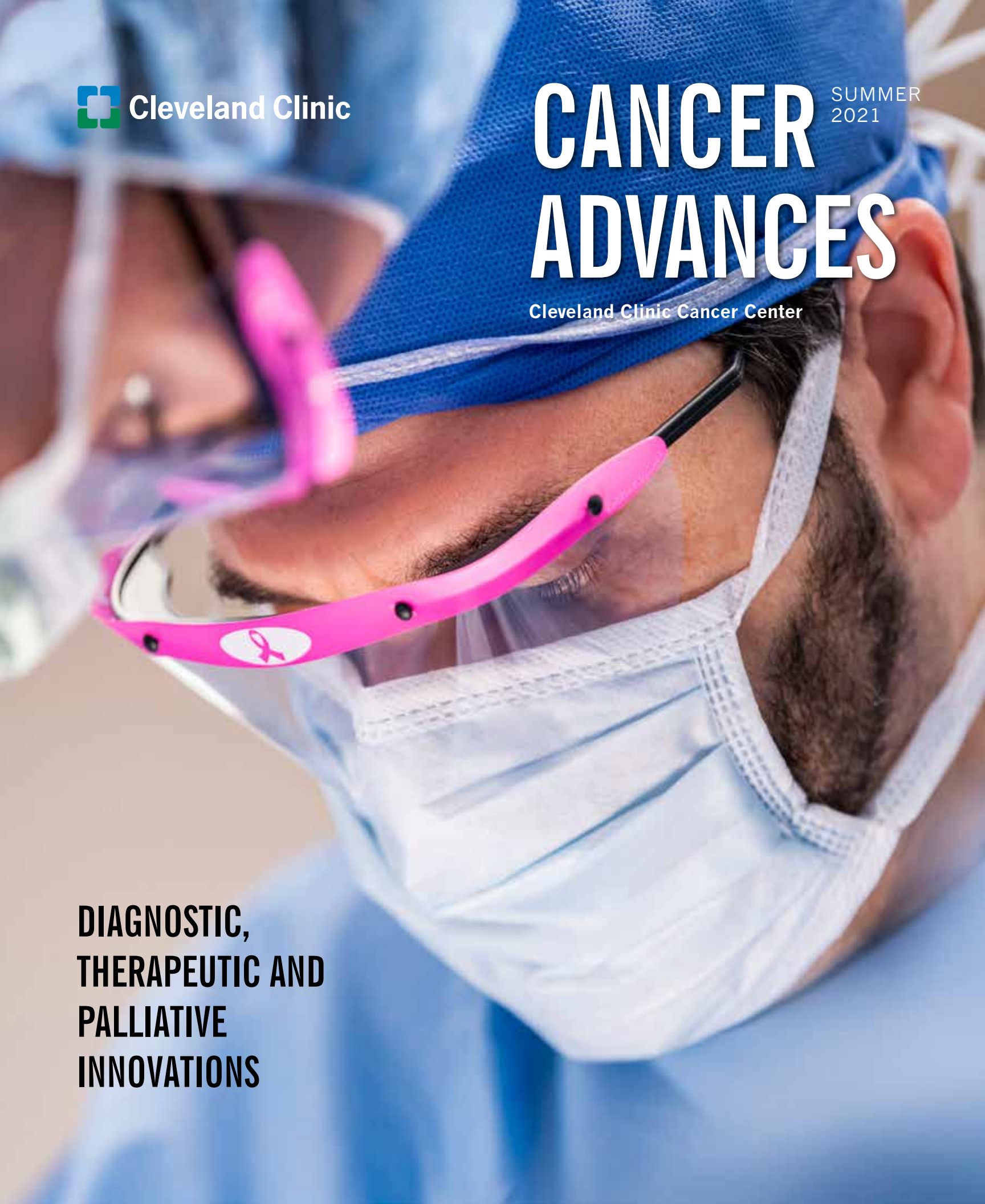


Cleveland Clinic

# CANCER ADVANCES

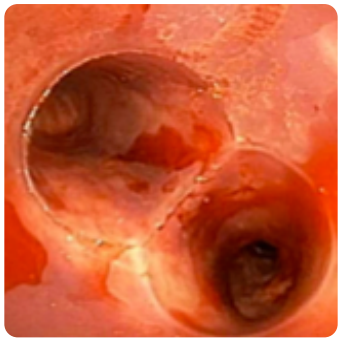
SUMMER 2021

Cleveland Clinic Cancer Center

## DIAGNOSTIC, THERAPEUTIC AND PALLIATIVE INNOVATIONS

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*.

# INSIDE





**ON THE COVER —** Robert DeBernardo, MD, debulks a tumor before performing hyperthermic intraperitoneal chemotherapy (HIPEC). Learn more on p. 15.

# DEAR COLLEAGUES,

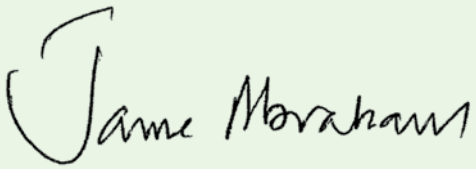
Welcome to the latest edition of *Cancer Advances.* The programs and projects described in this issue reflect Cleveland Clinic Cancer Center's emphasis on high-impact, translational cancer research and innovative therapies.


The work highlighted here is the result of dozens of talented clinicians and researchers working together to advance patient care.

As Acting Chair of the Cancer Center, I want to express deep gratitude on behalf of the entire team to Brian Bolwell, MD, as he embarks on his new role as Chair of Physician Leadership and Development at Cleveland Clinic. Dr. Bolwell made significant contributions during his tenure as Chair, including achieving national leadership in patient access and academic and clinical expertise, overseeing our amazing new facilities and launching VeloSano, which has generated $24 million to support cancer research. But most important, Dr. Bolwell worked tirelessly to build an empathetic culture and growth mindset among our caregivers. He is a true leader, and we wish him all the best.

As we look toward the future of Cleveland Clinic Cancer Center, we will continue to focus on access, high-quality care, research and training the next generation of cancer doctors.

Sincerely,



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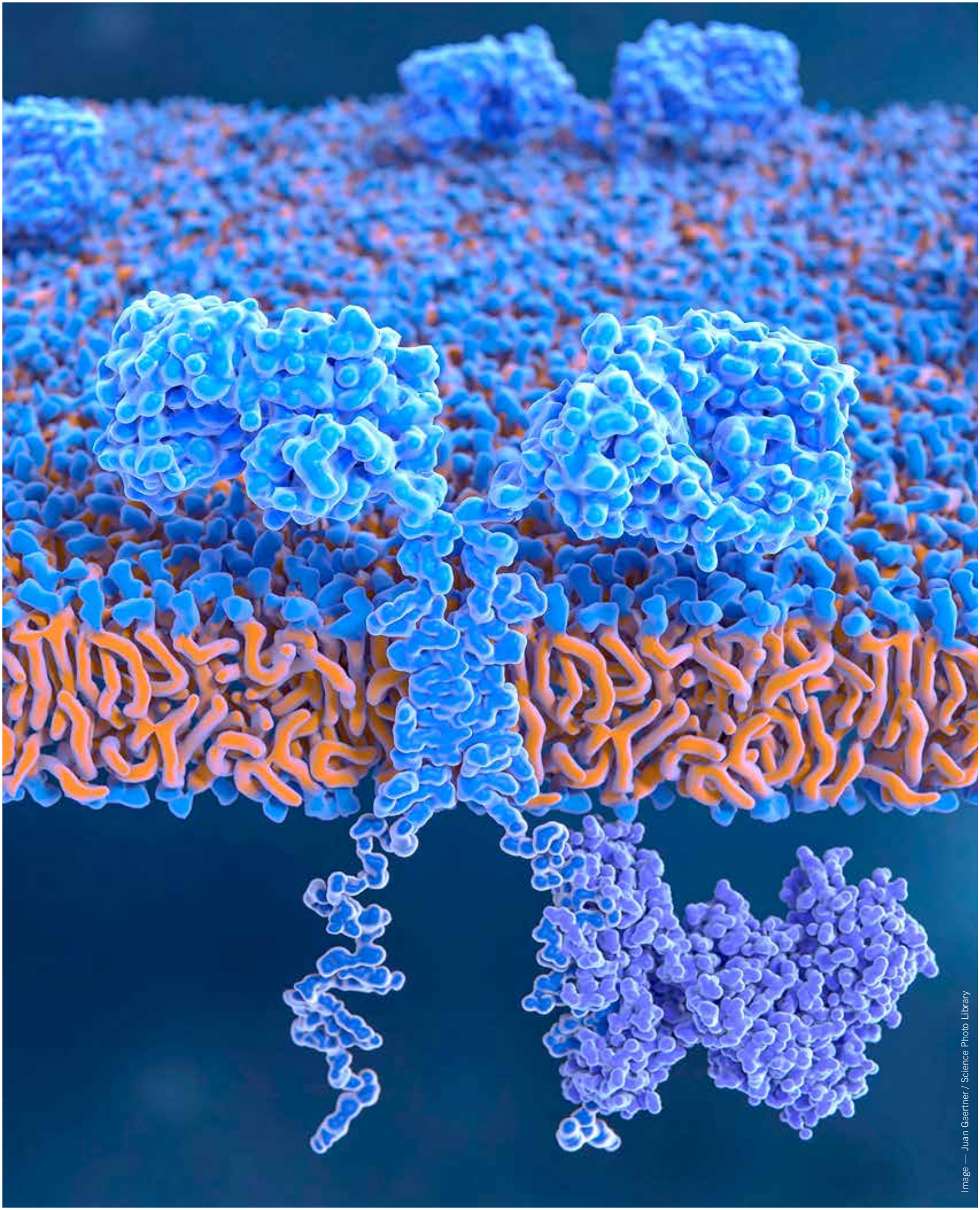


Image — Juan Gaertner / Science Photo Library

# CELLULAR THERAPY ACROSS CLEVELAND CLINIC

*A brief look at our programs*

Betty Hamilton, MD

Faiz Anwer, MD

Brian Gastman, MD

**LEFT —**
Chimeric antigen receptor (CAR) on T cell, illustration. The CAR structures are blue, with the cutaway foreground showing one spanning the cell membrane. These CARs are on the surface of an engineered T cell. CARs are engineered cell receptors that allow T cells to recognize and attack cancer cells in a specific way. They are built by connecting several functional parts from different proteins. This receptor has a signal protein (ZAP70, purple, lower right) attached to the intracellular domain (bottom).

In recent years, the momentum created by the initial effectiveness of chimeric antigen receptor (CAR) T-cell therapy has prompted team-based research efforts in cellular therapy at Cleveland Clinic.

Learn more about a few of our efforts below.

## RELAPSED/REFRACTORY MULTIPLE MYELOMA

Preliminary data from a phase 1 trial of allogeneic CAR T-cell therapy show therapeutic responses in relapsed/refractory multiple myeloma patients. In the UNIVERSAL trial, a multicenter study that includes Cleveland Clinic, patients are first treated with a lymphodepleting regimen of cyclophosphamide, fludarabine and ALLO-647, an anti-CD52 monoclonal antibody. Following ALLO-647, they are treated with the CAR T-cell therapy ALLO-715, which targets B-cell maturation antigen (BCMA). BCMA is highly expressed on plasma and multiple myeloma cells.

The trial is testing ALLO-715 as a single infusion across four doses: 40, 160, 320 or 480 x 106 CARs. Lymphodepletion regimens consist of fludarabine (F; 30 mg/m$^2$/day) plus cyclophosphamide (C; 300 mg/m$^2$/day) given on three days with ALLO-647 (A; 13-30 mg x 3 days; FCA) or cyclophosphamide plus ALLO-647 (CA).

The therapy generated the strongest response in patients who received ALLO-647 at 320 x 106 CARs. For this cohort, the overall response rate (ORR) was 60% among 10 patients, including three of six who received CARs with low-ALLO-647 FCA and three of four who had the therapy with high-ALLO-647 FCA. Overall, six patients had a very good partial-plus response (VGPR+), a complete response or a very good partial response. This included one patient at 160, four patients at 320 and one at 480 10 x 106 CARs. Of the VGPR+ patients, five were negative for measurable residual disease.

Additionally, six of nine patients treated at the 320 or 480 x 106 dose levels remain in response. Cleveland Clinic has one patient in the trial who has had a good response so far.

"We currently don't have good therapies for patients who have been treated with three or more prior therapies. CAR T-cell therapy could be a good option for relapsed patients who don't have the option of waiting," says Faiz Anwer, MD.

## ADVANCED MELANOMA AND MERKEL CELL CARCINOMA

Built on foundational work at the National Cancer Institute (NCI), Cleveland Clinic studies are in development to explore the use of autologous tumor-infiltrating lymphocytes (TILs) and natural killer (NK) cells to produce durable, complete responses for patients with refractory disease.

"Our main focus in melanoma is on recapitulating what has been done by NCI, and we are working with commercial companies to scale up TIL therapies," says Brian Gastman, MD. "We want to make these treatments available to our patients as soon as possible, if not as a potential cure, then as a bridge to other therapies that may be developed in the future."

"Administration of these immunotherapies is complicated, particularly when lymphodepletion is needed. Because of the potential for major side effects, we work closely not only with medical oncologists but also with our bone marrow transplantation team, which has tremendous experience." — BRIAN GASTMAN, MD

### Therapy with TILs

In Merkel cell carcinoma (MCC), researchers are testing the expansion of NK cells. In a recent phase 2 trial, treatment with the TIL therapy known as lifileucel produced an ORR of 36.4% and a disease control rate of 80.3% in patients with metastatic melanoma. The participants had a high baseline disease burden and disease that had progressed on multiple prior therapies, including anti-PD-1 and BRAF/MEK inhibitors.

"This therapy is not standard of care yet and is offered to patients in clinical trials as fifth- or sixth-line treatment," says Dr. Gastman. "Our hope would be to use TILs earlier to get more benefit, but even for late-stage melanoma, it represents a new option that we may soon be able to give to patients."

### Natural killer cells for MCC

While two trials of TILs for melanoma supported by Cleveland Clinic are still on the drawing board, one with NK cells in MCC is already recruiting. The phase 2, single-arm study will evaluate the immunotherapy in combination with the PD-L1 monoclonal antibody avelumab and the IL-15 agonist N-803.

"The cell therapy product we're studying for MCC combines modern immunotherapies with reinvigorating therapies," says Dr. Gastman. "The NK cell line has been engineered to produce endogenous, intracellularly retained IL-2 and to express CD16."

Unlike TILs, which target antigens in a tumor and are autologous, the NK cells target proteins and are allogeneic products. Both protocols, however, are complex, requiring specialized expertise and careful coordination of patient care at multiple steps.

"Administration of these immunotherapies is complicated," says Dr. Gastman, "and particularly when lymphodepletion is needed. Because of the potential for major side effects, we work closely not only with medical oncologists but also with Cleveland Clinic's bone marrow transplantation team, which has tremendous experience."

## MANAGING CELLULAR THERAPY ACROSS THE SYSTEM

Betty Hamilton, MD, is working to help coordinate and operationalize novel cellular therapies within different cancer programs across Cleveland Clinic Cancer Center to support participation in and expansion of new clinical trials.

Cleveland Clinic's Cellular Therapy Assist Team (CAT), housed within the Blood and Marrow Transplant program, supports cellular therapy program research groups, such as myeloma, leukemia, thoracic oncology and melanoma, in understanding how to manage cell therapy trials and resources.

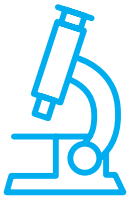
The team consists of physicians, research coordinators and nursing and program managers. Team members discuss the logistics and operations of cellular therapy collection and administration within clinical research trials. The group also reviews the portfolio of studies and opportunities for new research and expansion while collaborating between disease groups.

"We've created a successful model for collaborative research and experience in cellular therapy among different disease groups," says Dr. Hamilton. Since CAT's inception, six new cell therapy studies have been added to Cleveland Clinic's research portfolio in five months.

For a more in-depth look at our cellular therapy expertise, visit **ccf.org/CA21**.

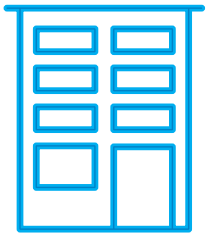
# BY THE NUMBERS

**9**
CAR T trials open to accrual



**9**
trials in startup stage

**3**
trials in site selection



**25**
total CAR T trials since 2015

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# USING ARTIFICIAL INTELLIGENCE TO DIAGNOSE KIDNEY CANCER

*Algorithm distinguishes between benign and malignant masses*

Christopher Weight, MD

Using artificial intelligence (AI), researchers at Cleveland Clinic have developed a reliable way of automating the characterization of kidneys and kidney tumors.

The key is semantic segmentation of kidneys and kidney tumors — linking each pixel in a CT scan to a specific label — and training a computer to recognize the images, in a method known as deep learning.

"It's similar to facial recognition software in that it's taking pixels from images and making mathematical representations of them by computer in the background," says Christopher Weight, MD. "We manually annotated about 40,000 slices from renal CT scans by drawing boundaries and indicating what was surrounding anatomy and what was tumor. After seeing enough examples, our computer model was able to look at slices it hadn't seen before and make predictions."

## Testing the algorithm

Now, they are on the brink of operationalizing an algorithm that will result in a fully automated nephrometry score, which may be the first of its kind. The process from annotation of the CT scans to this point has taken nearly four years.

So far, the algorithm has only been applied clinically on a retrospective basis. A paper detailing results with the automated nephrectomy score in a prospective cohort has been submitted for publication. "The area under the curve for the model was almost identical to human expert scores for predictions in domains including whether a kidney would require total or partial removal, was high- or low-grade, or was cancer or not," says Dr. Weight.

The team is also working on validating the algorithm in other cohorts to ensure that it performs well in a variety of populations.

## Expanding availability

The next step is a website through which a patient can upload a CT scan of a renal mass and get an AI reading of it. "It could be a valuable option for a second opinion," Dr. Weight believes, "with confirmation by an expert that the algorithm has performed correctly in that particular case."

To read more, visit **ccf.org/CA21**.

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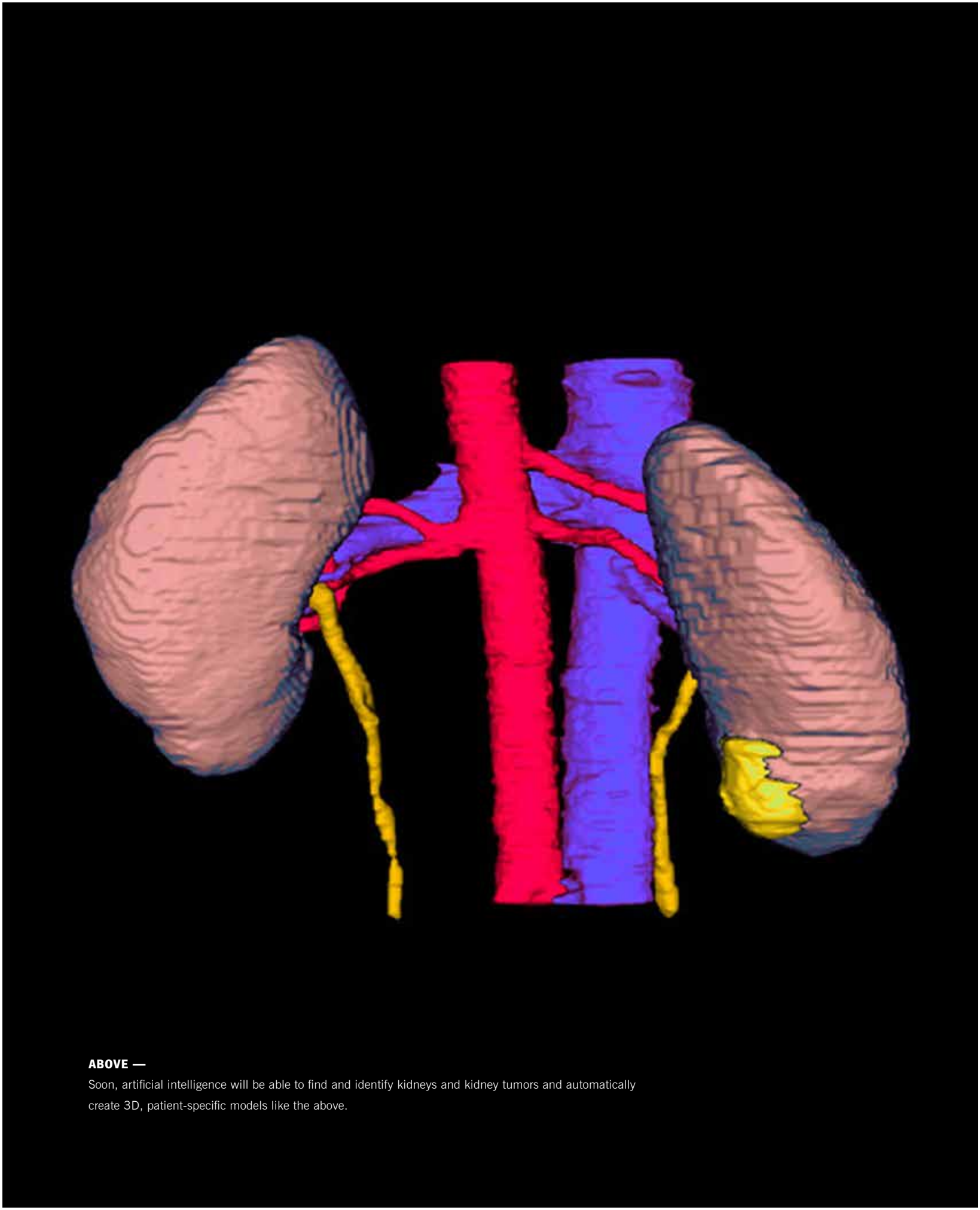

**ABOVE —**
Soon, artificial intelligence will be able to find and identify kidneys and kidney tumors and automatically create 3D, patient-specific models like the above.

# FIRST CLINICAL USE OF NEWLY APPROVED ABLATION DEVICE FOR LARGE LIVER TUMORS

*An alternative to open liver surgeries*

Eren Berber, MD

Cleveland Clinic is the first hospital in the world to use a recently FDA-approved ablation technology from Medtronic called the Emprint™ HP Ablation System with Thermosphere™ Technology.

The minimally invasive procedure uses a single needle connected to a powerful 150-watt microwave generator that can burn a malignant liver tumor as large as 2.4 inches (6 cm).

Eren Berber, MD, led a team that successfully used the device in October to treat a patient who had a 2.4-inch liver tumor. Following the minimally invasive procedure, the patient is doing well and postoperative imaging shows no trace of the tumor.

"We've been using the previous versions of this technology," says Dr. Berber. "But the challenge was that with a single needle, we were only able to create 4 cm burns. Now we can create 6 or 7 cm burns with a single stick. This allows us to treat larger tumors more confidently."

Cleveland Clinic has been using ablation technologies to treat smaller tumors up to about 4 cm in diameter and not amenable to liver resection. Dr. Berber and his team have treated close to 1,000 patients with ablation and more than 200 patients with microwave ablation. It was because of this extensive experience with the technique and device that Dr. Berber was selected as the first clinical user. "This microwave ablation technology is very powerful, and if you don't use it well, you can cause damage to the liver, you can cause bleeding or you can disrupt the tumor," says Dr. Berber. "As the technology becomes more advanced and more powerful, gaining ablation expertise through experience becomes even more important."

## Understanding the procedure

To perform the procedure, a laparoscopic camera and an ultrasound probe are inserted into the abdomen through two small incisions. Then, a microwave needle is inserted through the skin into the liver tumor. When ready, the generator delivers heat to burn and destroy the lesion.

"Over the past six years, ablation technology has evolved to incorporate microwave technology, which gives us a more homogeneous heating of the tissues by achieving higher temperatures," explains Dr. Berber. "There is more balanced heating, and we can now reach higher tissue temperatures. Because of that, the success of ablation has greatly improved; the failure rate went down from between 20% and 40% to about 10% or less."

To learn more, visit **ccf.org/CA21**.

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*Dr. Berber has a consulting agreement with Medtronic and has received honoraria for consulting activities. He notes that his consulting agreements do not affect his choice of the best treatment option for his patients.*

**LEFT —**
Dr. Berber prepares for surgery.

# MOLECULAR AND GENETIC MECHANISMS IN BONE MARROW FAILURE SYNDROMES AND MYELOID NEOPLASIA

*Results of two studies presented at the 2020 American Society of Hematology Annual Meeting*

Jaroslaw Maciejewski, MD, PhD

Jaroslaw Maciejewski, MD, PhD's groundbreaking research efforts over two decades continue to decode the complex molecular and genetic mechanisms of bone marrow failure syndromes (BMFS) and myeloid neoplasia (MN).

He shares his thoughts on two significant studies below.

## Applying lessons learned in aplastic anemia

The first of these key studies found that the progression of aplastic anemia to MN is characterized by certain leukemogenic mutations or mutations in human leukocyte antigen (HLA), enabling clonal escape from immune surveillance.

"Aplastic anemia has been a very instructive disease that has led to tremendous progress in medicine including introduction of bone marrow transplantation, the concept of hematopoietic stem cells and much more," says Dr. Maciejewski. "While there is growing success in treating aplastic anemia, one of the fearful complications of disease is the progression to leukemia and/or myelodysplastic syndrome (MDS)."

Researchers analyzed the progression from aplastic anemia to MDS to better understand the landscape of disease. The study examined 350 patients with aplastic anemia and paroxysmal nocturnal hemoglobinuria. Eleven percent (N = 38) developed a secondary MN. MDS was diagnosed in 77% of the patients, followed by acute myeloid leukemia in 21% of the patients. Pathogenic and likely pathogenic germline genetic variants included *NF1*, *CBLC*, *SBDS* and *SAMD9L*, and they were overall more frequently detected in del(7q) patients (76%). Chromosome 7 alterations were present in 47% of the patients (-7 in 35%; del(7q) in 12%), while complex karyotype involving chromosome 7 was found in 25% of the patients.

The analysis of myeloid and HLA panels revealed that, at the time of evolution, 34 of 38 patients had at least one of 148 somatic mutations detected, with an average of four somatic hits discovered per patient. Taken together, these findings demonstrate that the progression of aplastic anemia to MN is characterized by certain leukemogenic mutations or mutations in HLA, enabling clonal escape from immune surveillance.

## Hereditary factors associated with predisposition to BMFS and MN

Investigators aimed to define the contribution of pathogenic germline genetic variants to the development of BMFS and MN in adults. While genetic alterations are well established as causes of leukemia and aplastic anemia in children, the role of hereditary factors in the development of these disorders in adults is less established.

The investigators sequenced a large panel of 150 genes associated with predisposition to leukemia and BMFS and established the frequencies of pathogenic alleles in 350 adults with BMFS and 2,827 adults with MN.

**BELOW —** Confocal image showing the accumulation of myeloid hematopoietic cells throughout the mesenteric adipose tissue. Credit: National Institute of Allergy and Infectious Diseases. *Image: National Institutes of Health.*

The team discovered that 10% of patients in the BMFS cohort had pathogenic and likely pathogenic germline variants (Tier-1), and 44% had suspicious germline variants of unproven clinical significance (Tier-2). Seven percent (N = 27) of patients were compound heterozygous carriers. Tier-1 variants included pathogenic mutations with known disease association, highly recurrent missense mutations found at a low frequency in the general population and frameshift/nonsense mutations.

"The results for myeloid neoplasia were surprising because they revealed that a significant proportion of adult patients also harbors inherited genetic predisposition factors," notes Dr. Maciejewski.

"The classification of genetic alterations is evolving as we gain experience in assigning to them clinical significance," he adds. "Tier-1 is highly likely related to the pathogenesis, or almost certainly contributing to the disease, while our understanding of Tier-2 needs to improve."

To read more, visit **ccf.org/CA21**.

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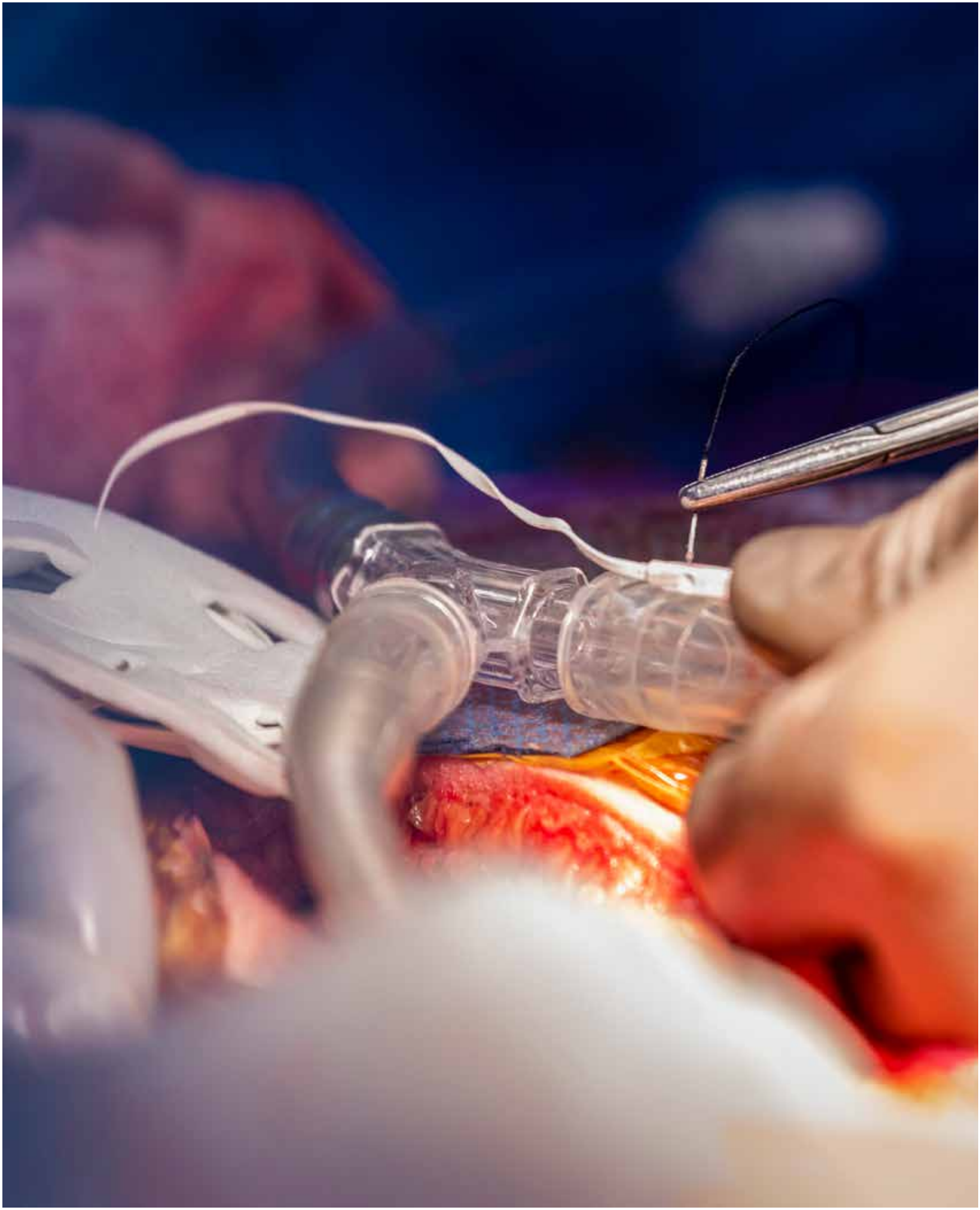

# HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY WITH CISPLATIN AND PACLITAXEL IMPROVES PROGRESSION-FREE SURVIVAL

*Combination improves outcomes without increasing postoperative morbidity*

Robert DeBernardo, MD

A recent Cleveland Clinic study suggests that hyperthermic intraperitoneal chemotherapy (HIPEC) using a combination of cisplatin and paclitaxel is associated with significantly improved progression-free survival (PFS) compared with single-agent cisplatin in patients with epithelial ovarian cancer.

The results were presented at the annual meeting of the Society for Gynecologic Oncology.

Fifty-four patients were given either cisplatin alone (80-100 mg/m$^2$ for 90 minutes; N = 28 [51.9%]) or paclitaxel (135-175 mg/m$^2$ for 90 minutes) with cisplatin (80-100 mg/m$^2$ for 45 minutes; N = 26 [48.1%]) in a perfusate of normal saline at 41°-43°C for 90 minutes. Within the cohort, there were no significant differences between patient groups in terms of demographics, operating time, comorbidities, disease stage or postoperative adverse events.

The mean PFS for the entire cohort was 15.7 months. When stratified by HIPEC regimen, however, a significant difference emerged. Patients who received a combination of cisplatin and paclitaxel had a mean PFS of 22.2 months compared with 10.9 months for patients receiving cisplatin alone.

"We were hoping we'd see a difference but didn't expect it to be at this magnitude — essentially doubling progression-free survival," says first author Laura Chambers, DO, a former gynecologic oncology fellow at Cleveland Clinic. "Additionally, we found no significant differences in mild, moderate or severe postoperative complications, no difference in length of stay and no difference in time to chemotherapy. There was a slight trend toward increased ICU admission with the combination therapy, but it wasn't statistically significant."

Despite the limitations of sample size, use of a prospective registry from a single institution and the possibility of selection bias, overall the study was received well by gynecologic oncologists, according to Robert DeBernardo, MD, Section Head of Gynecologic Oncology at Cleveland Clinic's Ob/Gyn & Women's Health Institute. "We hope it will inform future studies."

"There are several questions that still need to be answered about HIPEC," Dr. DeBernardo says. "What is the right regimen? Who is the optimal patient? When do we give it? Many of the studies our group has undertaken in the past few years have been aimed at answering those questions. Ideally, we would like to conduct a prospective randomized trial, but that takes time. We are in the process of assembling a multi-institutional consortium with other institutions that do HIPEC in an effort to increase the number of patients included in studies."

To read more, visit **ccf.org/CA21**.

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**LEFT —** Dr. DeBernardo debulks a tumor in preparation for HIPEC.


Cleveland Clinic
Eric A. Klein, M.

# INNOVATIONS IN PROSTATE CANCER CARE AT CLEVELAND CLINIC

*An overview of our leading-edge diagnostics and therapeutics*

Eric Klein, MD

Jay Ciezki, MD

Jihad Kaouk, MD

Experts at Cleveland Clinic have dedicated their careers to transforming the diagnosis and treatment of prostate cancer and providing individualized, high-quality care to patients. Below you'll find examples of groundbreaking research and new medical and surgical approaches that are leading the way in prostate cancer care.

## CHANGING THE DIAGNOSTIC PARADIGM

Cleveland Clinic became the first medical center to offer the IsoPSA™ test to patients in July 2020. Developed in partnership with Cleveland Diagnostics, Inc., the test is a novel prostate-specific antigen (PSA) assay for patients with a PSA level > 4 ng/mL who are facing a decision on prostate biopsy.

This blood-based diagnostic test has demonstrated superiority over conventional tests in predicting the presence of high-grade prostate cancer, potentially resulting in a significant decrease in unnecessary prostate biopsies, according to Eric Klein, MD.

"Our data show that the IsoPSA test reduces unnecessary prostate biopsies by about 45% by reliably differentiating between the risks of high-grade vs. low-grade cancer or benign biopsies," says Dr. Klein.

## BRACHYTHERAPY FOR LOCALIZED DISEASE

Brachytherapy for prostate cancer is an available treatment method at Cleveland Clinic for patients with localized prostate cancer. Jay Ciezki, MD, hopes widespread adoption of the modality is on the horizon, as Cleveland Clinic's program surpasses its 6,000th patient treated.

"This is a proven, convenient treatment method for patients with localized disease," says Dr. Ciezki. "We've shown that low- and high-dose brachytherapy works as monotherapy or in combination with other treatment methods for a variety of prostate cancer types, and I think all discussions of definitively managed prostate cancer treatment should include brachytherapy."

## EXTERNAL BEAM RADIATION + BRACHYTHERAPY FOR HIGH-RISK CASES

Localized treatment — adding brachytherapy to external beam radiotherapy — appears to improve survival outcomes for men with high-risk prostate cancer, according to a large retrospective study by Cleveland Clinic researchers published in *JAMA*.

The retrospective review of 1,809 patient records from 12 tertiary care centers compared the clinical outcomes of men with Gleason scores of 9-10 for prostate cancer who had received one of three treatment modalities:

- Radical prostatectomy (RP) (N = 639); median age 61 years.
- External beam radiotherapy plus androgen deprivation therapy (EBRT) (N = 734); median age 67.7 years.
- EBRT plus brachytherapy (EBRT+BT) boost (N = 436); median age 67.5 years.

**LEFT —**
Dr. Klein talks with a patient.

**RIGHT —**
A physician uses the Focal One high-intensity focused ultrasound (HIFU) device.

The study's data span 2000 through 2013, providing a birds'-eye view of the evolution of treatment modalities for this aggressive form of prostate cancer.

Table 1. Evolution in the treatment of aggressive prostate cancer

| Years | RP | EBRT | EBRT + BT |
|---|---|---|---|
| 2000-2005 | 24% | 44% | 31% |
| 2006-2010 | 32% | 43% | 25% |
| 2011-2013 | 53% | 32% | 15% |

## OUTPATIENT RADICAL PROSTATECTOMY

Robotic radical prostatectomy used to require five incisions in a patient's abdomen. Today it requires only one, using the da Vinci® SP Surgical System. Cleveland Clinic was the first U.S. medical center to begin using the single-port robot for urology procedures in late 2018. Since then, experts at Glickman Urological & Kidney Institute have used it to perform extraperitoneal prostatectomy in over 250 patients. It's especially beneficial in patients for whom procedures would be challenging, such as in those who are obese and those who have breathing problems.

"Performing the procedure extraperitoneally has several advantages," says Jihad Kaouk, MD. "By avoiding the sac in which the bowel is contained, the surgery is compartmentalized, limited to the area just around the prostate. The gas bubble in which the robotic arms work expands the peritoneum, pushing the bowel out of the way, allowing better visibility."

## FOCAL THERAPY PROGRAM

High-intensity focused ultrasound (HIFU), a type of focal therapy for treating localized prostate cancer, is emerging as an alternative to more traditional treatments, such as surgery and radiation, for select patients. The modality relies on high-frequency sound waves directed at the tumor through an ultrasound probe inserted into the rectum. The high-intensity waves cause the diseased tissue to heat up and die.

Improved HIFU technology, coupled with appropriate patient selection, is enabling us to provide this modality as an outpatient procedure. Cleveland Clinic recently acquired a Focal One® machine, making it one of approximately 14 sites nationally to offer this technology. It combines ablative and imaging techniques to target tumors in the prostate, enabling an attractive 1.5-hour, noninvasive procedure for clinically indicated patients.

## TRANSPERINEAL FUSION-GUIDED BIOPSY

Improved imaging technology and a shift in diagnostic practice are making transperineal fusion-guided biopsy a popular approach among urologists at Cleveland Clinic.

In fact, Dr. Klein thinks this biopsy technique will become the new gold standard. "It's more accurate and more comfortable for patients, plus there is a lower risk of infection," he says.

In transperineal biopsy, the urologist guides the biopsy needle through perineal skin and into the prostate, as opposed to the rectal wall. Though the ultrasound is still placed in the rectum, the risk for developing an infection decreases considerably, explains Dr. Klein. It's performed under sedation or with general anesthesia, and patients tend to report a better experience, he says. Only a handful of health systems utilize this approach to biopsy.

**RIGHT —**
Focal One HIFU machine.

This approach is particularly well suited for patients who have a history of infection or sepsis following transrectal biopsy or those at risk for bacteremia-induced complications. It also offers easier access to the anterior prostate, which is not well sampled with transrectal biopsy.

## ONCOTYPE DX

The assay Oncotype DX® Genomic Prostate Score (GPS) provides meaningful predictability associated with distant metastases and prostate cancer-specific mortality, according to a study published in *JCO Precision Oncology*. Cleveland Clinic researchers developed the assay in partnership with Exact Sciences (formerly known as Genomic Health, Inc.) over a decade ago.

GPS is a diagnostic tool that allows urologic oncologists to personalize a patient's course of treatment based on the tumor's biology as measured by gene expression profiling. It helps identify candidates for active surveillance versus candidates for immediate therapy. Genomic testing — in conjunction with an MRI — is a standard of care in the evaluation of prostate cancer at Cleveland Clinic.

"The validity of these tests is well documented, but we are starting to discover their clinical implications in the context of long-term outcomes," says Dr. Klein, "and this study shows the 20-year follow-up data to corroborate that."

For an in-depth look at each of these innovations, visit **ccf.org/CA21**.

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# WELCOME JULIE LANG, MD


Julie Lang, MD, joined Cleveland Clinic from the University of Southern California Norris Cancer Center, where she directed the Breast Cancer Research Program and served as principal investigator of the Breast Surgical Oncology Translational Research Laboratory.

"I am thrilled to join Halle Moore, MD, in directing the Comprehensive Breast Program in my hometown," says Dr. Lang. "As a physician scientist, I am looking forward to contributing to the already tremendous opportunities for translational research and the dedication to multidisciplinary patient care at Cleveland Clinic Cancer Center."

To learn more about Dr. Lang, visit **ccf.org/CA21**.

# AIRWAY STENTING FOR LUNG CANCER: DIAGNOSTIC, THERAPEUTIC, PALLIATIVE

*The role of interventional pulmonology in cancer care*

Thomas Gildea, MD, MS

Nathan Pennell, MD, PhD

Case presentation — In late 2017, a patient presented to the emergency department with progressive shortness of breath with cough and wheeze.

She was known to have chronic obstructive pulmonary disease (COPD), but initial treatment for this COPD exacerbation was not immediately helpful. A CT scan showed evidence of lung cancer invading the trachea and main carina.

Cancer invading the main carina is defined as unresectable T4 disease in most cases. She was referred to bronchoscopy for diagnosis and palliation. A rigid bronchoscopy with biopsy was performed to prepare for a stent to palliate the airway. A silicone Y stent, customized on-site to fit the patient, was placed in the trachea. After the stent placement, she immediately improved and then recovered from her exacerbation. Upon completion of her evaluation, she was found to have stage IIIB (cT4N2Mx) invasive squamous cell carcinoma, moderately differentiated.

After improvement with just two months of therapy and some procedures to manage the stent, a bronchoscopy was performed to determine whether stent removal was possible. The stent was easily removed with rigid bronchoscopy.

In 2020, lung nodules were noted during a surveillance scan. Endobronchial ultrasound, bronchoscopy and biopsy of a peripheral lung lesion were performed. Though the airway showed some evidence of radiation injury, the lymph nodes and lung lesion were nondiagnostic for malignancy. She remains in survivorship and surveillance.

## Airway stenting for lung cancer

This case highlights the value of multidisciplinary management of malignant central airway occlusion. When faced with critical airway emergencies, interventional pulmonologists can secure and palliate the airway while simultaneously obtaining diagnostic and staging tissue. “And when a patient does need a stent, we can customize it to fit properly, maintain it and then remove it when necessary,” says Thomas R. Gildea, MD, MS, Section Head of Bronchology in Cleveland Clinic’s Respiratory Institute.

Cleveland Clinic’s Respiratory Institute has seven American Association of Bronchoscopy and Interventional Pulmonology board-certified physicians, making it the largest program in the United States. “We work directly with the interventional pulmonology team on many of our lung cancer patients with airway issues,” says Nathan Pennell, MD, PhD, Director of Cleveland Clinic Cancer Center’s Lung Cancer Program. “It’s an important tool for diagnostics, therapeutics and palliation.”

Research has demonstrated that timely interventions are associated with increased survival and measurable improvements in quality of life and lung function. Recent data from a randomized, controlled trial suggest that early silicone stenting is associated with a more durable palliation of dyspnea and reduced unintended need for bronchoscopy compared with patients who did not receive stents. Further, the EVERMORE study, a multicenter retrospective

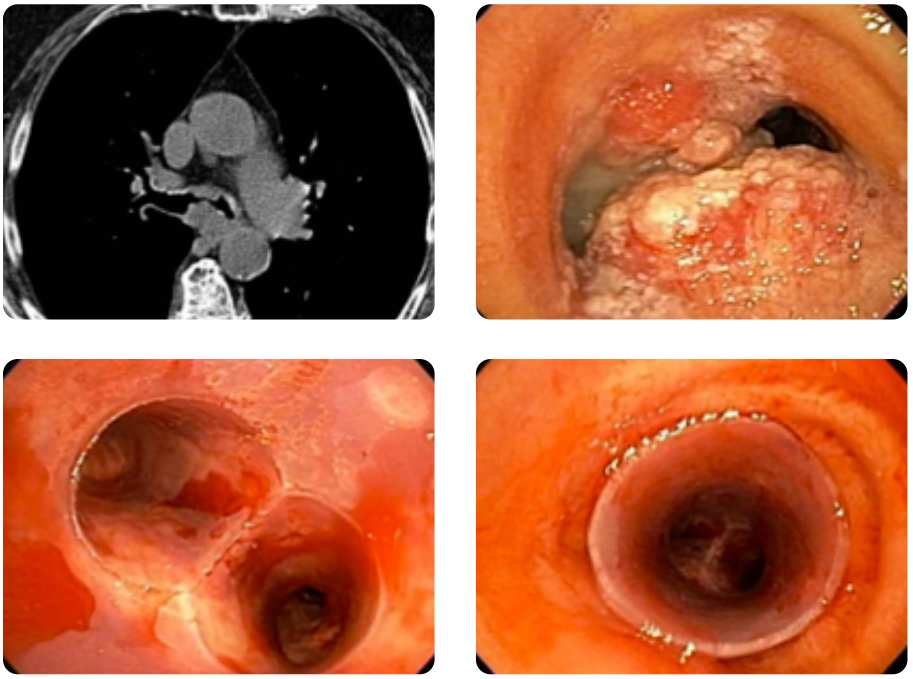

**FIGURE 1.** CT showing irregular mucosa at the main carina (top left). Bronchoscopy showing severe airway involvement (top right). After biopsy and silicone Y-stent placement (middle row).

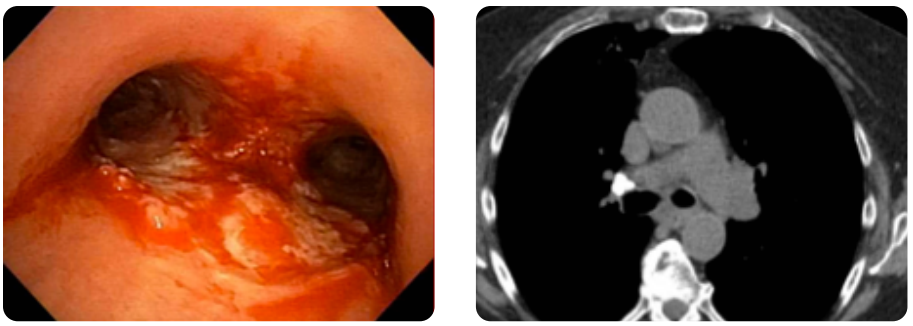

**FIGURE 2.** Although there was evidence of some tumor necrosis, the airway was much improved and the stent was no longer needed (left). CT follow-up imaging showed improvement at the site of the original lesion (right).

analysis from Spain, noted that unadjusted Kaplan-Meier estimates showed an increase in one-year survival for patients who received therapeutic bronchoscopy with chemo/radiotherapy compared with chemo/radiotherapy alone (HR = 2.1, 95% CI, 1.1-4.8, *P* = 0.003).

"We've also incorporated patient-specific airway stents into our practice, a process that we developed and that received FDA approval in 2019," says Dr. Gildea. "These stents can play an important role in allowing cancer patients the chance to undergo therapy and to overcome survivorship challenges."

To learn more, visit **ccf.org/CA21**.

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# COMBINATION MAINTENANCE THERAPY IN METASTATIC UROTHELIAL CANCER

*In search of improved outcomes for patients*

Shilpa Gupta, MD

A national phase 3 randomized trial will seek to determine whether maintenance therapy with avelumab and a vascular endothelial growth factor (VEGF) tyrosine kinase inhibitor can improve survival among patients with urothelial cancer.

"The first-line standard of care for metastatic urothelial cancer is platinum-based chemotherapy," notes the trial's principal investigator, Shilpa Gupta, MD. "Historically, patients who achieve stable disease or better were followed and, in the event of recurrence, treated with immunotherapy, which is approved in this setting.

"A recent phase 3 trial, JAVELIN Bladder 100, showed that moving the immunotherapy agent avelumab to the maintenance setting immediately following chemotherapy for patients who achieve stable disease or better improves overall survival versus waiting until they progress," she continues.

Based on these findings, avelumab was approved by the Food and Drug Administration in June 2020 for the maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma who had not progressed with first-line platinum-based chemotherapy.

However, there is a subgroup of patients who don't derive as much benefit from single-agent avelumab. "In an effort to address this gap, we are seeking to determine if intensification of maintenance avelumab can further improve the outcomes in these patients," Dr. Gupta explains.

## Novel combination for maintenance

Dr. Gupta and colleagues are developing a novel maintenance combination in this patient population — avelumab plus a VEGF tyrosine kinase inhibitor.

"Cabozantinib is an oral medication that affects the VEGF, MET and AXL receptors," says Dr. Gupta. "Data from multiple trials have demonstrated that when partnered with an immunotherapy agent, cabozantinib has efficacy in urothelial cancer.

"This is the first study in this setting, and in the field, taking a closer look at the intensification of maintenance therapy and this specific combination," she notes. "Our team is excited to explore this regimen and its potential impact on patient outcomes."

The researchers will enroll 654 patients with advanced or metastatic urothelial cancer who have received first-line treatment with platinum-based chemotherapy and do not progress after completion of chemotherapy. The primary outcome of the study is overall survival.

"In addition to evaluating the efficacy of a unique combination, this research will lead us to a better understanding of which patients may be resistant to immunotherapy and how this can be overcome with novel approaches," Dr. Gupta says.

Dr. Gupta and colleagues hope to establish that the combination of cabozantinib and avelumab is safe and tolerable and better than avelumab alone in the maintenance setting. "If we find

**BELOW —** Dr. Gupta and patient.

that the combination is safe and improves outcomes compared with avelumab alone, this research has the potential to be practice changing," she concludes.

To read more, visit **ccf.org/CA21**.

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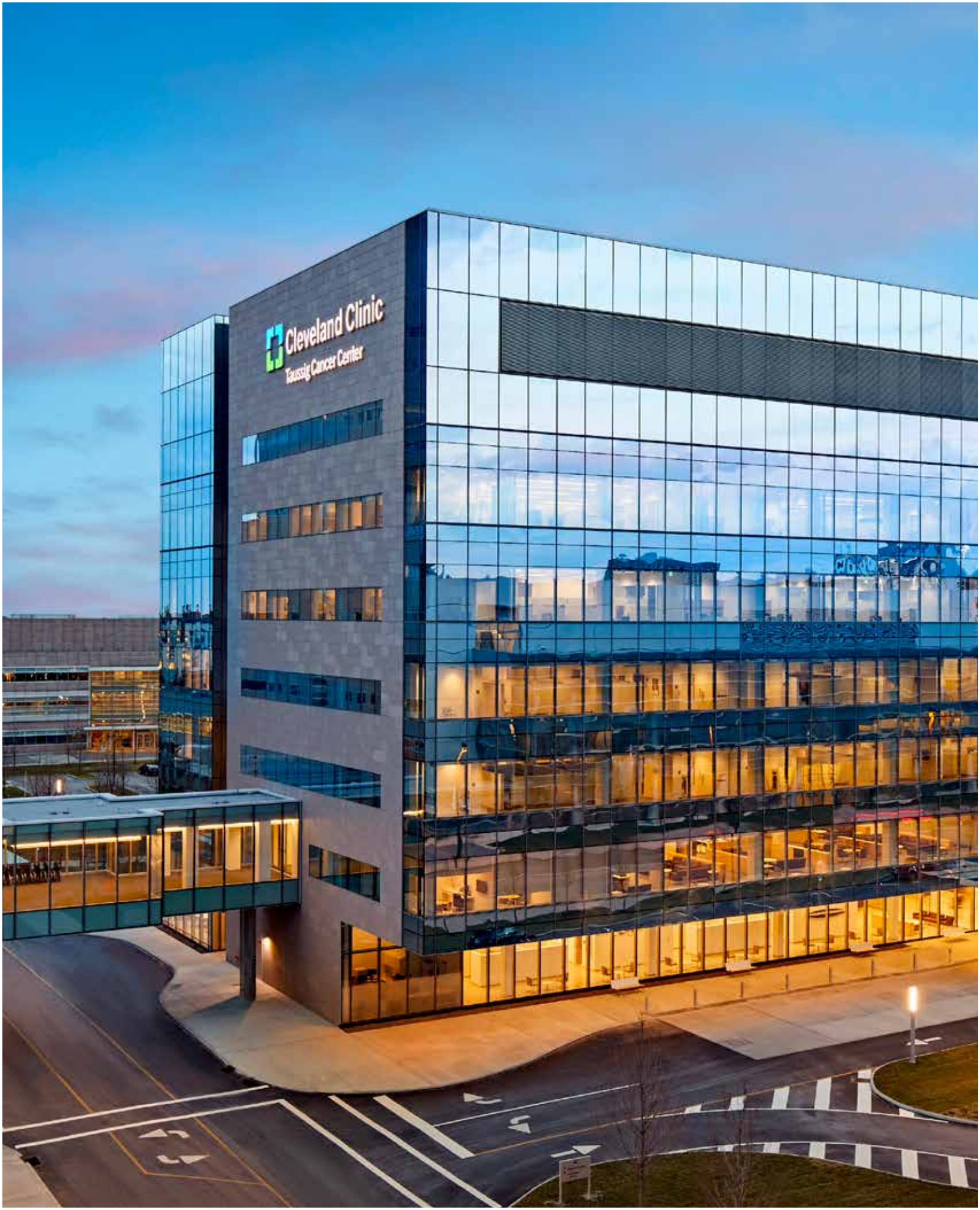
Cleveland Clinic
Taussig Cancer Center

# A PRIVILEGE AND AN HONOR

*Outgoing Chair reflects on his tenure*

Brian Bolwell, MD, FACP

It has been my privilege and honor to chair Taussig Cancer Institute for the past decade.

After I announced that I would be transitioning out of the Chair role, many people asked me about my proudest accomplishment during my tenure. I always answer that question the same way. I am most proud of the team we have been able to build, of the wonderful people who work at the Taussig Cancer Institute.

Building a strong, collaborative, focused and compassionate team is no easy or straightforward task, and yet I think we have built the strongest clinical institute in the United States. Over 70% of our physicians are new hires in the past decade. That's a lot of recruiting. We have also integrated team members from our regional locations and are truly operating as one Cleveland Clinic Cancer Center team.

This team has transformed clinical care over the past decade. We changed how we are organized to focus on cancer programming. Each cancer program is a disease-based team comprised of physicians from different specialties as well as nurses and other support staff. Programming allows us to prioritize and structure different aspects of team-based care, including multidisciplinary clinics, tumor boards, care paths and reduction in time to treat. Our time from initial diagnosis to first therapy is the fastest among major academic cancer centers in the United States.

Cancer care has experienced major clinical shifts during my tenure, in both how we classify and how we treat cancers, and our team has helped lead and shape that transformation. I'm proud that we aren't just adapting to change but leading it.

Our physical space has changed rapidly too. We were able to design and build the new cancer centers in Cleveland and Florida with patients' needs at the forefront, and we've acquired and integrated new regional cancer centers.

I've also seen a big change in myself. Looking back to my first leadership role 25 years ago, I'm somewhat embarrassed by my shortcomings, but I'm proof that anyone can become a better leader if they're motivated to do so and open to criticism and new ways of doing things. In my new role as Chair of Physician Leadership and Development in the Mandel Global Leadership & Learning Institute, I see the opportunity to try to educate people about the fundamental leadership principles I wish I had been aware of at a younger age and to spread our model of physician leadership beyond our enterprise.

While this has been an emotional transition for me, I have the utmost confidence in the Taussig Cancer Institute team and Acting Chair Jame Abraham, MD. Leading the Cancer Center has been the best part of my career, and I am forever grateful for the opportunity to have served such a talented, compassionate team.

Gratefully,

*Brian Bolwell, MD, FACP*
*Chair, Physician Leadership and Development*
*Cleveland Clinic Mandel Global Leadership & Learning Institute*

# NEW STAFF

**ARUN KUMAR, MD**

*Department of Hematology and Medical Oncology, Mansfield*

**JULIE LANG, MD**

*Section Head for Breast Services and Co-Director of the Breast Cancer Program*

**SUJATA PATIL, PhD**

*Head of the Cancer Biostatistics Section in the Department of Quantitative Health Sciences, Lerner Research Institute and Taussig Cancer Institute*

**DAN SILBIGER, DO**

*Department of Hematology and Medical Oncology, Twinsburg and Hillcrest*

**ELNORA SPRADLING, MD**

*Department of Hematology and Medical Oncology, Strongsville and Medina*

**EMRULLAH YILMAZ, MD, PhD**

*Department of Hematology and Medical Oncology, Head & Neck Cancer Program*

# NEW POSITIONS

**JAME ABRAHAM, MD**

*Acting Chair of Taussig Cancer Institute, Cleveland Clinic Cancer Center*

**SAMIR ABRAKSIA, MD**

*Community Director of Cancer Disparities Research*

**PAULINE FUNCHAIN, MD**

*Director of the Melanoma Medical Oncology Program and Co-Director of the Comprehensive Melanoma Program*

**JESSICA GEIGER, MD**

*Director of the Head & Neck Cancer Program*

**TIMOTHY GILLIGAN, MD, MS**

*Diversity, Equity and Inclusion Officer for Graduate Medical Education*

**SHILPA GUPTA, MD**

*Director of Genitourinary Medical Oncology and Co-Leader of the Genitourinary Oncology Program*


# FROM CARE TO CURE

VeloSano (Latin for “swift cure”) is a year-round fundraising initiative supporting cancer research at Cleveland Clinic. It funnels millions of dollars raised each year into projects that will build on and translate recent advancements in cancer research into new diagnostics and therapeutics with a high likelihood of leading to future grant funding. Thus far, VeloSano has raised over $24 million, which has supported 170 cancer research projects. Those projects often go on to earn research grants from the National Institutes of Health and elsewhere. The total return from additional external funding now surpasses $22 million, making the total impact of VeloSano more than $46 million.

“Bike to Cure” benefiting VeloSano is scheduled for Sat., Sept. 11, 2021.
Ride. Volunteer. Fundraise. Cheer. Inspire. Donate.

Learn more and get involved at **velosano.org**.

# CONNECT WITH US

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View Outcomes at clevelandclinic.org/outcomes.

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Visit ccfcme.org for convenient learning opportunities from Cleveland Clinic's Center for Continuing Education.

## 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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## NATIONAL EWING SARCOMA TUMOR BOARD

A team of Cleveland Clinic and Cleveland Clinic Children's physicians and multidisciplinary experts from cancer centers across the nation meet virtually each month and provide their expertise and educate on the treatment and management of Ewing sarcoma family tumors.

Physicians can submit their de-identified sarcoma cases for the team to review, and the group will share their knowledge of clinical trials and innovative treatments.

To learn more or submit a case, please visit **clevelandclinic.org/NEWSBoard**.

## VIRTUAL CME OPPORTUNITIES

Lessons from the Thoracic Tumor Board: Multidisciplinary Discussions, Debate and Treatments
Saturday, September 18

8th Annual Genetics Education Symposium — Genetics & Genomics: Applications for the Prevention, Detection and Treatment of Cancer
Thursday, September 30
cme.ccf.org/genetics

8th Annual Multidisciplinary Colorectal Oncology Course
Friday, October 22

Great Lakes Breast Cancer Symposium
Hosted by the Case Comprehensive Cancer Center
October 25-26

For more information, please contact **Sheryl Krall at kralls2@ccf.org**.

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