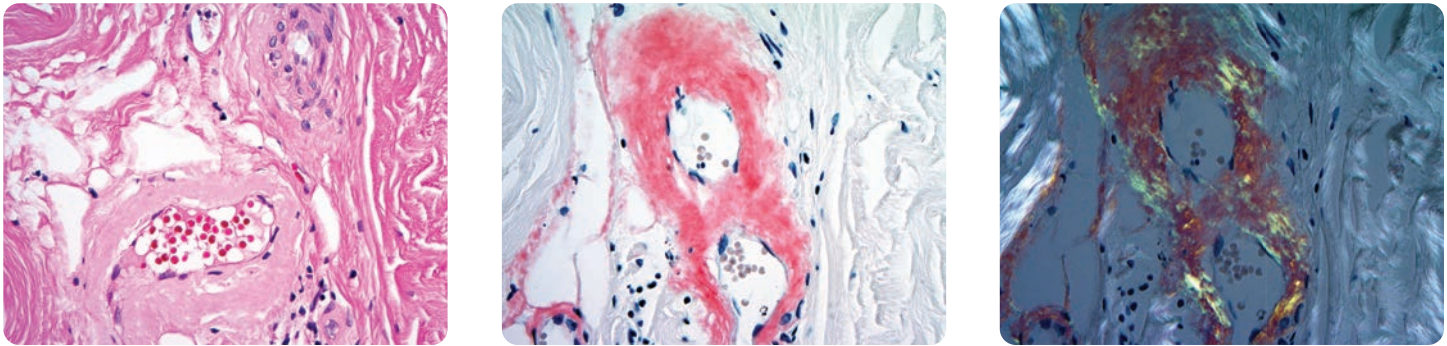
“A deep, rapid hematologic response is essential to the survival of patients with AL amyloidosis,” explains Jason Valent, MD, study co-author and Cleveland Clinic oncologist. “Unfortunately, the disease is already advanced by the time we see most of these cases, a reality that limits our treatment options and ability to improve long-term survival. Although targeted chemotherapy is the best way we’ve had to prevent the progressive disability and death that results from multiorgan involvement, the rate of hematologic complete response in these patients has been suboptimal. Now, however, there is good evidence that daratumumab as an adjunct to conventional therapies may improve organ function and survival.”

Study details

Patients with newly diagnosed AL amyloidosis were randomized to receive six cycles of bortezomib, cyclophosphamide and dexamethasone either alone or with subcutaneous daratumumab, followed by single-agent daratumumab every four weeks for up to 24 cycles in the patients treated with daratumumab. The primary end point was a hematologic complete response.

The percentage of patients who had a hematologic complete response was significantly higher in the daratumumab group than in the

BELOW — Daratumumab appears to offer significant benefits — including a promising safety profile — in patients with AL amyloidosis.



control group (53.3% vs. 18.1%). Survival free from major organ deterioration or hematologic progression favored the daratumumab group (hazard ratio for major organ deterioration, hematologic progression or death, 0.58; 95% CI, 0.36 to 0.93; *P* = 0.02). At six months, more cardiac and renal responses occurred in the daratumumab group than in the control group (41.5% vs. 22.2% and 53.0% vs. 23.9%, respectively).

The four most common grade 3 or 4 adverse events were lymphopenia (13.0% in the daratumumab group and 10.1% in the control group), pneumonia (7.8% and 4.3%, respectively), cardiac failure (6.2% and 4.8%) and diarrhea (5.7% and 3.7%). Systemic administration-related reactions to daratumumab occurred in 7.3% of study subjects. A total of 56 patients died (27 in the daratumumab group and 29 in the control group), most due to amyloidosis-related cardiomyopathy. Serious adverse events, most commonly pneumonia, occurred in 43.0% of those in the daratumumab group and 36.2% of those in the control group.

Survival free from major organ deterioration, hematologic progression or subsequent treatment was superior in the daratumumab group, as was the percentage of patients who experienced a cardiac or renal response.

“This is an important finding given that organ responses are objective measures of clinically relevant and observable end points for patients with AL amyloidosis as well as predictors of improved survival,” notes Valent.

The study authors also emphasize the important clinical advantages that subcutaneous daratumumab can provide patients with AL

amyloidosis, including reduced systemic injection-site reactions and a negligible volume of administration.

Promising future

Daratumumab has been approved as a monoclonal antibody for multiple myeloma since 2015 and is now the first drug approved by the FDA specifically for the treatment of AL amyloidosis. The results of the ANDROMEDA trial hold promise for clinicians like Dr. Valent, who strive to prolong the lives of patients with AL amyloidosis, a rare condition for which there has been no standard of care.

Long a major referral center for AL amyloidosis, Cleveland Clinic launched its multidisciplinary Amyloid Clinic in 2019. The clinic is composed of a hematologist, cardiologist, nephrologist and neurologist who work as a team to coordinate patient care.

“Continuity of care is integral to the successful treatment of AL amyloidosis,” says Dr. Valent. “Our ability to work as a dedicated team makes it possible to explore promising treatment avenues like the addition of daratumumab, which now provides a new standard of care in the treatment of AL amyloidosis.”

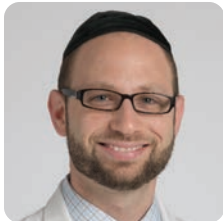
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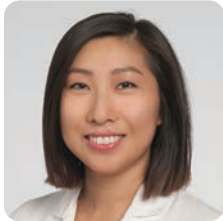
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CASE STUDY: CAN SURGERY SALVAGE THE NASOPHARYNX FROM EFFECTS OF AGGRESSIVE CHEMORADIATION?

What an experienced multidisciplinary surgical team can achieve with free tissue transfer



Shlomo Koyfman, MD



Jamie Ku, MD



Raj Sindwani, MD



Pablo Recinos, MD



Michael Fritz, MD

A 30-year-old man was diagnosed with embryonal rhabdomyosarcoma of the nasopharynx in 2018. His malignant soft-tissue tumor was highly aggressive, so he underwent several rounds of chemotherapy and radiation therapy at Cleveland Clinic with the aim of making the tumor more amenable to planned surgical resection.

Despite several months of therapy, the patient's tumor showed modest progression before surgery could be performed. This prompted palliative radiation therapy to the pharynx and two additional cycles of chemotherapy with differing regimens, including one with a monoclonal antibody.

The tumor responded to this additional treatment, but the extensive and intensive radiation and chemotherapy had caused chronic osteomyelitis and ulceration of the nasopharynx and oropharynx and raised concern about a potential immunocompromised state. The patient was unable to breathe through the nose and reported severe pain from the damaged pharynx tissue, prompting several visits to the emergency room. Narcotic pain relievers provided modest but inadequate relief. Cleveland Clinic doctors performed a tracheostomy and placed a feeding tube.

Imaging raised suspicion for possible tumor recurrence (see images), but the management path was unclear in view of the substantial morbidity from the cumulative chemoradiation. The Cleveland Clinic care team was uncertain whether surgery was still recommended or possible. The patient sought a second opinion from an out-of-state academic center, where he was told he was not a candidate for surgery and was recommended for palliative care.

Upon the patient's return to Cleveland, his radiation oncologist, Shlomo Koyfman, MD, reconvened a team of four Cleveland Clinic surgeons — head and neck surgeon Jamie Ku, MD; rhinologic surgeon Raj Sindwani, MD; skull base neurosurgeon Pablo Recinos, MD; and facial plastic and reconstructive surgeon Michael Fritz, MD — to meet with the patient and consider the feasibility of an operation to debride the highly damaged tissue and bone in the pharynx region in order to improve the patient's function and quality of life and assess for tumor recurrence. The group decided to attempt a coordinated combination of minimally invasive open and endoscopic surgical strategies customized to the patient's singular needs.

The operation in brief

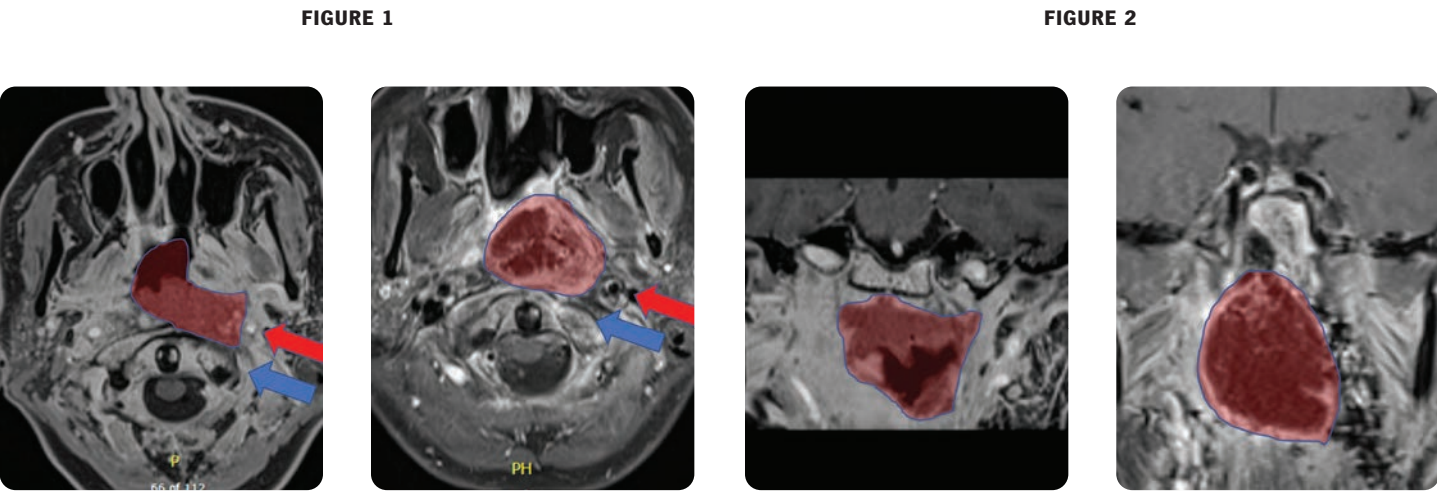
The four-surgeon team led an 18-hour operation that approached the pharynx and skull base from two directions to achieve debridement and detection of any remnant tumor tissue.

Dr. Ku accessed the lower pharynx through an incision at the root of the neck to debride all accessible osteonecrotic and ulcerated tissue and provide access to vessels for free tissue transfer. Drs. Sindwani and Recinos accessed the skull base by concurrent transoral and endonasal approaches, debriding those areas inaccessible to Dr. Ku. "The delicate skull base debridement

ABOVE — Head and neck surgeon Dr. Jamie Ku (right) debrides damaged tissue by accessing the patient's pharynx through an incision at the root of the neck.

FIGURE 1 — Preoperative and postoperative T1 axial images. Red shading indicates area of significant suspicion for recurrent tumor versus necrotic tissue (left), which was subsequently debrided/resected and filled in with healthy tissue from the free flap (right). Note that the left vertebral artery (red arrow) was very close to the edge of the necrotic tissue. In addition, due to the necrosis, erosion of the C1 vertebral arch of the spine was noted (blue arrow, left), and the subsequent erosion was stopped by protecting it with healthy tissue from the free flap (blue arrow, right).

FIGURE 2 — Preoperative and postoperative T1 coronal images. Red shading indicates area of significant suspicion for recurrent tumor versus necrotic tissue (left), which was subsequently debrided/resected and filled in with healthy tissue from the free flap (right).



involved drilling along critical structures, which was greatly facilitated by our two-surgeon, multihanded approach through the nose,” observes Dr. Sindwani.

Tissue sampling confirmed that the patient was tumor-free

After the debridement and diagnostic work was completed, Dr. Fritz, the reconstructive surgeon, harvested an anterolateral thigh free flap, sculpted it and inserted the highly vascularized pedicle flap via the prior incision at the neck root. Proper placement of the flap in the debrided area required a combined approach, with Dr. Fritz working from the neck incision and Drs. Sindwani and Recinos using endoscopy to work through the dual transoral/endonasal corridor to pull up the flap from its opposite end and guide precise placement. When coverage of the debrided area was achieved, Dr. Fritz made the requisite microvascular connections, which included sewing the flap to the transverse cervical artery and jugular vein to ensure robust blood supply.

Outcome and prognosis

The patient’s recovery was uneventful, with small amounts of nasal bleeding and mucus secretions. By his six-month follow-up, he was able to resume breathing through his nose and had started to consume a liquid diet and some solid foods. His pain in the pharynx region was markedly reduced and could be managed with nonsteroidal anti-inflammatory medication.

By one-year follow-up, he was off pain medications and pain free. His quality of life has improved with this significant resolution of pain and his ability to tolerate all diet by mouth. He was also able to get his tracheostomy tube removed safely. There was no evidence of tumor recurrence on examination and imaging, although he will continue regular surveillance follow-ups. Five-year survival rates for patients of his age with embryonal rhabdomyosarcoma of the nasopharynx are less than 30%.

“The experience of our multidisciplinary skull base surgery team suggested that this reconstructive option could provide effective repair of extreme morbidity where no other alternatives existed.” — PABLO RECINOS, MD

Why free tissue transfer was the only option

Although primary control of this patient’s aggressive tumor is attributable to the chemoradiation therapy prior to surgery, this control came at the cost of severe morbidity that another leading surgical oncology program deemed untreatable. The surgical strategy undertaken by the Cleveland Clinic team involved a rare application of microvascular free tissue transfer in the setting of endoscopic surgery. “The experience of our multidisciplinary skull base surgery team suggested that this reconstructive option could provide effective repair of extreme morbidity where no other alternatives existed,” says Dr. Recinos.

The team undertook the operation with extreme circumspection but ultimately decided to proceed based on its diverse experience in similar cases with no precedent or obvious surgical plan. “The ability and willingness to take on a case like this developed over years of interdisciplinary collaboration among our skull base surgery team,” Dr. Recinos notes.

That experience made clear that more common reconstructive options — a free graft or a local/regional vascularized pedicle flap — were not possible in this case.”

Whole greater than the sum of its parts

Perhaps more important, however, is the liberating effect of the team members’ experience-based knowledge of each other’s capabilities. “By collaborating on a diversity of skull base cases requiring reconstruction in the setting of endoscopic endonasal surgery,” Dr. Recinos says, “we have come to know what our colleagues in other surgical disciplines are capable of, which allows us to be a bit more aggressive than when we first started working together, and to do so without compromising safety.”

For more details, visit ccf.org/CA22.

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UTILITY OF GENOMIC-ADJUSTED RADIATION DOSE AS A PAN-CANCER PREDICTOR OF RADIATION THERAPY BENEFIT

Truly personalized radiotherapy may be within reach



Jacob Scott, MD, DPhil

A study published in *Lancet Oncology* finds that the genomic-adjusted radiation dose (GARD) model may be used to personalize radiotherapy (RT) to maximize the therapeutic effect of a given physical RT dose.

“As opposed to physical RT dose, which is the measure of what comes out of the machine and is delivered to the patient, GARD quantifies the biological effect on an individual patient of that delivered dose,” says Cleveland Clinic radiation oncologist Jacob G. Scott, MD, DPhil, first author of the study. “We’ve found that the physical dose of radiation does not associate with outcomes, but GARD does.”

A group of investigators from Cleveland Clinic, Case Western Reserve University School of Medicine and Moffitt Cancer Center authored the study, which represents the validation of a quantifiable parameter of the clinical effect of radiation, a parameter that serves as a predictor of the therapeutic benefit of RT for each individual patient.

Introducing GARD

According to Dr. Scott, despite recent advances in cancer genomics, the field of radiation oncology has, unlike medical oncology, not entered the precision medicine era, where patient-specific genomic data drive therapeutic decision-making. He notes that RT is still largely prescribed using an empiric approach that only considers the specific cancer diagnosis/tumor location to decide on standard dosing. In an attempt to move the field forward, his team of collaborators successfully devised and introduced the concept of GARD in a previous study.

“In our previous paper we showed the possibility of individualizing radiation dosing using patient tumor genomics and canonical models of radiation response. Using these models with genomics, GARD revealed significant heterogeneity within datasets that wasn’t visible before, and while it seemed to associate with outcomes in each disease site we analyzed, we lacked the statistical power to be certain,” he explains. “The thrust of that work was really to explain the derivation of GARD itself because it was a new concept.”

GARD is derived from the gene-expression-based radiation-sensitivity index (RSI) and the canonical linear quadratic model used to describe the biological response to radiation. RSI is, in turn, based on the expression of 10 specific genes in the biopsied tumor tissue and serves as a molecular estimate for cellular survival fraction at 2 Gy (SF2). Put simply, RSI reflects the tumor’s sensitivity to radiation.

The changes in the 10-gene signature that occur inside the tumor, the authors argue, are reflections of the changes that take place in the entire gene network, so they function like canaries in the coal mine, providing signals of radiation sensitivity secondary to many different possible changes at the genomic or epigenetic level. Many earlier studies have validated the gene-expression RSI/GARD as a biomarker of tumor radiosensitivity in patients across many cancer subtypes.

BELOW — Investigators Michael W. Kattan, PhD, and Jessica A. Scarborough, MS, MD/PhD candidate, led by oncologist Dr. Jacob G. Scott (far right) have validated a quantifiable parameter that can help predict the therapeutic benefit of RT in individual patients.



In explaining the utility of GARD, Dr. Scott notes that it quantifies the biologic effect of radiation into a numerical parameter that involves physical RT dose, giving oncologists an objective way to understand the relative therapeutic benefit of their prescribed RT, and allowing them to modify the physical dose of RT to optimize radiation therapy benefit for each individual patient. And because GARD integrates RSI and the patient’s individual tumor gene expression signature into its algorithm, it is a truly personalized tool, which, unlike standard biomarkers, allows the clinician to modulate the dose given based on each patient’s predicted response. GARD provides the first validated decision support tool that enables radiation oncologists to use genomic information to modulate the potential benefit of radiation therapy for each patient.

Implementing GARD and identifying disease-specific targets

Leaving behind a decades-old way of prescribing RT for cancer patients will take time, Dr. Scott says, but he is optimistic that the field will soon embrace GARD as a valuable tool for personalizing RT.

“This test is now available from a laboratory at Moffitt Cancer Center and will be available commercially very soon,” he says. “In this paper we show level 1 evidence for GARD’s utility, which should give clinicians the confidence to begin using this genomic decision support tool and adjusting dose within the standard of care. While we are eager to see adoption in the near term, we’re also interested in prospective trials, disease by disease, to begin defining disease-specific GARD-based dosing targets.”

For more details, visit ccf.org/CA22.

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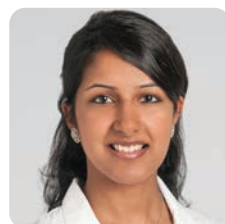
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NEW GENOMICS CLINIC HELPS CANCER PATIENTS DECIPHER NGS TESTING RESULTS

Virtual clinic supports oncologists by educating patients and making treatment recommendations



Pauline Funchain, MD



Meena Sadaps, MD

The sequencing of the human genome has given rise to precision oncology, which offers tailored treatments to patients by targeting specific molecular alterations in their tumors. Next-generation sequencing (NGS) techniques can detect single or global genomic alterations both on germline and somatic DNA.

While the evolution of NGS and subsequent novel targeted therapies offer promise, the complexity of data generated — including information on actionable mutations and associated therapies and clinical trials — can overwhelm patients and oncologists.

In October 2021, Cleveland Clinic launched a Genomics Clinic for patients with locally advanced and metastatic solid tumor malignancies to learn about NGS testing and the potential impact of their sequencing results.

“Cancer treatment is a rapidly expanding field, whether you’re talking about genomics, immunotherapy or cellular therapy. It’s a lot for even the most meticulous, well-read practitioners and their patients to keep up with,” says Pauline Funchain, MD, an oncologist and cancer genomics expert at Cleveland Clinic who co-founded the Genomics Clinic. “We hope to serve as a resource for primary oncologists, especially those who treat multiple histologies.”

Shining light on genomic testing and results

The Genomics Clinic, which operates virtually Tuesday and Wednesday mornings, is run by co-founder Meena Sadaps, MD, a Cleveland Clinic GI oncologist and cancer genomics expert. She partners with a genetic counselor to identify patients who should be referred for genetic testing and counseling, particularly those

with pathologic alterations of high-variant allele frequencies suggestive of germline origin.

Education before and after NGS testing is a primary goal of the 30-minute appointments.

“Patients are often asked to submit saliva samples for partnered germline sequencing without properly understanding the rationale and the implications these results may carry,” explains Dr. Sadaps. During appointments, she discusses the difference between genetic and genomic testing, as well as what NGS testing entails and reveals.

If patients have already been tested, Dr. Sadaps performs a curated review of the results to determine what targeted on-label and off-label therapies and/or clinical trials they may be eligible for and from which they may obtain the highest clinical benefit.

The Genomics Clinic is also supported by Cleveland Clinic’s bimonthly Genomics Tumor Board. Potential off-label considerations and sequencing of therapies are discussed by the board, which includes medical oncologists, pathologists and genetic counselors. The board also reviews NGS results for any discrepancies that may require repeat testing or further evaluation.

“One of the benefits of the Genomics Tumor Board is that we have content experts — whether on the pathway, tumor type or both — who help us



LEFT — Cancer genomics expert Dr. Meena Sadaps (right) performs a curated review of each patient’s NGS test results to determine an ideal therapeutic plan.

navigate the complexity of precision oncology in their respective histologies,” says Dr. Funchain.

Opening up treatment and trial opportunities

Dr. Sadaps had virtual appointments with two patients soon after the Genomics Clinic was launched. Both had targetable mutations. One patient was eligible for two clinical trials being conducted at the University of Texas MD Anderson Cancer Center, where she will meet with oncologists to determine which to pursue.

“Getting NGS testing can open doors for patients who might not otherwise have standard-of-care options, whether through clinical trials or off-label therapies,” says Dr. Sadaps.

Drs. Funchain and Sadaps were co-authors on a study published in 2018 in *JCO® Precision Oncology* on the therapeutic impact of precision oncology. In the retrospective review of 600 patients being treated for incurable solid tumor malignancies who underwent tumor genomic profiling, targeted therapies were recommended for 51.7% of cases. Tumor genomic profiling influenced the treatment of 15.8% of the patients in the study.

Providing cutting-edge information on genomics-driven therapy

Dr. Sadaps encourages oncologists to consider NGS testing for patients early in the course of their disease. The 2018 study showed that one of the main obstacles in patients from receiving targeted therapies was that their performance status was often poor at the time the results were obtained, making them ineligible for any potential clinical trials.

“If there are treatable mutations, we want to act on them, so early testing is critical,” explains Dr. Sadaps. “In parallel, we encourage clinicians to refer patients to us soon after their test results arrive so we can talk about options while patients are doing well clinically.”

Understanding all potential options is the goal

“This is life or death for a lot of patients, so it’s comforting to know that you’ve covered all your bases. And as clinicians, we want our patients to have access to every possible treatment option,” says Dr. Funchain. “The Genomics Clinic provides a way for both patients and practitioners to feel like they have the most up-to-date information and opinions in the field of genomics-driven therapy.”

For more details, visit ccf.org/CA22.

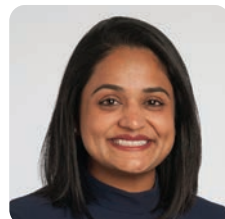
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SURVIVORSHIP IS THE FOCUS OF NEW CANCER GENOMICS PROGRAM

Specialized clinic addresses long-term wellness through the study of somatic mutations



Bhumika Patel, MD



Jessica Geiger, MD

A new Cleveland Clinic program aims to integrate research and preventive care to improve the survivorship of patients with newly diagnosed cancers.

The novel initiative will use next-generation sequencing to prospectively identify potential therapeutic targets while retrospectively evaluating mutations and other changes that may impact patients' long-term health.

The program, which helps patients transition from cancer treatment to recovery while addressing their future risks, is part of Cleveland Clinic Cancer Center's new CHIP Clinic. The first of its kind in Ohio and one of only a few in the U.S., the clinic screens and monitors patients with clonal hematopoiesis of indeterminate potential (CHIP): somatic mutations in blood or bone marrow cells that increase the risk of blood cancers and heart disease.

Although the new Survivorship Program will initially focus on the study of breast and head and neck malignancies, Taussig Cancer Institute hematologist/oncologist Bhumika Patel, MD, says her team's goal is to eventually serve patients in all disease groups.

"Genomic testing is already playing a vital role in our ability to target certain cancers, but it is poised to one day become standard care for patients with other chronic disorders," explains Dr. Patel, who helped establish the CHIP Clinic in 2020. "This new program will enable us to collect and interpret meaningful data that can be used to improve disease classification, streamline the identification of available treatments and more accurately predict patient outcomes."

Targeted research

In recent years, several large studies of healthy populations have found age-related mutations that are commonly seen in patients with myelodysplastic syndrome (MDS) and acute myeloid leukemia. Dr. Patel says these discoveries inspired the development of the CHIP Clinic.

Clonal hematopoiesis (CH) is represented by acquired mutations in leukemia-associated genes such as *DNMT3A*, *TET2*, *ASXL1* and others, although there may be non-leukemia-associated CH mutations in a small population of blood cells as well.

Cleveland Clinic researchers strive to better understand the biology of CH, develop clinical trials and establish guidelines for managing patients with CH.

"By studying these mutations in cancer patients, we can learn an enormous amount about the progression of CHIP — knowledge that ultimately benefits our patients through customized interventions, education and preventive care," explains oncologist Jessica Geiger, MD, who co-directs the Survivorship Program.

Patients with newly diagnosed cancers as well as those who have already undergone treatment will be included in the program.

Empowering patients

Dr. Geiger explains that the program is designed to give cancer survivors a certain level of control over their treatment and long-term wellness.



LEFT — A new Survivorship Program co-directed by Dr. Bhumika Patel helps patients transition from cancer treatment to recovery while addressing their future risks.

"Cancer survivors are often faced with long-lasting or late-onset effects of their disease or its subsequent treatment. Our team has the opportunity to connect patients with the resources they need to address these health concerns head-on and, we hope, achieve an optimum quality of life — now and in the future," she says.

The Survivorship Program will continue to evolve as cancer treatments improve and more is learned about CH, explains Dr. Patel. She notes that the chance to participate in meaningful research has empowered many of her patients, who are eager to support the recovery of their fellow cancer survivors.

"Our patients are invested in this process; they want to do everything they can to improve their own long-term health and prevent suffering in other cancer survivors," says Dr. Patel. "As clinicians, we want to do all we can to mitigate our patients' risk factors and develop customized, targeted cancer therapies. Ultimately, we are all in this together."

For more details, visit ccf.org/CA22.

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NOVEL PROGRAM OPTIMIZES DIAGNOSTIC AND TREATMENT STRATEGIES FOR RARE DISEASES

Multidisciplinary team tackles the management of 84 uncommon cancers and blood disorders



Sudipto Mukherjee, MD, PhD, MPH

Approximately 20% of all patients diagnosed with cancer in the United States have a rare form of the disease. For such patients, as well as those with rare blood disorders, access to clinical and pathologic expertise is often limited due to the rarity of their diagnosis.

These patients often require personalized treatment options that depend on the activation of specific pathways or the identification of gene mutations.

To address the challenges faced by those with rare cancers, Cleveland Clinic has developed a Rare Cancers and Blood Diseases Program designed to harness the expertise of highly subspecialized medical and radiation oncologists, surgeons, radiologists, pathologists, pharmacists and social workers. This unique multidisciplinary program provides patients with the rarest of conditions access to extensive diagnostic capabilities, comprehensive genomic analysis, approved targeted treatments and clinical trials focused on the development of potentially groundbreaking therapies.

Few cancer centers have access to the level of expertise, research infrastructure and portfolio of clinical trials needed to effectively diagnose and treat these uncommon diseases, explains hematologist and medical oncologist Sudipto Mukherjee, MD, PhD, MPH. As a result, these patients often visit multiple institutions and face long waiting periods when seeking solutions to their complex medical disorders. Unfortunately, rare diseases can be difficult and time-consuming to diagnose. This means that they are often detected late — a problem that contributes to delayed treatment, poor quality of life and less-than-optimal outcomes.

The expertise that comes with specialty care

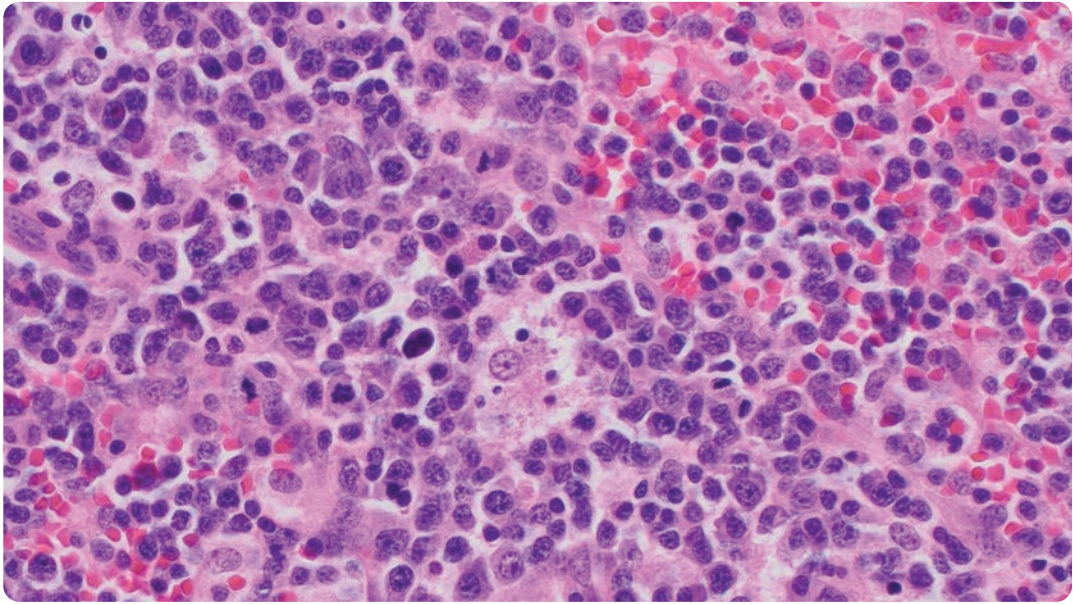
“Because some of these rare cancers involve multiple organ systems, we developed a physician disease matrix that integrates multiple specialties,” explains Dr. Mukherjee, who directs the program at Cleveland Clinic’s Taussig Cancer Institute. “Our efforts to establish a separate stand-alone program for rare diseases and cancers have resulted in an impressive, steady increase in patient volumes over the past three years.”

The clinical, surgical and pathological expertise developed by the program’s physicians has continued to evolve thanks to the number and variety of cases they see, adds Dr. Mukherjee. Since its creation in 2018, the program has grown to serve more than 150 to 200 patients with rare cancers or blood diseases annually.

Enabling rapid clinical decisions

Before the Rare Cancers and Blood Diseases Program was developed, patients were frequently assigned to a clinician who may — or may not — have a clinical or research interest in that patient’s particular disease, Dr. Mukherjee explains.

“We have changed our workflow so that when a patient is referred or presents with any one of the 84 diseases we manage, the scheduling team can quickly connect the patient with the concerned physicians who specialize in that



LEFT — Novel clinic uses genomic analysis and cutting-edge research to provide personalized treatment to patients with rare diseases like Langerhans cell histiocytosis (pictured).

particular disease,” he explains. “This fine-tuned approach has dramatically improved patient access and the speed at which we can definitively establish or rule out a diagnosis. It has also allowed us to minimize clinical ‘shopping’ by managing patients in a much more efficient and convenient way.”

Because patient access is one of the key goals of the program, any rare cancer patient referred to the program is seen within five business days.

Patients gain access to the program via several paths, including referrals from support or advocacy groups, and other providers and Cleveland Clinic patients.

Ultimately, the aim is to shorten the time to accurate diagnosis and improve outcomes in those with rare diseases. Dr. Mukherjee adds, “I would like to see improvement in these metrics soon. For example, extensive genomic analysis is now routinely performed on almost all rare cancers and blood conditions. In almost every instance, patients with targetable mutations are either enrolled in a clinical trial or treated with FDA-approved targeted therapies.”

Access to clinical research

Because some diseases have no approved treatment, enrollment in a clinical trial of an experimental therapy is sometimes a patient’s only option. Patients are more willing to travel for medical care when they are provided access to robust clinical research, Dr. Mukherjee adds.

Recently published studies involving research conducted by the Rare Cancers and Blood Diseases Program include:

- Identifying genetic mutations that may predict which patients with aplastic anemia will progress to myelodysplastic syndromes
- Using gene expression profiling to determine prognostic factors and potential therapeutic targets in small-cell bladder cancer
- Improving the staging and risk stratification for patients with Merkel cell carcinoma
- Evaluating optimal treatment combinations for patients with rare forms of diffuse large B-cell lymphoma

A number of studies involving novel blood diseases and rare solid and hematologic malignancies are ongoing or planned.

For more details, visit ccf.org/CA22.


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NOTEWORTHY

CONGRATULATIONS TO OUR STAFF ON THE FOLLOWING GRANTS:

- **Jarek Maciejewski, MD, PHD**, received a \$3 million grant from the National Institutes of Health and National Cancer Institute for his groundbreaking genomics discoveries related to leukemia and cancer precision medicine.
- **Jennifer Yu, MD, PhD**, received a \$2.7 million research grant from the National Institutes of Health and National Institute of Neurological Disorders and Stroke to support her mechanistic studies of lncRNA and its role in regulating glioma progression, as well as a \$300,000 award from the Falk Medical Research Trust to develop therapeutics designed to target lncRNA.
- **Nima Sharifi, MD**, and **Jame Abraham, MD**, received a \$1.1 million grant from the U.S. Department of Defense to support their study “Genetic and Metabolic Basis for Hormonally Driven Postmenopausal Breast Cancer.”
- **Jacob Scott, MD, DPhil**, was awarded \$200,000 by the Carson Sarcoma Foundation to purchase new equipment for Cleveland Clinic’s Theory Division lab to study cancer evolution.



CANCER ADVANCES

A Cleveland Clinic podcast for medical professionals, exploring the latest innovative research and clinical advances in the field of oncology.

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UPCOMING CME EVENTS

- Management of Checkpoint Inhibitor-Related Toxicity**
March 3-4, 2022
InterContinental Hotel, Cleveland
ccfme.org/toxicitymgmt22
- 2022 Multidisciplinary Head and Neck Cancer Update**
March 18-19, 2022
Marriott Harbor Beach Resort & Spa
Fort Lauderdale, FL
ccfme.org/headandneck22

VELOSANO PARTICIPANTS RAISE MORE THAN \$5 MILLION FOR CANCER RESEARCH AT CLEVELAND CLINIC

A record-high \$5.1 million was raised for VeloSano in 2021, 100% of which will support lifesaving cancer research at Cleveland Clinic. The year-round fundraising initiative has raised a cumulative total of more than \$29 million since its inception in 2014.

VeloSano (Latin for “swift cure”) has gained significant momentum in raising money for cancer research at Cleveland Clinic due to the support of its partners, including the Kohl Fund, the Cleveland Guardians, Adcom, Jones Day, Lexus, Zack Bruell Events, Advance Ohio, Amgen, Hileman Group, House of LaRose/Michelob Ultra, KeyBank, The Lerner Foundation, Oscar Health and Ranpak.

Cleveland Clinic cancer researchers across the enterprise compete for funds raised by VeloSano, with the money being awarded to research proposals with the greatest promise. Thus far, VeloSano has supported 170 cancer research projects. Those projects often go on to earn research grants from the National Institutes of Health and others. To date, an additional \$22 million in funding has been received thanks to the promise shown by VeloSano-funded projects.

Learn more about VeloSano and projects funded by visiting impact.velosano.org.



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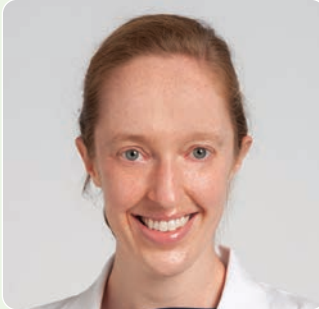
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CANCER CENTER HITS STRIDE WITH PIONEERING INITIATIVES

Specialists provide novel therapies, clinical trials designed to crack even the toughest cancer cases



Jame Abraham, MD, FACP

Science is the cornerstone of clinical progress — a truism that becomes increasingly evident with each passing year. Time and again, Taussig Cancer Institute has been recognized for its comprehensive, leading-edge vision — a multidisciplinary approach that provides individualized cancer therapies informed by the most advanced research available.

Despite the limitations imposed by the ongoing COVID-19 pandemic, Cleveland Clinic continues to innovate the management of cancers for which there traditionally have been limited therapeutic options. Among our center’s most promising bench-to-bedside initiatives is the first-ever study of a novel vaccine designed to prevent triple-negative breast cancer, the most aggressive and lethal subtype of the disease.

In an ongoing effort to connect patients with potentially life-saving clinical trials, Cleveland Clinic recently granted \$400,000 to establish the Cleveland Clinic Breast Cancer Center of Excellence, co-led by research scientist Ruth Keri, PhD, and cancer geneticist Charis Eng, MD, PhD. In addition, a new multidisciplinary Center for Young-Onset Colorectal Cancer was created in collaboration with Cleveland Clinic’s Digestive Disease & Surgery Institute.

We also expanded our center’s cancer genomic testing capabilities to provide whole exome sequencing, an indispensable tool for detecting the somatic defects that may drive cancer growth. The momentum created by the initial effectiveness of chimeric antigen receptor (CAR) T-cell therapy has also prompted new Cleveland Clinic studies of novel cellular cancer therapies.

I’m proud to report that several talented Taussig Cancer Institute physicians were honored with major federal grants in 2021. The largest award went to Jarek Maciejewski, MD, who received \$3 million for his groundbreaking genomic discoveries related to leukemia and cancer precision medicine. Radiation oncologist Jennifer Yu, MD, PhD, received \$2.7 million to foster brain cancer research, and cancer biologist Nima Sharifi, MD was awarded \$1.1 million to further our studies on breast cancer.

Our department also gave back by raising \$5.1 million for cancer research through VeloSano — our greatest contribution to the fundraising initiative to date.







It goes without saying that none of the work we do would be possible without our unparalleled team of physician scientists. The sheer breadth, depth and impact of their work echoes the enormity of our mission to provide the best clinical care possible.

I hope you find inspiration on these pages for your own work. It is the support of caregivers like you that enables us to attract world-class researchers, sustain our innovative clinical practices, and discover new ways to enhance and lengthen patients’ lives through science.

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ABOUT CLEVELAND CLINIC

Cleveland Clinic is a nonprofit, multispecialty academic medical center integrating outpatient and hospital care with research and education for better patient outcomes and experience. More than 4,500 staff physicians and researchers provide services through 20 patient-centered institutes. Cleveland Clinic is a 6,026-bed healthcare system with a main campus in Cleveland, 18 hospitals and over 220 outpatient locations. The health system includes five hospitals in Southeast Florida with more than 1,000 beds, a medical center for brain health in Las Vegas, a sports and executive health center in Toronto, and a 364-bed hospital in Abu Dhabi. Cleveland Clinic London, a 184-bed hospital, will open in 2022. Cleveland Clinic is currently ranked as one of the nation’s top hospitals by *U.S. News & World Report*.

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