



CANCER ADVANCES

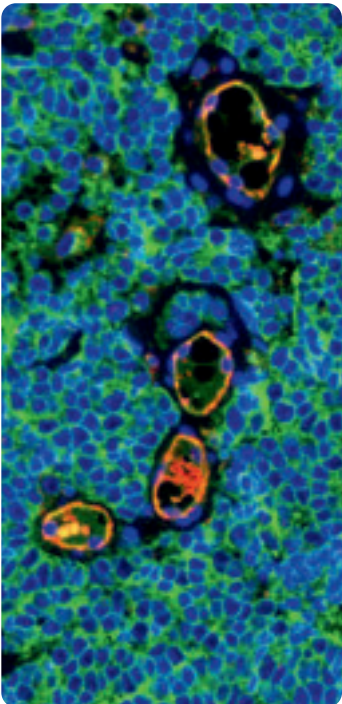
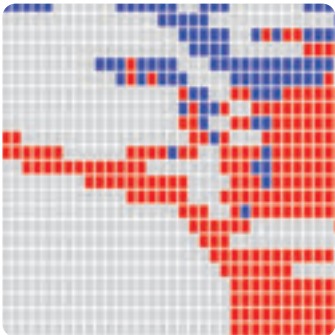
SUMMER
2020

Cleveland Clinic Cancer Center

**CHEMO PLUS
IMMUNOTHERAPY
SHOWS PROMISE FOR
ADVANCED
BLADDER CANCER**

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 26 other clinical and special-expertise institutes, as well as cancer specialists at our regional hospitals, health centers, Cleveland Clinic Florida and Cleveland Clinic Abu Dhabi. Cleveland Clinic is a nonprofit academic medical center ranked as a top hospital in the country (*U.S. News & World Report*), where more than 3,900 staff physicians and researchers in 180 specialties collaborate to give every patient the best outcome and experience.

INSIDE



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DEAR COLLEAGUES,

As oncologists, we know how hard a cancer diagnosis is for our patients. A rare cancer makes matters even more difficult.

Patients with unusual cancers and blood diseases often have trouble finding clinicians knowledgeable about their condition. They may have to travel far from home to receive care. Diagnoses frequently are not made until the disease has reached an advanced stage, further complicating treatment and reducing survival. Effective treatments are lacking.

At Cleveland Clinic Cancer Center, we are dedicated to improving this situation. Our Rare Cancers and Blood Diseases Initiative, described on p. 32, comprises dozens of oncology specialists with expertise in treating and researching these conditions. On p. 24 you will see one example of the progress we are making: a body of research that could lead to better staging and risk stratification for Merkel cell carcinoma.

Our cover story about a new neoadjuvant treatment regimen for muscle-invasive bladder cancer (p. 4) demonstrates the impact that targeted immunotherapies are having in the fight against cancer. The addition to our staff of noted cancer researcher Timothy Chan, MD, PhD, who will direct our new Center for Immunotherapy and Precision Immuno-Oncology (p. 28), signals our commitment to developing next-generation precision immunotherapies, using the power of genomic analysis and high-throughput immunoprofiling.

One of the reasons Dr. Chan cited for coming to Cleveland Clinic is the scale of our cancer care and research enterprise. That footprint is growing internationally with the formation of the Oncology Institute at Cleveland Clinic Abu Dhabi and the construction of a nine-story, 200,000-square-foot cancer treatment and research facility that will open in 2022. You can learn more about it on p. 34.

This issue of *Cancer Advances* contains more noteworthy news, including our role in evaluating a promising multicancer screening test (p. 12) and a clinical trial that validates a link between an adrenal-permissive variant of the *HSD3B1* gene and poor outcomes in prostate cancer (p. 18).

As this edition goes to press, the effects of the novel coronavirus pandemic are still being felt around the world. Caring for vulnerable

cancer patients during this time of contagion has been a challenge unlike anything we physicians have faced.

I am extremely proud of Cleveland Clinic's response, and of the devotion, innovation and compassion of my colleagues at Cleveland Clinic Cancer Center.

With telemedicine visits — which increased at our institution by more than 70% in just six weeks — we have maintained access for cancer patients needing nonurgent care while establishing precautions that have allowed us to continue in-person treatment for patients whose cancers require it. The volume of our patients receiving infusion has remained high. Gamma Knife® treatments for brain tumors are on pace for a record year. In addition to treating our own cancer patients, we reached out to oncologists in other parts of the country hard-hit by the pandemic to offer temporary assistance with their cancer patients.


Cleveland Clinic Cancer Center staff members have worked tirelessly and collaboratively during this demanding time, true to the credo of our hospital's physician founders to "think and act as a unit." For example, when it became clear that VeloSano, our July cycling weekend that has raised more than \$21 million since 2014 for cancer research, could not take place as usual, our organizers quickly pivoted to create a "Virtual VeloSano" fundraising event. Visit velosano.org to donate and to follow our progress.

We will get through these challenges together. As always, I welcome the opportunity to discuss the work we do, and to help you in any way we can.

Sincerely,



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CHEMO PLUS IMMUNOTHERAPY SHOWS PROMISE FOR ADVANCED BLADDER CANCER

RIGHT: Shilpa Gupta, MD



CHEMO PLUS IMMUNOTHERAPY SHOWS PROMISE FOR ADVANCED BLADDER CANCER

New neoadjuvant treatment regimen offers hope to patients facing a poor prognosis

KEY POINTS

The standard of care for muscle-invasive bladder cancer is chemotherapy followed by radical cystectomy; but less than half of patients respond, and most still have disease recurrence after surgery.

Cleveland Clinic Cancer Center researchers sought to determine whether chemotherapy and immunotherapy could heighten response at surgery in patients with localized disease.

Study participants received gemcitabine-cisplatin plus nivolumab, followed by radical cystectomy within eight weeks.

Initial results indicate that the immunotherapy/chemotherapy combination is safe and effective, with significant pathologic responses, manageable toxicities, no delays to surgery and no patient deaths.

The combination of nivolumab, gemcitabine and cisplatin produces significant pathologic response rates in patients with muscle-invasive bladder cancer (MIBC) in the neoadjuvant setting, according to new data from the phase II Bladder Cancer Signal Seeking Trial (BLASST-1).

Preliminary findings, which also demonstrate the safety of this immunotherapy/chemotherapy approach, recently were presented at the American Society of Clinical Oncology's 2020 Genitourinary Cancers Symposium.

The targeted immunotherapy drug nivolumab is a checkpoint inhibitor that blocks the programmed cell death protein 1/programmed death ligand 1 (PD-1/PD-L1) immune response pathway. Gemcitabine is an antimetabolite. Cisplatin is a DNA cross-linking agent.

"Immunotherapy has really advanced the treatment for metastatic bladder cancer patients," notes BLASST-1 study chair Shilpa Gupta, MD, a Cleveland Clinic Cancer Center oncologist who initiated the trial to explore the potential synergistic benefits of the nivolumab/gemcitabine/cisplatin combination in the neoadjuvant setting. "We wanted to understand the impact of immunotherapy in combination with chemotherapy for patients with localized disease who had yet to undergo surgery."

With immunotherapy moving into earlier stages of disease, this trial addressed an unmet need for bladder cancer patients, according to Dr. Gupta. "Standard of care for MIBC is chemotherapy followed by radical cystectomy, but that only results in responses among 30%-40% of patients, and the majority still have disease

recurrence after surgery despite chemotherapy," she explains. "We wanted to combine chemotherapy with immunotherapy to see if we could achieve higher responses at surgery."

Study details

Between February 2018 and June 2019, 41 patients were enrolled at three sites. Their median age was 66, and 63% were male. The majority of patients (90%) had T2N0 disease, followed by T3N0 (7%) and T2-4N1 (3%).

Participants received gemcitabine-cisplatin plus nivolumab, followed by radical cystectomy within eight weeks. Thirty-eight received four cycles of the combination, two received two cycles, and one was treated with a single cycle. Forty patients underwent surgery.

The study's primary endpoint was pathologic response. "We determined that the study would be a success if we achieved a pathologic downstaging rate of 55% at cystectomy," says Dr. Gupta, who leads Cleveland Clinic Cancer Center's Bladder Cancer Program.

Safety as well as progression-free survival at two years were the secondary endpoints. "Safety is key in these patients," Dr. Gupta emphasizes. "If the addition of an agent results in more toxicities or delayed surgery, then we are doing a disservice to the patient."

“If the addition of an agent results in more toxicities or delayed surgery, then we are doing a disservice to the patient.”

— SHILPA GUPTA, MD

Initial results indicate that the immunotherapy/chemotherapy combination is safe and effective for the treatment of MIBC, with significant pathologic responses, manageable toxicities, no delays to surgery and no patient deaths.

“We found that the primary endpoint was exceeded, with pathological downstaging of 66%,” reports Dr. Gupta. “Pathologic complete responses were observed in 49% of patients. Additionally, the combination was found to be safe, with no added toxicities from the immunotherapy. The majority of the hematologic toxicities were seen from chemotherapy” and included grades 3-4 neutropenia and thrombocytopenia.

Harnessing immunotherapy

Immunotherapy has impacted the treatment of a number of cancer types, including metastatic bladder cancer. A growing body of research supports its efficacy, and Dr. Gupta believes it will become the backbone of neoadjuvant treatment moving forward.

What still needs to be understood, she says, is how much benefit can be derived from combining immunotherapy with chemotherapy in this patient population. “Does immunotherapy work better alone, or with chemo? This question, along with safety, is being addressed in ongoing randomized trials.”

“It is also key that we make sure immunotherapy and chemotherapy combined does not lead to excessive toxicities,” she says. “We did not see that in our single-arm phase II study, which is very reassuring. However, it will be helpful to validate this with data from phase III randomized trials.”

Next steps, ongoing research

Additional findings from the BLASST-1 study will be released as they become available. “The secondary endpoint of progression-free survival at two years will be updated when that milestone is achieved next year,” Dr. Gupta says. “Also, the ongoing correlative

work looking at whole genome sequencing, molecular subtyping and other immunologic biomarkers will be completed in the near future.”

The phase III ENERGIZE trial already is underway and enrolling patients, according to Dr. Gupta, who is the principal investigator for this study at Cleveland Clinic. The randomized trial will evaluate gemcitabine/cisplatin alone versus gemcitabine/cisplatin plus nivolumab with or without BMS-986205, an indoleamine 2, 3-dioxygenase 1 inhibitor, for treatment of advanced bladder cancer. The outcome should further inform the results of the BLASST-1 study, she says.

“Muscle-invasive bladder cancer is a highly aggressive disease, and even after surgery, more than 50% of patients have recurrence and eventually develop metastatic disease, which is incurable,” Dr. Gupta notes. “We really need to harness strategies that can downstage more and more patients at the time of surgery to improve their outcomes because their responses at the time of surgery correlate with the long-term survival outcomes. Our goal is to have effective therapies with no added toxicities in this space.”

Dr. Gupta recently received a two-year, \$573,850 grant from the Department of Defense to study biomarkers of response and resistance to immunotherapy and to apply machine learning algorithms to generate a comprehensive biomarker database. The award will assist her team in the identification of biomarkers to help predict whether MIBC patients will be responsive or resistant to immunotherapy.

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NEW CLINIC TACKLES MUTATIONS THAT INCREASE RISK OF BLOOD CANCERS AND HEART DISEASE

CHIP Clinic's goals: Research, preventive care

KEY POINTS

Somatic mutations in blood or bone marrow cells, known as clonal hematopoiesis of indeterminate potential (CHIP), can increase the risk of blood cancers and heart disease.

Cleveland Clinic Cancer Center's new CHIP Clinic will study the mutations in cancer survivors to improve understanding of prevalence and progression and to devise tailored interventions including education and preventive care.

Initial screening efforts will focus on breast and head and neck cancer patients, with plans to eventually expand to all disease groups.

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. — 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.

The clinic was approved by Cleveland Clinic's Institutional Review Board and opened in early 2020, according to hematologist/oncologist Bhumika Patel, MD, who helped develop the program along with hematologist/oncologist Hetty Carraway, MD, and Jaroslaw Maciejewski, MD, PhD, Chair of Cleveland Clinic Taussig Cancer Institute's Department of Translational Hematology and Oncology Research.

"In the past five years, there have been several large studies conducted in healthy populations that found mutations associated with aging that we commonly see in myelodysplastic syndrome (MDS) and acute myeloid leukemia patients," Dr. Patel says. "This has sparked interest in learning more and inspired us to launch the CHIP Clinic."

"Studying these mutations in our cancer survivorship population will help us improve our understanding of their prevalence as well as the progression of CHIP," she says. "Additionally, we will be able to better tailor interventions for these patients, including education and preventive care."

The basics of CHIP

Clonal hematopoiesis (CH) — acquired gene mutations in a population of related myeloid cells — typically involves leukemia-associated genes

such as *DNMT3A*, *TET2* or *ASXL1*, although there may be non-leukemia-associated CH mutations as well.

Detection by next-generation DNA sequencing often is inadvertent, occurring when patients are being evaluated for hematologic or other disorders. However, the presence of a CH variant (usually only a single mutated gene rather than multiple ones) is not definitively determinative of progression to hematologic malignancy. Clinical outcomes of hematopoietic clonality range from asymptomatic apparent normalcy, as seen in the majority of the affected population, to cytopenia, cardiovascular complications and/or overt blood cancers. The dynamics of progression are unclear. CH prevalence is thought to be rare in persons younger than 40 but increases with age, affecting 10% of those older than 70.

CHIP is defined as the presence of a variant allele frequency of $\geq 2\%$ of a leukemia-associated somatic mutation, but with normal peripheral blood count and no evidence of hematologic malignancy. Research shows CHIP is associated with heightened risks of all-cause mortality and hematologic cancer compared with the general population. The increased overall mortality may be due more to heart disease and stroke than to hematologic cancer.

Based on current knowledge about CH, there are no consensus guidelines on screening or monitoring for patients with CHIP.

Multidisciplinary approach

Initially, screening efforts of the CHIP Clinic will focus on breast and head and neck cancer patients due to well-established survivorship programs for those malignancies, with plans to eventually expand to all disease groups. This will include patients who have already undergone treatment as well as those who are newly diagnosed, to help researchers better understand the origin and evolution of CH mutations and determine whether cancer therapies may affect that process, according to Dr. Patel.

“Our research team will be working closely with clinicians to provide information to our patients and integrate data to study the implications of CH,” Dr. Patel says.

Through the clinic’s work, Dr. Patel and her colleagues aim to better understand the biology of CH, develop clinical trials and establish guidelines to manage individuals with CHIP mutations, with the goal of preventing progression to a hematologic malignancy, such as MDS or leukemia, or cardiovascular disease.

“We hope to prevent the complications associated with CHIP, as well as develop ways to manage these patients and eventually provide targeted interventions,” she says.

The clinic will screen patients with standard blood tests and next-generation sequencing, Dr. Patel explains. “Those who are identified as having a CHIP mutation will have the opportunity to meet with Dr. Carraway, Dr. Maciejewski or me to discuss their results and further monitoring, and to be referred to the appropriate specialists in preventive cardiology to help control risk factors through lifestyle modifications and other interventions,” she says.

Participating patients will receive ongoing blood tests and annual next-generation genetic sequencing. The team intends to screen approximately 50 patients per month initially, but over time hopes to add more, including patients with additional cancer types.

The CHIP Clinic will work closely with Cleveland Clinic Sydell and Arnold Miller Family Heart, Vascular & Thoracic Institute’s

Preventive Cardiology and Rehabilitation Section. “The team and their multidisciplinary approach are fantastic,” Dr. Patel notes. “They risk-stratify patients, monitor them and offer a variety of resources depending on patients’ needs, to help them stop smoking, improve physical fitness and nutrition, or obtain an endocrinology evaluation.”

“This is what makes the CHIP Clinic so valuable,” she says. “We have the opportunity to provide a new level of care and connect patients with the resources they need to improve their health and ideally mitigate risk factors associated with CHIP.”

Long-term implications

As cancer therapeutics continue to improve and more is learned about CHIP mutations, the clinic also will evolve.

“With more therapeutic options and an aging population of cancer survivors, the CHIP Clinic will continue to grow,” Dr. Patel says. “The clinic will be a platform to improve our understanding of the biology of these mutations and better equip us to provide early interventions to cancer survivors.”

This is just the beginning for the CHIP Clinic, which has the potential to significantly impact not only Cleveland Clinic patients, but wider CHIP research efforts.

“We are going to be evaluating these patients longitudinally,” Dr. Patel notes. “This program is an opportunity to study patients with CHIP in a very broad, multidimensional way.”

“And, in the long term, we will have concrete data on the mutations, including the genomic impact of our interventions,” she says. “This will allow us to be at the forefront when it comes to developing guidelines to better manage these patients and their needs.”

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STUDY REINFORCES CONCERNS ABOUT DIETARY SUPPLEMENT USE AND BREAST CANCER TREATMENT

Some supplements associated with negative patient outcomes

KEY POINTS

Many cancer patients, especially those with breast cancer, use dietary supplements to try to mitigate therapy's adverse effects, although there is little conclusive research about the products' safety and efficacy in conjunction with cancer treatment.

Cleveland Clinic researchers, in collaboration with 12 other cancer programs, conducted a prospective observational study examining supplement use and breast cancer outcomes.

The latest results show a link between antioxidant use and poor outcomes: an increased risk of cancer recurrence and, to a lesser extent, an increased risk of death.

Understanding why certain supplements negatively affect survival and recurrence requires further research.

The researchers recommend that clinicians counsel patients to refrain from taking high-dose antioxidants during chemotherapy.

Breast cancer patients' use of certain dietary supplements before and during chemotherapy is linked to an increased risk of disease recurrence and death, a recent study involving Cleveland Clinic researchers, published in the *Journal of Clinical Oncology*, has found.

The results, while not definitive, suggest that clinicians and their breast cancer patients should be cautious about supplement use, other than multivitamins, while treatment is underway.

Research rationale

A large percentage of cancer patients, especially those with breast cancer, turn to dietary supplements in hopes of mitigating adverse effects of therapy. However, there is little conclusive, evidence-based research about the safety and efficacy of these products in conjunction with cancer treatment.

Amid concerns that certain supplements, particularly antioxidants, could decrease the cytotoxicity of chemotherapy by reducing the production of reactive oxygen species, Cleveland Clinic researchers, in collaboration with 12 other cancer programs, including Roswell Park Comprehensive Cancer Center and SWOG Cancer Research Network, conducted a prospective observational study called Diet, Exercise, Lifestyle and Cancer Prognosis (DELCaP) examining supplement use and breast cancer outcomes.

The DELCaP study queried patients enrolled in SWOG S0221, a randomized phase III breast cancer clinical trial that sought to

determine the optimal dose and schedule for three chemotherapy drugs: doxorubicin, cyclophosphamide and paclitaxel.

The DELCaP investigators — who include Cleveland Clinic Cancer Center oncologists G. Thomas Budd, MD, and Halle Moore, MD, Director of Breast Medical Oncology and Co-Director of the Comprehensive Breast Cancer Program — previously reported on the prevalence of supplement use among SWOG S0221 participants. Later, the DELCaP researchers found that multivitamins may be associated with a beneficial effect in breast cancer patients: a reduced risk of chemotherapy-induced peripheral neuropathy.

Key findings

In the most recent DELCaP study, Dr. Budd and his colleagues sought to determine whether use of supplements during chemotherapy, particularly antioxidants, impacted survival outcomes.

Participating patients received questionnaires regarding their supplement use before and during treatment. A total of 1,134 patients provided complete responses. The researchers found that usage was less than expected based on previous research and declined during treatment. Dr. Budd, one of the study's senior co-authors,

suggests this could be partly due to the fact that, during the course of the trial, some patients were advised by their treating physician of concerns regarding supplement intake.

As a result, it was difficult to draw statistically valid conclusions about the effects of individual supplements; however, the study did show a link between antioxidant (vitamins A, C and E; carotenoids; coenzyme Q10) use and poor outcomes. "Taking an antioxidant was associated with an increased risk of cancer recurrence and, to a lesser extent, an increased risk of death," reports Dr. Budd.

The researchers also found that vitamin B12 usage before and during chemotherapy was significantly associated with poorer disease-free and overall survival. Iron intake prior to and during treatment was linked with disease recurrence. Conversely, adverse survival outcomes were not associated with multivitamin use.

Understanding why certain supplements negatively affect survival and recurrence requires further exploration. "It is not clear why B12 and iron supplements are associated with worse outcomes," says Dr. Budd. "In terms of antioxidants, research suggests that these supplements could mitigate the antitumor effect of chemotherapy."

"The bottom line is that physicians should recommend that patients refrain from taking high-dose antioxidants during chemotherapy, while a multivitamin appears safe," he says, although noting that these findings are not conclusive enough to support formal clinical recommendations.

Based on the current study as well as the previous DELCaP findings regarding chemotherapy-induced peripheral neuropathy, Dr. Budd says it is acceptable for patients to take a multivitamin during treatment. He acknowledges that researchers still do not have a clear understanding of why multivitamins could reduce this adverse event.

[Additional study required](#)

More research is needed to fully understand the impact dietary supplements have on the effectiveness of cancer treatments.

"These findings need to be validated in another group of patients," says Dr. Budd. "This is best done in the context of an ongoing clinical trial, where treatment is standardized."

[Increasing use](#)

Despite a lack of evidence supporting the safety and efficacy of dietary supplements during cancer treatment, patient interest continues to grow.

The explanation, according to Dr. Budd, stems from patients' desire to feel more in control of their treatment and its effects. "Patients want to empower themselves," he says. "They also have family and friends encouraging them to take a variety of supplements to feel better. These recommendations are wellintentioned but not scientifically informed."

Given this trend, it is more important than ever for physicians to have an open line of communication with their patients. Healthcare providers should not only be aware of any supplements that patients are taking, but also educate them about current research results.

With a plethora of misinformation available online, physicians should direct their patients to evidence-based resources. Dr. Budd recommends websites such as the National Cancer Institute, the American Cancer Society and the American Society of Clinical Oncology's cancer.net.

When discussing supplements with his patients, Dr. Budd emphasizes the importance of a healthy lifestyle. "While I will tell them that a multivitamin is acceptable to fill nutrient gaps, I always recommend they eat a balanced diet and try to get their vitamins from a dietary source."

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Dr. Budd is a staff member of Cleveland Clinic Cancer Center's Department of Hematology and Medical Oncology and Professor of Medicine at Cleveland Clinic Lerner College of Medicine.

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NEW BLOOD TEST DETECTS MULTIPLE CANCER TYPES WITH HIGH ACCURACY

Screening assay effective across all stages, can identify tissue of origin

KEY POINTS

An effective multicancer screening test could transform oncology care, improving survival chances and treatment outcomes.

A prototype blood-based screening test evaluated by Cleveland Clinic researchers and others accurately identifies the presence and originating site of 12 high-mortality cancer types, across all stages of progression, with a low false-positive rate.

The new screening test targets circulating cell-free DNA (cfDNA) deposited in the bloodstream due to cellular necrosis, apoptosis, secretion or other processes.

The test utilizes next-generation deep sequencing and a custom hybridization panel to determine the presence or absence of cancer by obtaining cfDNA's methylation state and characteristics.

The test's specificity was 99.3%. Stage I-III sensitivity was 67.3% in a pre-specified set of 12 cancer types that account for >63% of U.S. cancer deaths annually.

More research is needed to determine how well the new test performs in an asymptomatic screening population and whether its clinical use reduces cancer mortality.

A prototype blood-based screening test evaluated by Cleveland Clinic researchers and other experts can accurately identify the presence and originating site of 12 high-mortality cancer types, across all stages of progression, with a low false-positive rate, according to the latest results of an ongoing national clinical trial.

The screening test's sensitivity (its probability of detection or true-positive rate) was 67.3% for stages I-III of the 12 cancer types: anus, bladder, colon/rectum, esophagus, head and neck, liver/bile duct, lung, lymphoma, ovary, pancreas, stomach and plasma cell neoplasm. Together, those cancers account for more than 63% of all U.S. cancer deaths. The test's sensitivity increased with higher-stage malignancies, ranging from 39% in stage I to 92% in stage IV among the 12 pre-specified cancers.

Its specificity was 99.3%, meaning a 0.7% false-positive rate — less than 1% of individuals without cancer would be wrongly identified as having cancer. In the 96% of cases where the test was able to predict the tissue where the malignancy originated, its accuracy was 93%.

Those promising findings raise hopes that the assay will help achieve the long-sought goal of population-scale, broad-based, early detection of cancer in asymptomatic patients. An effective multicancer screening test — particularly one that can detect lethal cancer types for which no current screening paradigm exists — could transform oncology care, improving survival chances and treatment outcomes.

At present, only four single-cancer screening regimens exist: the prostate-specific antigen test, mammography, colonoscopy, and computerized tomography to screen patients at high risk for lung cancer. Each has inherent issues and limitations, including cost, access, utilization and invasiveness.

“The goal of screening is to cure more cancer and prevent deaths,” says Eric Klein, MD, Chairman of Cleveland Clinic's Glickman Urological & Kidney Institute, a senior author of the *Annals of Oncology* report and the co-principal investigator of Cleveland Clinic's portion of the study along with Taussig Cancer Institute oncologist and Vice Chair for Research Mikkael Sekeres, MD, MS. “Having a blood test is a simpler approach and likely would be met with a high degree of patient acceptance.”

The multicancer assay's preliminary results are “positive in a way that I think people hoped for but were surprised by,” Dr. Klein says. “Although it's a first-generation test, I think it sets the paradigm for liquid biopsy as a screening tool for cancers.”

Dr. Sekeres adds: “The study's findings also have the potential to impact how we monitor patients with an established cancer diagnosis — using a simple blood test, instead of the need for multiple scans or repeated biopsies —

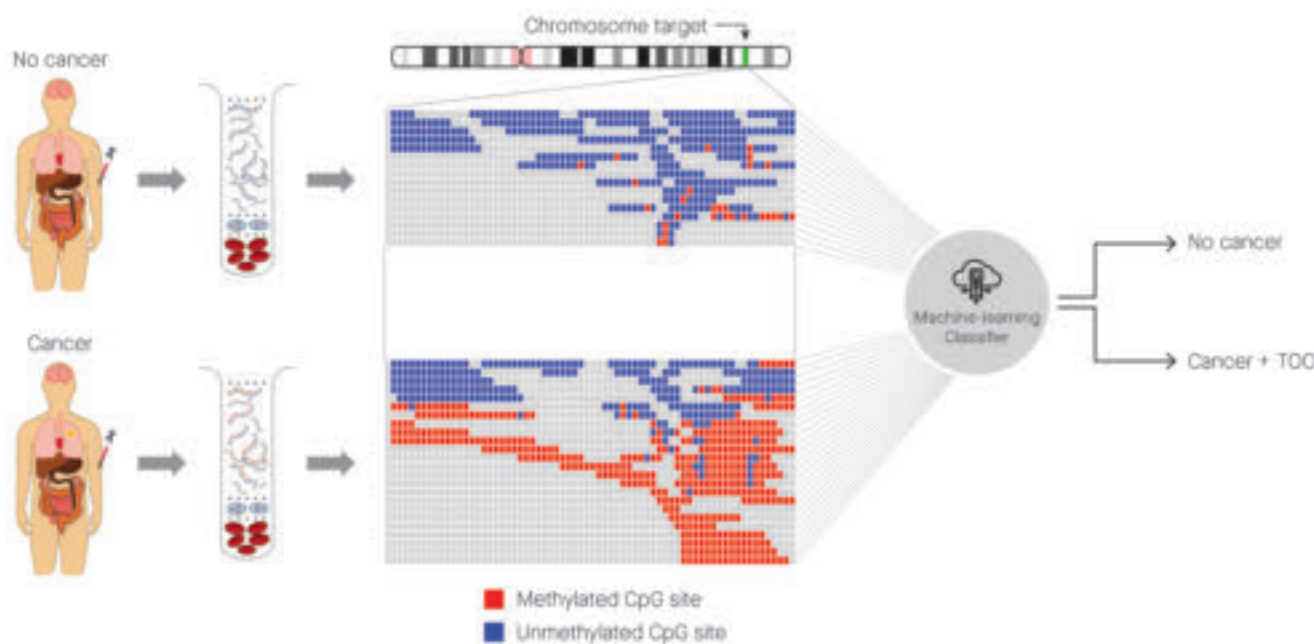


FIGURE: Identification of cancer status for more than 50 cancer types, as well as tissue of origin localization, from a single blood draw. Cell-free DNA is isolated from blood samples drawn from a patient without cancer (top) or with cancer (bottom) and subjected to a targeted methylation sequencing assay. Sequencing results identifying methylated (red) or unmethylated (blue) CpG regions are fed into a machine-learning classifier that can identify the presence or absence of cancer, as well as identify the tissue of origin.

Credit: Allen McCrodden, Associate Director, Creative Group, ProEd Communications.

and have implications for screening patients for cancer across the entire population.”

Annals of Oncology Editor-in-Chief Fabrice André, Professor and Director of Research at France’s Institut Gustave Roussy, says:

“This is a landmark study and a first step toward the development of easy-to-use screening tools. Earlier detection of more than 50% of cancers could save millions of lives every year worldwide and could dramatically reduce morbidity induced by aggressive treatments.”

Interrogating the whole body for cancer signals

Unlike traditional biopsies, which analyze tissue from a single organ or tissue site to detect a single cancer type, a liquid biopsy in principle can sample the entire body for multiple malignancy types by looking for cancer biomarkers circulating in blood.

The new screening test targets circulating cell-free DNA (cfDNA), which are short, nonencapsulated nucleic DNA fragments deposited in the bloodstream as a consequence of cellular necrosis, apoptosis, secretion or other processes. In a person with cancer, a small portion of the plasma cfDNA load is circulating tumor DNA

(ctDNA), originating from the primary tumor or circulating tumor cells and carrying the same molecular aberrations as the source tumor, including genetic mutations and epigenetic modifications.

The test utilizes next-generation deep sequencing and a custom hybridization panel to determine the presence or absence of cancer by obtaining cfDNA’s methylation state and characteristics. Unique methylation patterns of key genes involved in oncogenesis are indicative of specific cancer cell types and the tissue where the tumor originates. These methylomic signatures enable simultaneous detection and localization with a single test.

The assay was developed by GRAIL Inc., a California-based healthcare company backed by prominent investors including Microsoft co-founder Bill Gates and Amazon founder Jeff Bezos. The test is being evaluated in a multisite, three-phase, case-control, observational clinical trial known as the Circulating Cell-free Genome Atlas (CCGA), funded by GRAIL. Cleveland Clinic is one of the CCGA’s 142 study locations and enrolled the largest number of patients of any site — more than 1,500.

Finding the most effective screening approach

The liquid biopsy approach utilizing cfDNA sequencing and analysis has shown potential in post-diagnostic cancer clinical applications, such as guiding therapy selection and indicating tumor burden, treatment response, resistance and impending relapse. But there had been skepticism about cfDNA's utility for detecting cancers, particularly at the early stage of oncogenesis when only extremely small amounts of ctDNA are present in plasma.

Since cancer initiation and progression are regulated by both genetic (DNA sequence alterations) and epigenetic (alterations in gene expression and activity) events, there was also uncertainty about where to focus the search for a reliable multicancer screening biomarker.

The CCGA's initial discovery phase substudy evaluated three potential screening methods to characterize cancer-specific plasma cfDNA signals:

- Whole-genome sequencing to interrogate copy number variants.
- Targeted sequencing of selected genomic regions to interrogate single nucleotide variants and small insertions and deletions.
- Whole-genome bisulfite sequencing to interrogate genomewide methylation patterns.

Normally, DNA methylation helps regulate gene expression and stable gene silencing. As research from the Cancer Genome Atlas Program has shown, certain patterns of densely clustered methylation alterations of DNA sequences involved in transcription initiation — specifically, hypermethylation of certain 5'-C-phosphate-G-3' sites, or CpG islands — are indicative of cancer and of individual tumor types.

The CCGA discovery-phase substudy found that the methylation-based assay outperformed the whole-genome and targeted sequencing approaches for multicancer detection across stages, with high specificity. That superiority likely is due to methylation's pervasiveness as a potential signal compared with the mutation sites that other liquid biopsy tests typically sample. Genetic mutation-based screening tests also can be confounded by highly prevalent mutations resulting from biological processes, such as clonal hematopoiesis of indeterminate potential.

"It turned out that, for a variety of reasons, methylation was the best," Dr. Klein says. "All three methodologies had roughly the same detection rate, but the practical aspects of targeted methylation detection are that it's cheaper and less complicated to do. And you can develop individual methylation assays for each type of tumor."

Refining the search

With methylation identified as the preferred basis for the screening assay, the second (current) CCGA substudy sought to train and validate a machine-learning classifier (an algorithm) to distinguish cancer versus noncancer and the origin site of any detected malignancy from a plasma specimen. The classifier was used to predict cancer presence and location based on methylation patterns in ctDNA.

The substudy's 6,689 participants were divided into a cancer/non-cancer training set and an independent validation set. The training and validation cohorts were generally comparable in demographics. The participants with cancer represented more than 50 primary cancer types across all clinical stages. The large noncancer cohort included significant numbers of patients with potentially confounding conditions, allowing the researchers to gauge the assay's specificity in population-level-like screening conditions.

Whole-genome bisulfite sequencing of plasma cfDNA produced 3,508 analyzable samples. Using those results and methylation array data from the Cancer Genome Atlas, the CCGA researchers identified regions of the Genome Reference Consortium human reference genome GRCh37 (hg19) expected to contain cancer- and/or tissue-specific methylation patterns. With training, the classifier derived the most informative targets, ultimately allowing the investigators to create a targeted methylation panel that covered 103,456 genomic regions and 1.1 million CpGs. Methylation patterns determined a sample's cancer/noncancer status and, for any detected malignancy, the tissue of origin.

Measuring effectiveness

To be effective as a population-level cancer screening test, a candidate assay should be:

- Highly specific (to minimize false positives).
- Capable of discovering and discriminating among multiple cancer types (to yield more detectable cancers than a single-

cancer test would, since most cancers have low prevalence in a screening population).

- › Able to determine the cancer's originating tissue (to reduce unnecessary diagnostic costs and resources).
- › Able to detect early-stage, asymptomatic cancers as well as later-stage malignancies that are yet to be diagnosed.

The targeted methylation-based multicancer test meets those criteria, the CCGA investigators say.

"The really exciting part is that not only do we see positive detection results in cancers for which there is no screening paradigm, but there's a low false-positive rate and highly accurate predictions for what organ the tumor is located in among those who have a positive test," Dr. Klein says.

In pancreatic cancer, for instance — which accounts for 7% of all cancer deaths and is usually diagnosed at an advanced stage and lacks a screening test — the assay's sensitivity was 63% in stage I, 83% in stage II, 75% in stage III and 100% in stage IV.

While a screening test's sensitivity is important for an individual subject, its specificity is the more relevant metric for widespread use, Dr. Klein says, "At a population level, it's more important to find as many cancers as are prevalent. Even if a screening test detects only 50% of early-stage cancers, that's still 50% more than are currently detected."

A prospective trial using an asymptomatic cohort is needed to precisely calculate the test's positive predictive value (PPV, the probability that a positive result is indicative of actual disease). But if a similarly performing assay were applied to a population with an annual cancer incidence of 1.3%, the CCGA researchers calculated that the test would identify 715 cancers per 100,000 screened persons and would yield 691 false-positive results requiring diagnostic workups to rule out disease: a PPV of 51%.

By comparison, U.S. Preventive Services Task Force-recommended screening tests for breast, colorectal and lung cancer have PPVs ranging from 3.7% to 4.4%.

The path forward

Additional studies are needed to determine how well the new test performs in an asymptomatic screening population and whether its clinical use reduces cancer mortality. Other limitations of the

current study are that, at the time of the analysis, not all patients had been followed for a year, which is needed to ensure their noncancer status is accurate, and that some inaccuracy occurred in the detection of tissue of origin for cancers driven by the human papillomavirus.

GRAIL is conducting several research projects in diverse populations to further validate the multicancer detection approach. They include a third CCGA substudy and an observational trial known as PATHFINDER that will assess the test's use in clinical practice, to determine its impact on diagnostic resolution after detection of a cancer signal and how the results affect patients. Cleveland Clinic plans to participate in PATHFINDER later in 2020.

"One of PATHFINDER's goals is to figure out if the test accelerates the diagnosis of cancer in patients who are screened," Dr. Klein says. "The other thing we're going to be looking at is physician behavior. What happens after a test is positive? What does the physician do? And what is the patient's reaction to having a test, including those who receive a negative result? In addition, we will follow patients for a year to determine if the negative tests miss anything."

With those data and other independent validation results, GRAIL can then make its case for Food and Drug Administration approval of the screening test.

Disclosure: Dr. Klein is a consultant for GRAIL.

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THERMORADIO THERAPY FOUND TO BE SAFE, EFFECTIVE IN PATIENTS WITH RECURRENT BREAST CANCER

Study shows even patients with extensive disease benefit from treatment

KEY POINTS

Breast cancer patients who have failed chemotherapy, radiation therapy and hormone therapy need new treatment options.

Hyperthermia can increase tumor cells' radiosensitivity.

A Cleveland Clinic study shows that the combination of hyperthermia and radiation therapy provides effective local control of recurrent breast cancer, even in patients with extensive disease and prior treatment failures.

Hyperthermia should be considered for recurrent or aggressive breast cancer because it can improve cancer control with minimal toxicity.

Combining hyperthermia with radiation therapy produces effective local control of recurrent breast cancer, with manageable side effects, even in patients with extensive disease whose previous therapies had failed, a Cleveland Clinic study published in the *International Journal of Hyperthermia* has found. Hyperthermia's benefits are most apparent in patients whose prior treatment included radiation.

The retrospective study's results can guide clinicians managing these difficult cases. Therapeutic decision-making in cases of locally recurrent breast cancer must take into account the increased risk of side effects in patients who often already have undergone substantial amounts of chemo- and radiotherapy, and who may have considerable tumor volumes, both of which complicate treatment.

Hyperthermia's ability to increase cancer cells' radiosensitivity means lower radiation doses can result in greater tumor control than radiation alone.

"This is the first research from Cleveland Clinic that has shown we can achieve excellent results in terms of tumor control in patients with extensive disease," says Cleveland Clinic Cancer Center radiation oncologist Jennifer Yu, MD, PhD, the study's corresponding author. "Many of the patients we've treated have failed other types of treatments. They failed their initial radiation and many types of chemotherapy; some have failed hormone therapy as well, and they have no other treatment options."

Dr. Yu and her colleagues found that thermoradiotherapy produced either a complete disappearance of disease or a measurable reduction in a majority of the study's patients,

including some of the most challenging cases.

[Thermoradiotherapy improves outcomes across the board](#)

The study included 36 patients with recurrent breast cancer who received hyperthermia and radiation at Cleveland Clinic between 2011 and 2017. Median length of follow-up was 11 months.

Prior to recurrence, 33 of those patients (91.7%) had been treated with chemotherapy, 30 (83.3%) received radiation therapy (median dose 60.4 Gy, range 50.4–66.0 Gy), and 29 (80.5%) had a partial, complete or double mastectomy.

After recurrence, 13 patients were treated with electron therapy, 12 received intensity-modulated radiation therapy (IMRT) and 11 received conventional photon therapy with or without regional nodal irradiation. The median radiation dose and median fraction size were 35.5 Gy and 3.0 Gy, respectively. IMRT enables treatment of patients with extensive recurrences that require complex radiation fields while minimizing collateral dosing to nearby organs.

Hyperthermia, lasting 60 minutes per session, was given twice per week. For patients with extensive volumes of disease, hyperthermia was delivered using two to three hyperthermia fields.

A 915 MHz microwave unit was used to heat the treated area and thermistors placed on the tumor's surface recorded the temperature. Hyperthermia's effectiveness depends in part on maintaining target temperature during the treatment period. The study's median T_{90} — the temperature exceeded by 90% of the measured temperature readings — was 40.2°C.

Hyperthermia improves cancer control by increasing cancer cell death caused by radiation and chemotherapy and altering the tumor microenvironment. Specifically, hyperthermia has been shown to:

- › Help activate and recruit cytotoxic immune cells to tumor regions.
- › Enhance tumor cell perfusion to increase drug delivery.
- › Increase tumor cell oxygenation to improve radiation efficacy.
- › Impair DNA damage repair in cancer cells, ultimately leading to cancer cell death.

"Our main goal was to show that hyperthermia can improve tumor control in patients that have breast cancer, particularly for patients that needed repeat radiation — those patients who have progressed after prior radiation treatment," Dr. Yu explains.

Details of the results

In the study, thermoradiotherapy produced an overall response rate of 61.1%. Previous studies reported higher overall response rates; Dr. Yu and her colleagues explain that the Cleveland Clinic study's response rate may have been influenced by inclusion of patients with large tumor burdens, for whom only a partial response is likely.

Seventeen patients (47.2%) experienced a complete response. Five patients (13.9%) had a partial response. Eleven patients' disease (30.6%) remained stable, while three patients (8.3%) developed progressive disease.

The most common acute side effects of treatment included pain (36.1%), erythema (27.8%) and edema (16.7%). The most common long-term side effects were hyperpigmentation/tanning (22.2%), lymphedema (16.7%) and scarring/fibrosis (13.9%).

Hyperthermia as an add-on therapy in recurrent breast cancer

Hyperthermia currently is not part of standard first-line treatment for breast cancer because effective therapies already are available for many patients with early-stage disease, Dr. Yu says.

However, recurrent and aggressive disease is significantly more challenging because it is more difficult to achieve remission with existing therapies.

"For recurrent breast cancers, there is no standard per se," Dr. Yu says. Therefore, "hyperthermia should be considered for recurrent or aggressive breast cancer because it can improve cancer control with minimal toxicity."

Her recommendations are based on data from phase III clinical trials and multiple meta-analyses that found hyperthermia and radiation yield improved complete responses compared with radiation alone. Prior studies have shown a complete response rate of about 60% for thermoradiotherapy compared with about 40% for radiation alone in patients with superficial breast cancers.

"With thermoradiotherapy, a complete response rate is 150% of the response rate for radiation alone," she says. "For patients that have had prior radiation, you're looking at [achieving] complete responses in about two-thirds of patients and that is very, very high."

Additional hyperthermia studies

Dr. Yu's team is conducting a preclinical study to assess whether hyperthermia can improve immune response to various cancers. On the clinical side, the researchers are examining how hyperthermia affects patients with sarcoma, skin cancer and bone metastases. She emphasizes that timely referral for thermoradiotherapy, early in the course of disease, is critical to its success.

"If patients came to us sooner for hyperthermia and radiation, their tumors would be smaller and, therefore, we would need to treat less area," she says. Early treatment is beneficial in two ways: "It is easier for us to control a smaller tumor, and the side effects of treatment are also reduced."

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Dr. Yu is the founder and Director of Cleveland Clinic Cancer Center's Center for Hyperthermia and a staff member of the departments of Radiation Oncology, Cancer Biology and the Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center. She also is an Associate Professor of Molecular Medicine at Cleveland Clinic Lerner College of Medicine.

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RESEARCHERS VALIDATE LINK BETWEEN GENETIC VARIANT AND POOR OUTCOMES IN ADVANCED PROSTATE CANCER

Cleveland Clinic-led study lays groundwork for more personalized treatments

KEY POINTS

Advanced prostate tumors eventually are able to overcome medical or surgical castration by synthesizing their own androgens using extragonadal precursor steroids.

The enzyme 3 β -hydroxysteroid dehydrogenase isoenzyme-1 (3 β HSD1), encoded by the *HSD3B1* gene, catalyzes the first and rate-limiting step in prostate cancer cells' metabolic conversion of adrenal dehydroepiandrosterone (DHEA) to 5 α -dihydrotestosterone (DHT), permitting tumors to grow in the absence of gonadal testosterone.

An adrenal-permissive variant of the *HSD3B1* gene encodes for a stable form of the 3 β HSD1 enzyme that supports rapid conversion from DHEA to DHT and high levels of DHT in tumor tissue.

New Cleveland Clinic-led research shows that metastatic prostate cancer patients with the adrenal-permissive mutation are more likely to have aggressive, early castration-resistant disease and shorter survival.

Genetic testing for the presence of the adrenal-permissive allele may help physicians identify patients most likely to benefit from escalated treatment.

Metastatic prostate cancer patients with an adrenal-permissive variant of the *HSD3B1* gene are more likely to have aggressive, early castration-resistant disease and shorter survival, a Cleveland Clinic-led study has found.

The research — the first prospective clinical trial validation of the relationship between *HSD3B1* status and clinical outcomes — suggests that genetic testing for the presence of the inherited adrenal-permissive *HSD3B1*(1245C) allele may help physicians identify patients most likely to benefit from additional, escalated treatment.

Medical oncologist and physician-researcher Nima Sharifi, MD, of Cleveland Clinic's Lerner Research Institute, Glickman Urological & Kidney Institute and Taussig Cancer Institute, is the study's senior author.

While androgen deprivation therapy (ADT) to deplete circulating gonadal testosterone is initially effective for treating advanced prostate cancer, tumors eventually are able to overcome medical or surgical castration by synthesizing their own androgens using extragonadal precursor steroids. The recent addition of novel agents such as docetaxel, abiraterone, enzalutamide and apalutamide along with ADT as upfront therapy for advanced prostate cancer has produced a survival benefit, but there are significant outcome variations among patients that indicate tumors' underlying biologic variability.

The enzyme 3 β -hydroxysteroid dehydrogenase isoenzyme-1 (3 β HSD1), encoded by the *HSD3B1* gene, catalyzes the first and rate-limiting step in prostate cancer cells' metabolic conversion of adrenal dehydroepiandrosterone (DHEA) to 5 α -dihydrotestosterone (DHT). Dr. Sharifi's previous research identified the first gain-of-function genetic mutation that increases the conversion of precursor steroids to DHT, permitting tumors to grow in the absence of gonadal testosterone.

The variant adrenal-permissive *HSD3B1*(1245C) allele encodes for a stable form of the 3 β HSD1 enzyme that supports rapid conversion from DHEA to DHT and high levels of DHT in tumor tissue. The stable enzymatic accumulation increases androgen synthesis, enhances androgen receptor activation and accelerates tumor proliferation. In essence, the adrenal-permissive genotype opens the floodgates to DHT, allowing for clinical progression to castration-resistant disease.

The population frequency of the adrenal-permissive variant is disproportionately higher in white men. Retrospective studies by Dr. Sharifi and others involving men with nonmetastatic and metastatic prostate cancer

“If men carry this specific testosterone-related genetic abnormality, we may be able to individualize their therapy.”

— NIMA SHARIFI, MD

have indicated an association between the adrenal-permissive *HSD3B1*(1245C) variant and accelerated time to development of castration-resistant disease, reduced metastasis-free survival and reduced overall survival. But these findings have not been validated with prospective studies.

Examining *HSD3B1*(1245C)'s impact

For the latest study, Dr. Sharifi and colleagues analyzed data from 475 participants already enrolled in a large, multicenter national phase 3 clinical trial (the Chemohormonal Therapy vs. Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer, or CHAARTED) intended to assess the efficacy of ADT alone or in combination with docetaxel in prostate cancer.

Dr. Sharifi and his co-investigators compared clinical outcomes between men who carried the adrenal-permissive variant (one or more *HSD3B1*[1245C] alleles) and those who did not. Eighty-five percent of the CHAARTED trial's participants were white, as were 90% of the subjects whose DNA was available for genotyping. The analysis conducted by Dr. Sharifi and colleagues focused only on white patients in order to avoid potential confounding genomic factors that could vary by race.

The researchers found that adrenal-permissive *HSD3B1*(1245C) inheritance is associated with faster progression to treatment resistance and shorter overall survival in men with low-volume metastatic prostate cancer, regardless of the use of docetaxel. Freedom from castration-resistant prostate cancer at two years post-treatment was significantly lower in patients with low-volume disease and the adrenal-permissive genotype as compared to those with the adrenal-restrictive genotype. Overall survival at five

years post-treatment also was significantly worse in the adrenal-permissive cohort.

Interestingly, the genetic variant led to shortened survival despite the administration of any other therapies following the development of treatment resistance.

“These findings lay the groundwork for more personalized and effective treatments for prostate cancer,” says Dr. Sharifi. “If men carry this specific testosterone-related genetic abnormality, we may be able to individualize their therapy.”

HSD3B1(1245C) was not found to influence clinical outcomes in men with high-volume prostate cancer (defined as the presence of visceral metastases or four or more bone metastases with one or more lesions beyond the pelvis and vertebrae). Dr. Sharifi notes this is not surprising, since previous studies have shown that disease progression and burden are vastly different between high- and low-volume prostate cancer.

He and his colleagues speculate that the increased genomic alterations present in high-volume disease may make cancer cells less reliant on extragonadally driven androgen receptor stimulation and may improve access to alternative androgen synthesis pathways, tempering the advantage conferred by the adrenal-permissive allele.

A journey from bench to bedside

Taken together, the study's findings suggest that the presence of the adrenal-permissive genetic variant can be used to identify men with low-volume metastatic prostate cancer most at risk for quick progression to treatment resistance and earlier death — a

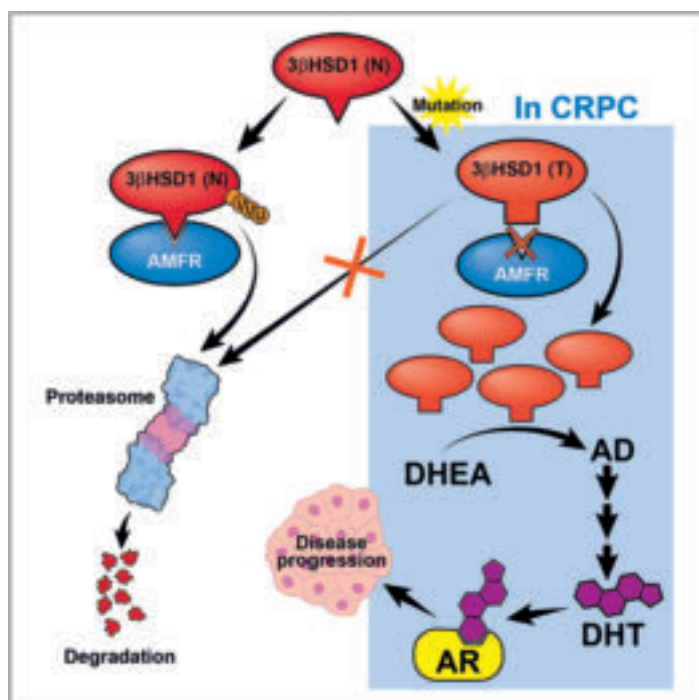


FIGURE: This graphical abstract illustrates how the gain-of-function 3βHSD1 mutation increases DHT synthesis.

Credit: Chang KH, Li R, Kuri B, et al. A gain-of-function mutation in DHT synthesis in castration-resistant prostate cancer. *Cell*. 2013;154(5):1074–1084.

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discovery with significant implications for clinical care and genetic counseling. A positive germline *HSD3B1*(1245C) genotyping result could help clinicians determine which patients might benefit from escalated efforts to inhibit the androgen receptor axis in addition to gonadal testosterone suppression.

“These findings represent a seven-year research story that started at the lab bench and has now reached the patient bedside,” says Dr. Sharifi. “As the team has shown here, incorporating genetic testing in prostate cancer as part of routine care has significant potential to improve treatment success and quality and length of life for men with prostate cancer who carry the *HSD3B1*(1245C) variant. This work is another step in that direction.”

A limitation of the study was its lack of diversity due to the restriction of its cohort to white patients to reduce potential confounders. Using a more diverse population to validate the association between *HSD3B1*(1245C) and adverse clinical outcomes will be an important next line of investigation, Dr. Sharifi says.

The research was supported in part by the National Cancer Institute, the U.S. Department of Defense and the Prostate Cancer Foundation. In 2017, he received the national Top Ten Clinical Achievement Award from the Clinical Research Forum for his discoveries linking *HSD3B1*(1245C) with poor prostate cancer outcomes.

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Dr. Sharifi holds the Kendrick Family Chair for Prostate Cancer Research at Cleveland Clinic and directs the Genitourinary Malignancies Research Center. He has joint appointments in the Taussig Cancer Institute, Glickman Urological & Kidney Institute and Lerner Research Institute and is a Professor of Medicine at Cleveland Clinic Lerner College of Medicine.

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NEW APPROACH LEADS TO TRANSFUSION INDEPENDENCE IN LOW-RISK MDS

Luspatercept shows promise for patients with few options

KEY POINTS

Chronic anemia is a critical issue in patients with myelodysplastic syndromes (MDS); many eventually require regular transfusions and face anemia-related complications and reduced survival.

Luspatercept aids erythroid maturation and is approved for the treatment of anemia in adult patients with beta thalassemia.

A new phase 3 study involving Cleveland Clinic Cancer Center shows luspatercept significantly lessens anemia severity and reduces or eliminates the need for transfusions in patients with low-risk MDS.

The findings suggest luspatercept may provide a new approach for MDS patients with few current options.

The investigational agent luspatercept significantly lessens anemia severity and reduces or eliminates the need for transfusions in patients with low-risk myelodysplastic syndromes (MDS), a new phase 3 study published in the *New England Journal of Medicine* has found.

The encouraging results support the prospect of a new, well-tolerated drug for MDS patients, who currently have few alternatives.

Chronic anemia is a critical issue in MDS patients, most of whom are elderly when diagnosed. In those patients' bone marrow cells, signaling on the SMAD2/3 regulatory pathway is elevated, which inhibits maturation of red blood cells. Many MDS patients eventually require regular transfusions and face anemia-related complications such as heart disease, fractures and reduced survival.

"Over two-thirds of patients with myelodysplastic syndromes have some type of anemia," says study co-author Mikkael Sekeres, MD, Cleveland Clinic Cancer Center's Vice Chair for Clinical Research and Director of the Leukemia Program. "The most common initial therapy for those patients is to use an erythropoietin-stimulating agent such as recombinant humanized erythropoietin or darbepoetin. These agents work in about 20%-40% of patients and, on average, for about a year. Once they stop working, limited options are available."

Luspatercept is a recombinant fusion protein that aids erythroid maturation by reducing SMAD2/3 signaling. It was approved in 2019 for the treatment of anemia in adult patients with

beta thalassemia, and also has shown promise in lower-risk MDS. A 2017 phase 2 study published in *Lancet Oncology* showed that 38% of luspatercept-treated patients had transfusion independence for eight weeks or longer.

Recognizing the need for additional therapeutic approaches, Dr. Sekeres and his colleagues sought to further explore the potential of luspatercept among MDS patients.

Study details and key findings

Patients in this double-blind, placebo-controlled, phase 3 trial known as MEDALIST, which took place at Cleveland Clinic Cancer Center and 64 other institutions in 11 countries, were randomly assigned (2-to-1) to receive either luspatercept (N=153) or placebo (N=76), administered subcutaneously every three weeks for 24 weeks. Luspatercept was given at a dose of 1.0-1.75 mg per kilogram of body weight.

Eligible patients included those with very-low-risk, low-risk or intermediate-risk MDS with ring sideroblasts who had been receiving regular red blood cell transfusions. Additional criteria were that patients' disease was refractory to, or unlikely to respond to, erythropoiesis-stimulating agents, or that they had discontinued these agents due to an adverse event.

Patients' median age was 71 years (range 26-95), and 63% were men. Ten percent of the enrolled patients had MDS defined as very low risk, 72% as low risk and 17% as intermediate risk.

The primary endpoint was transfusion independence for eight weeks or longer during weeks 1-24 of the trial, according to Dr. Sekeres. The key secondary objective was transfusion independence for 12 weeks or longer.

"Patients who received luspatercept were significantly more likely to achieve transfusion independence compared with those in the placebo group (38% vs. 13%)," says Dr. Sekeres, who is the primary investigator of the National MDS Natural History Study and chair of the expert panel preparing the American Society of Hematology's clinical practice guidelines for treating older adults with acute myeloid leukemia. "The duration of transfusion independence lasted a median of about 31 weeks, with some people going a couple of years and longer without requiring a transfusion."

Patients who were treated with luspatercept were more likely to reach the key secondary endpoint than those who received the placebo (28% vs. 8% for weeks 1-24, and 33% vs. 12% for weeks 1-48).

Fatigue (27%), diarrhea (22%), asthenia (20%), nausea (20%) and dizziness (20%) were the most commonly reported luspatercept-associated adverse events. Sixty-five patients (42%) in the luspatercept group had grade 3 or 4 adverse events compared with 34 (45%) in the placebo arm. Forty-eight patients (31%) who were treated with luspatercept had at least one serious adverse event versus 23 (30%) of those who received placebo.

In the luspatercept treatment arm, dose reductions due to adverse events occurred in seven patients (5%). Thirteen patients (8%) in the luspatercept group and six (8%) treated with placebo discontinued the regimen as a result of adverse events.

"Patients with lower-risk myelodysplastic syndromes with ring sideroblasts for whom erythropoiesis-stimulating agents are not effective or are not an option have limited treatment options available beyond continued transfusions," the study authors concluded. "Luspatercept significantly reduced the transfusion burden in a substantial proportion of these patients and was associated with mainly low-grade toxic effects."

[A new hope for MDS](#)

These findings suggest luspatercept can be added to the MDS arsenal, offering patients with few options a new approach.

"We haven't had a drug approved specifically for MDS in 14 years," Dr. Sekeres says. "It's been a desert of treatment options for our patients; and, typically, once our patients have exhausted erythropoiesis-stimulating agents, we move on to treat them with drugs that have a lot of side effects and limited efficacy because we don't have many tools in our toolbox."

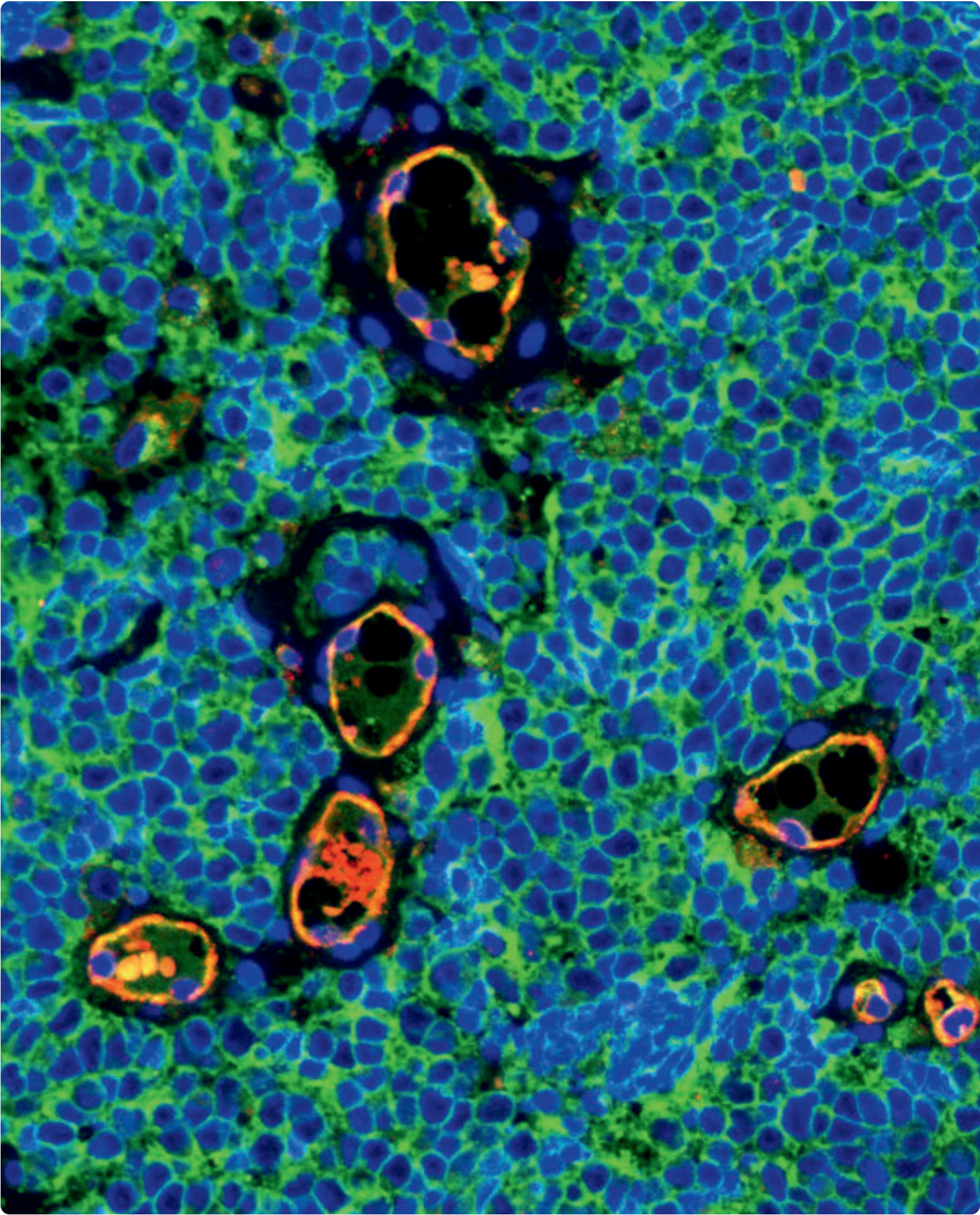
"[Luspatercept] would give us a really nice option for another drug that has very few side effects," he says. "While I would love a drug that works in 100% of my patients, the cold, hard reality of treatments for MDS is that drugs tend to work for 20%-40% of patients. This drug is closer to 40%, with a strong safety profile, making it a significant development for this patient population."

Dr. Sekeres is designing a phase I/II study led by Cleveland Clinic Cancer Center that will evaluate the combination of luspatercept and another MDS drug to treat MDS-associated anemia.

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Dr. Sekeres is Taussig Cancer Institute's Vice Chair for Research, Director of the Leukemia Program and Professor of Medicine at Cleveland Clinic Lerner College of Medicine.

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RESEARCHERS UNLOCK KEYS TO STAGING AND RISK STRATIFICATION OF MERKEL CELL CARCINOMA

Leveraging the prognostic significance of sentinel lymph node biopsy histologic patterns

KEY POINTS

Sentinel lymph node (SLN) biopsy is increasingly used to plan treatment for Merkel cell carcinoma (MCC), but its pathologic prognostic significance in patients without clinically evident positive nodes has been unclear.

Recent research from Cleveland Clinic Cancer Center reveals more about the potential value of SLN biopsy in MCC.

The research addresses how histologic patterns in SLN biopsies can be used to stratify stage III disease, which factors independently predict that SLN biopsies will be positive and how solid- versus nonsolid-appearing microscopic metastases affect patient outcomes.

The results indicate treatment decisions for MCC patients should consider immune status, how many lymph nodes are involved, the type of cell pattern and whether the pattern is solid or nonsolid.

Cleveland Clinic Cancer Center investigators have published a body of research that may herald an era of improved staging and risk stratification for patients with Merkel cell carcinoma (MCC), an aggressive and lethal form of skin cancer.

The focus of their work is sentinel lymph node (SLN) biopsy, a technique increasingly used for MCC treatment planning but whose pathologic prognostic significance in patients without clinically evident positive nodes has been unclear.

Because MCC is uncommon, few studies have been done to evaluate the predictive value of the variable numbers and patterns of cancer cells detected in SLN biopsies from patients with the disease. Only 2,500 cases of MCC are diagnosed annually in the United States, but the incidence is increasing. Eighty percent of MCC cases are caused by infection with a DNA oncovirus, Merkel cell polyomavirus; the remainder result from cumulative exposure to ultraviolet radiation.

Three recent studies by a multidisciplinary Cleveland Clinic Cancer Center research team shed new light on the potential value of SLN biopsy in MCC. Key members of the team are dermatopathologist Jennifer Ko, MD, PhD; medical oncologist Pauline Funchain, MD; and plastic surgeon Brian Gastman, MD, the Medical and Surgical Director of the Melanoma and High-Risk Skin Cancer Program.

“Merkel cell carcinoma is one of the most immunogenic tumors,” says Dr. Ko. “The tumor cells are small, and they can be hard to detect in a whole sea of immune cells that populate

the lymph nodes. We wanted to know how patient prognosis was impacted by findings of different patterns of tumor cells seen with immunohistochemical staining and various amounts of disease on sentinel lymph node biopsy. The impact on prognosis had not been reported in the literature before.”

The team’s analyses provide novel information in three areas for management of patients with MCC:

- How histologic patterns in SLN biopsies can be used to stratify stage III disease.
- What factors independently predict that SLN biopsies will be positive.
- The impact of solid- versus nonsolid-appearing microscopic metastasis on patient outcomes.

Histologic patterns and stratification

The team’s initial study was a retrospective review of histologic patterns of SNL in 64 patients with stage III MCC, intended to identify clinicopathologic predictors of outcome. Five metastatic patterns were characterized: a diffuse, sheetlike solid growth of lymph node parenchyma (N = 38, 59%); nonsolid, parafollicular growth (N = 4, 6%); scattered,

dyshesive tumor cells of varying number in the subcapsular sinus, the draining sinuses, or both sites (N = 11, 17%); tight perivascular hilar (N = 1, 2%); and rare, scattered parenchymal cells (N = 10, 16%).

At the time of follow-up, 30 patients (48%) had died and 21 of the deaths (33%) were attributable to MCC. Survival was poorer overall in patients with the sheet-like pattern of metastases than in those with the other metastasis pattern types ($p = 0.03$), with 22 of the deaths (73%) occurring in patients with the solid, sheet-like pattern. In contrast, three deaths (10%, all involving immunosuppressed patients) were associated with the rare scattered parenchymal cell pattern; four deaths (13%) were associated with the sinusoidal pattern; and one death (3%) was in a patient with the nonsolid parafollicular pattern.

In multivariable analysis, the number of positive SLN (1 or 2 vs. > 2 , $p < .0001$), patient age (< 70 vs. ≥ 70 , $p = .01$), SLN metastasis pattern (sheet-like vs. the other four types, $p = .02$) and immune status (immunocompetent vs. suppressed, $p = .03$) were independent predictors of outcome. The researchers also found that those characteristics could be used to stratify stage III patients into three groups with significantly different outcomes.

“This was the first study to investigate the meaning of various patterns of sentinel lymph node involvement by Merkel cell carcinoma, including the meaning of disease identified with immunohistochemistry alone,” says Dr. Ko, the paper’s first author. “Our findings suggest improved survival in patients with metastatic tumor involving sentinel lymph nodes detected only by immunohistochemistry, and raise the question of whether these patients deserve separate classification and different management, analogous to what is standard of care in breast carcinoma.”

Predictors of SLN positivity

The Cleveland Clinic team next took on the challenge of determining what characteristics of MCC are associated with a positive SLN and decreased overall survival (OS). To do so, they analyzed data from 3,048 patients with MCC in the National Cancer Database from 2012 to 2014, of whom 1,174 had undergone SLN biopsy.

Predictors of SLN positivity were evaluated using logistic regression. OS was evaluated using a Cox proportional hazards model.

“In our other two studies, we used patient subsets from Cleveland Clinic and cooperating institutions,” says Dr. Ko. “For this analysis, we were fortunate to have access to a huge dataset of patients from across the country. The question we wanted to answer was whether there is a way to narrow down which patients might not need sentinel lymph node biopsy, based on different tumor parameters.”

Multivariate analysis showed that a positive SLN was more likely in patients with MCC who had primary lesions on the trunk (odds ratio [OR], 1.98; 95% confidence interval [CI], 1.23-3.17; $p = .004$), tumor-infiltrating lymphocytes (OR, 1.58; 95% CI, 1.01-2.45; $p = .04$) or lymphovascular invasion (OR, 3.5; 95% CI, 2.51-4.76; $p < .001$). OS was lower in patients who were age 75 or older (hazard ratio [HR], 2.55; 95% CI, 1.36-4.77; $p = .003$), male (HR, 1.78; 95% CI, 1.09-2.19, $p = .022$), immunosuppressed (HR, 3.51; 95% CI, 1.72-7.13; $p = .001$) and who had a positive SLN (HR, 3.15; 95% CI, 1.98-5.04; $p < .001$).

At this point, SLN biopsy is still recommended for all MCC patients, Dr. Ko says.

Nonsolid metastasis significance

The team’s most recently published research involved the prognostic significance of nonsolid microscopic metastasis in SLN for MCC. The findings suggest that outcomes for patients with nonsolid metastases are similar to those of patients with negative SLN biopsies. The exception is patients with a sinusoidal SLN biopsy pattern, which in the study was associated with worse outcomes.

The researchers retrospectively analyzed the presence and patterns of metastases in 38 patients with MCC: 16 whose SLN biopsies were positive and 22 whose SLN biopsies were negative. Five-level, stepwise sectioning at 250- μ m intervals was performed in all SLN blocks, with an immunohistochemical stain for cytokeratin 20 performed on all levels. Median follow-up was 56.3 months overall

“These data may help us stratify patients with stage III Merkel cell carcinoma according to prognosis and make better choices about the kind of treatment and surveillance they might need.”

— JENNIFER KO, MD, PHD

and 50.4 months and 66.8 months, respectively, for the SLN biopsy-positive and biopsy-negative groups.

OS and disease-specific survival (DSS) did not differ between the two diagnostic groups but did differ by immune status (immunocompetent vs. immunosuppressed, OS $p = 0.03$, DSS $p = 0.005$) and primary tumor category (OS $p < 0.0001$, DSS $p = 0.001$). On deeper sectioning, all 16 diagnostically positive SLN biopsies continued to show nonsolid microscopic metastasis, and 32% (7/22) of diagnostically negative SLN biopsies revealed nonsolid metastasis. Sinusoidal metastasis was associated with worse DSS than were all other patterns ($p = 0.02$).

“In this study, patients with the rare-cell pattern — up to 10 cells in scanning magnification — seemed to do just as well as patients who had a negative sentinel lymph node biopsy,” says Dr. Ko.

“These data may help us stratify patients with stage III Merkel cell carcinoma according to prognosis and make better choices about the kind of treatment and surveillance they might need.”

Collectively, the Cleveland Clinic team’s findings strongly indicate that nonsolid microscopic tumor cell growth patterns in MCC SLN biopsies represent less aggressive disease than do solid metastatic patterns.

[The bottom line](#)

The researchers’ next steps include a study of primary tumor tissue from a cohort of Cleveland Clinic Cancer Center MCC patients

treated with immunotherapy, to attempt to understand why some tumors respond to the treatment and some do not.

They also hope that pathologists in other institutions will start including information about MCC cell patterns of SLN involvement in pathology reports. Those data could form the basis of a larger national cohort for studies to validate the findings of the three existing reports.

For clinicians treating MCC patients, the key take-home message from the Cleveland Clinic Cancer Center studies is to look at the whole picture, not just at whether a lymph node is positive or negative, according to Dr. Ko.

“Clinicians should consider a patient’s immune status, how many lymph nodes are involved, what the cell pattern is, and whether the pattern was solid or nonsolid,” she says. “Putting all those pieces together will give you a more accurate idea of how well a patient is likely to do and how aggressive treatment should be.”

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Dr. Ko is a staff member of Cleveland Clinic’s Department of Anatomic Pathology, an associate staff member of the Department of Inflammation and Immunity, and Clinical Assistant Professor of Pathology at Cleveland Clinic Lerner College of Medicine.

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ADVANCING IMMUNOTHERAPY: A CONVERSATION WITH TIMOTHY CHAN, MD, PHD

Meet the Director of Cleveland Clinic's new Center for Immunotherapy and Precision Immuno-Oncology

KEY POINTS

Internationally known cancer researcher Timothy Chan, MD, PhD, has joined Cleveland Clinic Cancer Center to direct the new Center for Immunotherapy and Precision Immuno-Oncology.

The center will bring together researchers from multiple disciplines to develop innovative immune system-based personalized cancer treatments utilizing genomic analysis and high-throughput immunoprofiling.

Cleveland Clinic's new Center for Immunotherapy and Precision Immuno-Oncology, directed by renowned cancer researcher Timothy Chan, MD, PhD, plans to unite researchers in multiple disciplines to advance personalized cancer care and develop novel immune system-based treatments.

"In the last seven or eight years, immunotherapy has arisen as one of the main pillars of cancer therapy," says Dr. Chan, who joined Cleveland Clinic in April 2020 from Memorial Sloan Kettering Cancer Center and Weill Cornell School of Medicine. "Moreover, new immunotherapy agents are transforming other types of care, such as for autoimmune disorders and infectious disease."

"Our new center resides in both the research and the therapeutic realms," he says. "The plan is to build a leading-edge, enterprise-level organization to discover, as well as to bring into the clinic, new immunotherapies. We're focusing on big data — on experimental therapeutics, driven by genomic analysis and high-throughput immunoprofiling — and we're leveraging all the strengths of the Cleveland Clinic enterprise to do this. I'm ecstatic to be here."

"Innovation in precision immunotherapy is one of the most exciting areas in cancer research," says Taussig Cancer Institute Chairman Brian J. Bolwell, MD. "The addition of Dr. Chan and the new center's focus on research and clinical trials will strengthen our ability to provide advanced treatment options for our patients."

Dr. Chan is an international expert in precision immuno-oncology and a pioneer in using genomics to determine patients' response to immunotherapies. His lab at Memorial Sloan

Kettering (MSK) made foundational discoveries, including the finding that immune checkpoint inhibitors ultimately target somatic mutations. This has led to a global effort to understand and use neoantigens in cancer therapies. It also spurred the development of a new generation of cancer vaccines aimed at unleashing the immune system against mutations in tumors. At MSK, he ran a successful cooperative center, the Immunogenomics and Precision Oncology Platform, that propelled translational immunology research and trial work.

Dr. Chan has published more than 200 peer-reviewed articles and has made landmark discoveries in his field, such as how immune checkpoint therapies work in patients, how immunotherapies alter tumors during treatment and how individual genes enable certain patients to benefit more from immunotherapy. He has received numerous awards, including the National Cancer Institute Outstanding Investigator Award in 2018.

In addition to directing the new center, Dr. Chan will hold staff positions in the Lerner Research Institute's Genomic Medicine Institute and the Taussig Cancer Institute's Department of Radiation Oncology. He joins the leadership of the National Center for Regenerative Medicine at Case Western Reserve University as Co-Director, with Stanton Gerson, MD. Dr. Chan

also will collaborate with experts in Cleveland Clinic's new Center for Global and Emerging Pathogens Research, which is focused on broadening understanding of immunology and microbial pathogenesis with the goal of improving treatment for a variety of diseases, including virus-induced cancers.

He earned his MD and PhD in genetics from Johns Hopkins University, where he completed a residency in radiation oncology and a postdoctoral fellowship in tumor biology. He is board-certified in radiation oncology and is an elected member of the Association of American Physicians.

In a wide-ranging conversation, Dr. Chan discusses his research, immunotherapy's progress and potential, and his goals for the new center.

Q: How did you become interested in cancer genomics and immuno-oncology?

Dr. Chan: At Johns Hopkins, where I did my MD/PhD work, I trained as a cancer geneticist, with Bert Vogelstein and others. Even though it wasn't fully appreciated yet that the immune system plays a major role in facilitating treatment response as well as control of tumors, there was still a lot of research by people I knew there that really piqued my interest, including Drew Pardoll and Lieping Chen, whose work has really revolutionized the field of immunotherapy.

When I moved to Memorial Sloan Kettering, Jim Allison, whose lab was upstairs, and others had been developing the concept of immune checkpoint blockade. Back then, nobody had any idea that cancer genetics was linked to immunotherapy. Ipilimumab, one of the first foundational immune checkpoint blockade agents, had just come on the scene. There was a lot of skepticism about the whole concept. It was thought that there was something wrong with the immune cells themselves. Our group worked with investigators developing the first immune checkpoint agents and formulated a collaboration to try to understand how immunotherapy works and how to use this knowledge to develop new and better therapies.

The first discovery that came from our group was that it was really the cancer-specific mutations that the immune system saw and targeted when a patient got the drug to reawaken the immune

system. The mutations necessary for cancer cells to proliferate cause the cancer cells themselves to appear foreign. And that's what the immune system is all about — identifying what is foreign to the body and eliminating it. So that was a fundamental link. The mutations themselves are the targets for immunotherapy. Therefore, the more mutations a tumor has, the better one does. This concept has become fundamental in the field and contributed to the first pan-cancer FDA approval of a drug: the approval of anti-PD1 for mismatch repair-deficient tumors.

Q: That concept seems so basic now.

Dr. Chan: It was highly controversial at the time. It took a while for people to get comfortable with the idea.

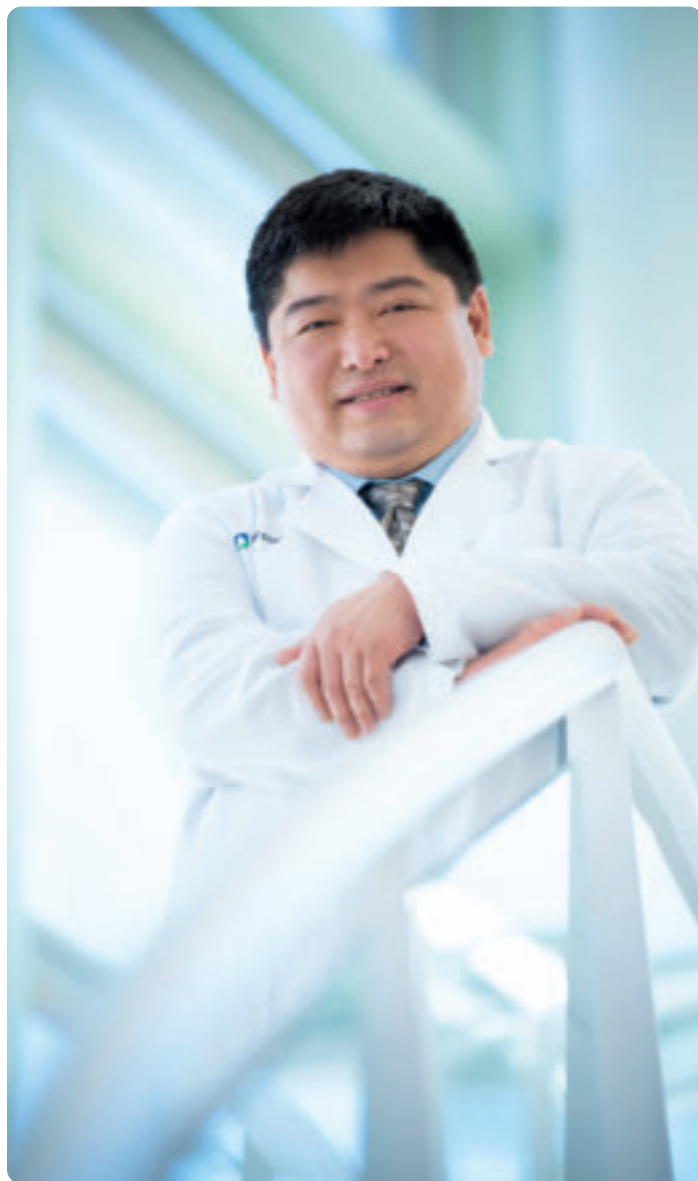
Q: The idea that cancer varies from individual to individual?

Dr. Chan: That, and that the mutation profile itself was determining the response of immunotherapy agents. I'm particularly proud that this concept has led to worldwide efforts to find smarter and better targets for cell therapy, CAR [chimeric antigen receptor] T-cells, vaccines, all sorts of things. A very good friend of mine, Luis Diaz, ran a clinical trial that showed that cancers with high mutation burdens due to mismatch repair deficiencies responded well to immunotherapy. That led to the very first FDA approval of an anticancer agent [pembrolizumab] based on a cancer's specific genetic profile and not the site where the tumor originates. That fundamentally changes how we think about things and potentially how the FDA will move forward in approving drugs.

Q: The amount of individual variation in cancer patients' tumors suggests that combinations of immunotherapy agents are the path forward.

Dr. Chan: I totally agree. And that's a good segue into some of the things that we're going to do in the Center for Immunotherapy and Precision Immuno-Oncology. We want to use big data to rationally design next-generation combination therapies. Some of the things that we're doing already, based on this concept, have pushed response rates for hard-to-treat cancers like renal cell carcinoma to about 70% to 80% with the right immunotherapy combinations. I've been treating patients for a long time, and to see response rates that were stuck at 1%-2% go beyond 70% is unbelievable.

BELOW: Timothy Chan, MD, PhD



Q: Are those response rates durable?

Dr. Chan: Yes. And I think this is just the tip of the iceberg. Using big data and identifying the new sets of rules that regulate and define success in this new family of therapies that involve the immune system are critical. With the advent of high-throughput immunoprofiling capabilities, we can really understand what drug combinations to use. This will ultimately be helpful for patients in

clinical trials because the chances of something working are going to be much greater and patients will benefit even in early-phase trials. It will also save a lot of resources and allow us to accurately and efficiently design large phase III confirmatory trials.

Q: If you're doing true precision immuno-oncology, with individually tailored treatments, how do you test that?

Dr. Chan: Cancers have multiple levels of differences and similarities. At the fundamental level, Patient A's cancer may have different mutations than Patient B's cancer. But when you move a bit broader, there are commonalities like high mutation burden or hypermethylation that can be targeted and used to design molecular-based trials, such as basket trials. A further step is an N of 1 trial design, where one can profile an individual patient and use algorithms to determine what the targeted lesions are likely to be susceptible to.

Enterprise-level cancer profiling enables the application of this philosophy — that every patient's tumor may be different, but there may be certain combinations of mutations that enable effective targeting. Identifying these immunotherapy targets is one of the most active fields in cancer research. It takes a team: people running clinical trials, computational engineers, bioinformaticians, experimental immunologists. There are a lot of very talented people here at the Taussig Cancer Institute and the Lerner Research Institute, the Robert J. Tomisch Pathology & Laboratory Medicine Institute, and all across Cleveland Clinic. The reason I was excited to come here is because the foundation for a highly impactful translational enterprise for immunotherapy is already here.

Q: Did the international scale of Cleveland Clinic's health system factor into your decision to relocate?

Dr. Chan: I think the footprint Cleveland Clinic has established, being a global enterprise, allows immunotherapy development to operate at a much higher level. We're realizing, for instance, that people around the globe have different responses to treatment, and the utility of immunotherapy may vary in different places. There's global variation, not only in cancer but in infectious diseases. We have the opportunity to conduct clinical trials, develop therapies and improve the understanding of immuno-oncology. We want

patients throughout the Cleveland Clinic system to have access to these clinical trials and to be able to get their mutation profiles, and for tailored therapies to be available based on these data. The goal is to enhance immunotherapy capability at all our different sites, so patients in each part of the world can benefit. We have opportunities to make an impact not just in cancer treatment, but in other areas such as long-term rejection in organ transplant. Cleveland Clinic is one of the largest organ transplant centers in the world. It's a great place to tackle these questions.

Q: Will the center recruit additional researchers as well as work with existing ones?

Dr. Chan: Yes. For example, we have a mandate to recruit folks who can help develop the next generation of engineered CAR T-cells, going beyond CD 19 — finding new targets, more accurate targets, for solid tumors, for instance. This will be in collaboration with the Case Comprehensive Cancer Center, which has a state-of-the-art GMP [Good Manufacturing Practice]-compliant cellular therapy manufacturing facility with six cleanrooms. There are very few like it in the United States in academic institutions. This will be a perfect seed to begin to develop new agents here that will eventually go for IND [investigational new drug] status.

Q: You've mentioned checkpoint inhibitors and engineered T-cells. What about cancer vaccines? Will that be a research priority?

Dr. Chan: The major focus of our immunotherapy efforts is vaccine development. This is something we're really going to encourage and work on collaboratively ... to build a cancer vaccine program at Cleveland Clinic. The vaccine world has undergone monumental shifts. In the past, people were largely targeting proteins that were expressed throughout the body, and in the absence of immune checkpoint blockade, there was a lot of tolerance. That's why for decades cancer vaccines have really not advanced. Partly as a result of our initial findings that tumor mutations are the targets of immunotherapy, the focus of cancer vaccines is now shifting to target neoantigens — these mutations that develop that are foreign to the body.

Q: As a radiation oncologist, you're caring for cancer patients as well as conducting research. Why do you do both?

Dr. Chan: I'll be seeing brain cancer patients and am very much looking forward to working with my colleagues in the Rose Ella Burkhardt Brain Tumor & Neuro-Oncology Center. Depending on the type of brain tumor, you can make a big difference. Some are curable, and there's a lot of joy in that. Taking part in clinical activity is critical for translational research, which is what we're all about. It pushes you to keep up with clinical literature, with what's happening in the clinical trial space, because your patients are depending on it. I cannot ever see myself not seeing patients.

Q: Considering the rapid pace of recent progress in immunotherapy and precision immuno-oncology, where do you expect the field will be in 10 or 20 years?

Dr. Chan: My dream is that we no longer need the center — that we can cure cancers, or at least extend patients' lives, by making cancer a chronic illness. But I think I would be happy if we were able to control several more diseases, if we were able to identify new therapeutic combinations and modalities that help push understanding forward. If our efforts allow patients to respond better to current and new immunotherapies and experience deep disease remission, so that a parent can see their child graduate from college or another can meet their new grandchild when previously that would have been impossible, I would call that a success.

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Dr. Chan is Director of Cleveland Clinic Cancer Center's Center for Immunotherapy and Precision Immuno-Oncology and a staff member of the Department of Radiation Oncology and the Genomic Medicine Institute.

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PRIORITIZING PATIENTS WITH RARE CANCERS AND BLOOD DISORDERS

Initiative improves access to specialists and advanced treatments

KEY POINTS

Rare cancers and blood diseases pose diagnostic and treatment challenges and often have poor outcomes.

Cleveland Clinic Cancer Center's Rare Cancers and Blood Diseases Initiative uses a multidisciplinary approach, with more than 80 experts providing clinical care and conducting research.

The initiative encompasses 40 solid tumor types and 47 liquid diseases.

Clinical trials give patients with novel cancers and blood diseases access to the latest therapeutic options.

Patients with rare cancers and blood diseases often have difficulty finding clinicians with the necessary expertise, and when they do, significant travel often is necessary to receive treatment. As a result, rare diseases are more frequently diagnosed in late stages, leading to therapeutic challenges and poor outcomes.

What defines a rare disease? While there is debate about the exact definition, at Cleveland Clinic Cancer Center a condition is considered rare when the annual incidence of new cases is two or less per 100,000 people.

"There are huge complexities associated with the diagnoses of rare conditions due to the level of pathologic expertise required, which may not be available at many institutions," notes Sudipto Mukherjee, MD, MPH, Co-Leader of Cleveland Clinic Cancer Center's Rare Cancers and Blood Diseases Initiative. "Patients can end up going to multiple doctors and facilities over several years before an accurate diagnosis is made and appropriate treatment initiated."

"Cancer centers oftentimes don't have a consistent level of evidence and research available when it comes to the best course of treatment for these uncommon diseases," adds Co-Leader Dale Shepard, MD, PhD, who focuses on solid tumors. "Without a clear path forward, this can lead to under- or overtreatment, depending on the case."

Team approach is key

Cleveland Clinic Cancer Center's Rare Cancers and Blood Diseases initiative uses a multidisciplinary approach that includes a highly sub-specialized team of medical and radiation oncologists, surgeons, radiologists and pathologists.

With more than 80 experts and growing, the rare cancers team is well-equipped to tackle

the challenges associated with these conditions. Currently, the initiative encompasses 40 solid tumors and 47 liquid diseases, including chest wall sarcomas, histologic variants of bladder cancer, B-cell neoplasms and chronic myeloid leukemia (CML).

Launched two years ago, the initiative has seen a dramatic increase in the volume of patients receiving treatment. "On the hematologic side alone, we are seeing roughly 100 to 120 cases every year," says Dr. Mukherjee, who manages hematologic malignancies and blood diseases within the initiative.

"Our efforts help ensure that patients are scheduled with an appropriate specialist within our seven-day access timeframe," he says. "This process is supported by an all-encompassing physician matrix that helps us match patients to the multidisciplinary team that best meets their needs. It highlights our team-of-teams approach to care."

Because Cleveland Clinic is a major referral center, patients may access the Rare Cancers and Blood Disease teams through multiple paths. Community providers frequently reach out to the rare cancers team when a case requires special expertise. Other times, patients themselves seek a second opinion. Additional referral avenues include support groups and social media.

"Most of these conditions have advocacy groups that we work with to help provide education, and

often we receive referrals from them as well,” says Dr. Shepard. “We are working to further develop our connection to these groups so that they know we are here to help in any way we can. We have also realized the importance of support groups on Facebook, for example, to reach patients who need assistance as they navigate an uncharted path”

Exploring new research avenues

In addition to providing highly specialized clinical care, the Rare Cancers and Blood Diseases Initiative is using its expertise and connections to build a strong research component.

“For most patients with rare diseases, there is no such thing as a standard of care,” explains Dr. Mukherjee. “In an effort to change this, we have several clinical trials underway and are in the process of opening more in the months and years ahead.”

For instance, Dr. Shepard opened a trial for patients with epithelioid hemangioendothelioma, a rare subtype of sarcoma that only has about 300 new cases diagnosed per year.

“Within a fairly short period of time, we put three patients on the clinical trial, which will hopefully help us better understand the optimal treatment approach,” he says. “This is an example of how we are tapping into the expertise of our team to benefit the research community and, ultimately, our patients.”

Recently published studies involving Rare Cancers and Blood Diseases research include:

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

There are a number of ongoing and planned studies involving rare solid and liquid tumors, as well as novel blood diseases.

“In the near future, we will be opening a clinical trial that will include whole exome sequencing on the tissue specimens of patients with histiocytic disorders and Castleman disease,” says Dr. Mukherjee. “I believe, when that study is finished, we will gain a fundamental

understanding about any novel mutations, which could become therapeutic targets in future clinical trials.”

The rare cancers initiative also collaborates with organizations that support research and facilitate connections among scientists at various institutions. “We are a participating member of the Castleman Disease Collaborative Network and the North American Consortium for Histiocytosis,” says Dr. Mukherjee.

“Cleveland Clinic Cancer Center is also part of the Cure CML Consortium, which allows us to open clinical trials more quickly and give patients access to new therapeutic options,” he says. “Our team is seeking additional opportunities to help facilitate the growth of other rare disease consortiums.”

Making the commitment

Building a foundation that supports rare conditions requires significant commitment and resources. Cleveland Clinic and the Taussig Cancer Institute have provided that, the two physicians say.

“This endeavor is a top priority across our institution,” Dr. Shepard says. “Rare diseases actually constitute a larger portion of the cancer patient population than most people realize. We want to ensure that these patients receive comprehensive, responsible care.”

The Rare Cancers and Blood Diseases team is committed to broadening its expertise and scope.

“We have been offering patients with traditional cancers access to exceptional care for years,” Dr. Mukherjee says. “We want to be able to do the same for those with rare conditions. Our team is dedicated to developing our expertise and skills so we can confidently say that rare diseases are not rare to us.”

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Dr. Mukherjee is a staff member of Cleveland Clinic Cancer Center’s Department of Hematology and Medical Oncology and a Clinical Assistant Professor of Medicine at Cleveland Clinic Lerner College of Medicine.

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CANCER PROGRAM ON THE RISE AT CLEVELAND CLINIC ABU DHABI

New oncology building will help centralize treatment and research

The nine-story tower rising on the campus of Cleveland Clinic Abu Dhabi is more than a building under construction. It is evidence of an ambitious project: to re-create one of the United States' top cancer care and research programs in a new setting and adapt it to meet the needs of Middle Eastern patients.

"Our goal is to transform the approach to cancer care across the region," says Stephen Grobmyer, MD, Chair of Cleveland Clinic Abu Dhabi's Oncology Institute, which will be housed in the 200,000-square-foot building opening in 2022. "We plan to utilize our strong relationships with Cleveland Clinic Cancer Center, learn from the many successes the oncology program has had at our main campus and apply those lessons here."

Planning for the oncology program began soon after Cleveland Clinic Abu Dhabi's opening in 2015. Cancer treatment services currently include advanced diagnostic imaging and surgical procedures, as well as chemotherapy and other infusions, supported by disease-specific tumor boards.

When the Oncology Institute's new facility opens, services will expand to include radiation oncology, and patients will have access to multidisciplinary teams and multimodal care in a single location.

"There is a huge opportunity to standardize and streamline care and to improve things like survivorship and palliative care, which historically have not been part of the mainstream of cancer care in the region," says Dr. Grobmyer. "Our long-term goal is to offer everything that is available at main campus."

In the new center, reducing time from cancer diagnosis to treatment will remain a focus. Further, there will be increasing coordination among care providers, leveraging knowledge from Cleveland Clinic Cancer Center as well as its expertise in genetic counseling and cancer pathology. The two institutions plan to collaborate on tumor boards.

The Oncology Institute also plans to increase the availability of genetic testing to inform and personalize cancer treatment.

"We've gained a lot of knowledge about the genetic causes of cancer,

but patients in this region have historically been underrepresented in those studies," Dr. Grobmyer says. "We want to understand whether genetic associations with certain cancers apply here, or whether we have different issues in terms of addressing cancer prevention and treatment relative to our patient populations. Based on our experience, the region seems to have an increased incidence of thyroid cancer that we don't understand. We're starting some studies to examine possible genetic markers. There may also be environmental factors. It's our mission to address the specific cancer issues of people in the Gulf region."

Another major Oncology Institute effort will be to improve access to clinical trials for the region's cancer patients. "For many types and stages of cancer, clinical trials are the gold standard of care," Dr. Grobmyer says. "We need to make it possible for our patients to participate." The diversity of the region's population, in turn, will improve the generalizability of the clinical trials' results.

The Oncology Institute is working to enhance cancer data collection with a tumor registry that will contribute to improved understanding of cancer patterns in the region.

The institute also is leading the way in cancer screening — an important initiative in a part of the world where cancer incidence and deaths are projected to nearly double by 2030. Cleveland Clinic Abu Dhabi offers cervical and colon cancer screening and recently launched breast cancer screening, and it operates the only center for lung cancer screening in Abu Dhabi.

The institute currently is recruiting cancer specialists from around the world for its staff and eventually will establish a residency program to train future oncologists. Dr. Grobmyer says staff members "are attracted by the tremendous opportunity to create something new and to improve the diagnosis and treatment of cancer."

CLEVELAND CLINIC CANCER CENTER WELCOMES RECENTLY APPOINTED STAFF MEMBERS

[Mohammed Yaser Al-Marrawi, MD](#), is a staff member of the Department of Regional Oncology. Dr. Al-Marrawi received his medical degree from Damascus University. He completed an internship and an internal medicine residency at Reading Health System in Reading, Pennsylvania, a hematology/oncology research fellowship at Cleveland Clinic, and a hematology/oncology fellowship at Penn State Health Milton S. Hershey Medical Center.

[Adriana Alvarez, MD](#), is an associate staff member of the Department of Regional Oncology. Dr. Alvarez received her medical degree from Universidad Nacional de Cordoba-Argentina. She completed an internal medicine internship at Air Force Hospital, Cordoba, Argentina; an internal medicine residency at Danbury Hospital, Connecticut; and a hospice and palliative medicine fellowship at Cleveland Clinic.

[Shilpa Gupta, MD](#), is a staff member of the Department of Hematology and Medical Oncology specializing in genitourinary cancers. Dr. Gupta received her medical degree from the Lady Hardinge Medical College in New Delhi, India. She completed an internal medicine residency at the University of Connecticut Health Center, and fellowships in hematology-oncology and genitourinary oncology translational research at Thomas Jefferson University in Philadelphia. Prior to joining Cleveland Clinic, Dr. Gupta was a faculty member of the University of Minnesota's Masonic Cancer Center, where she led the Interdisciplinary Solid Tumor Phase 1 Program.

[Khaled Hassan, MD](#), is a staff member of the Department of Hematology and Medical Oncology specializing in lung cancer. Dr. Hassan received his medical degree from Russia's Kursk State Medical University. He completed an internal medicine residency at Good Samaritan Hospital of Maryland and a hematology/medical oncology fellowship at the University of Michigan.

[Suneel Kamath, MD](#), is a staff member of the Department of Hematology and Medical Oncology specializing in gastrointestinal cancers. Dr. Kamath received his medical degree from Columbia University Medical Center. He completed an internship, an internal medicine residency and a hematology/oncology fellowship at

McGaw Medical Center of Northwestern University.

[Jack Khouri, MD](#), is an associate staff member of the Department of Hematology and Medical Oncology specializing in myeloma. Dr. Khouri received his medical degree from the University of Balamand, Tripoli, Al-Kura, Lebanon. He completed an internal medicine internship at Saint George Hospital, Ashrafieh, Lebanon; an internal medicine residency at Tufts University School of Medicine; and a hematology/oncology fellowship at Cleveland Clinic.

[Erin Roesch, MD](#), is an associate staff member of the Department of Hematology and Medical Oncology specializing in breast cancer. Dr. Roesch received her medical degree from the University of Toledo College of Medicine. She completed an internal medicine residency at The Ohio State University Wexner Medical Center and a hematology/oncology fellowship at Georgetown University Hospital.

[Melissa Walt, PsyD](#), is a staff member of Cleveland Clinic Cancer Center specializing in the psychological treatment of individuals with cancer, including adjustment to initial diagnosis and chronic illness, issues of grief and loss, chronic pain management, mood and anxiety disorders, and stress management. Dr. Walt received her clinical psychology degree from Adler University in Chicago. She completed a clinical psychology residency at the Veterans Administration Southern Nevada Healthcare System and a psychology fellowship at the Memphis Veterans Administration Medical Center.

[Elizabeth Weinstein, MD](#), is a staff member of the Department of Hematology and Medical Oncology specializing in palliative medicine. Dr. Weinstein received her medical degree from the University of Pittsburgh School of Medicine. She completed an internal medicine residency at Montefiore Hospital/University Health Center of Pittsburgh and a hospice and palliative medicine fellowship at the University of Pittsburgh.

[Allison Winter, MD](#), is an associate staff member of the Department of Hematology and Medical Oncology specializing in lymphoma. Dr. Winter received her medical degree from the Wake Forest School of Medicine. She completed an internal medicine residency and a hematology/oncology fellowship at Cleveland Clinic.

LEADERSHIP APPOINTMENTS AND HONORS

NEW BREAST CANCER AND CASE COMPREHENSIVE CANCER LEADERSHIP

Halle Moore, MD, recently was named Cleveland Clinic Cancer Center's Director of Breast Medical Oncology and Co-Director of the Comprehensive Breast Program.

Dr. Moore is a board-certified medical oncologist who has served in the Department of Hematology and Medical Oncology since 1999. She is an Associate Professor of Medicine at Cleveland Clinic Lerner College of Medicine. She specializes in the medical management of breast cancer. Her research focuses on breast cancer treatment and issues related to cancer survivorship.

Dr. Moore was lead investigator and author of the practice-changing Prevention of Early Menopause Study, which demonstrated a method of protecting ovarian function during chemotherapy treatment for breast cancer in young women. She is a national co-chair for the SWOG Cancer Research Network's Survivorship Committee and serves on the survivorship panel for the National Comprehensive Cancer Network's Clinical Practice Guidelines.

Dr. Moore intends to continue the breast cancer program's focus on survivorship, research and innovation and to support collaboration throughout the enterprise to grow the program. "We already have a great foundation on which to build," she says. "I am looking forward to developing our areas of expertise even further."

Mikhael Sekeres, MD, MS, has been appointed Associate Director for Clinical Research for the Case Comprehensive Cancer Center (CCCC). In this position, Dr. Sekeres will oversee the CCCC's portfolio of clinical trials, translation of basic laboratory findings to clinical application and the conduct of clinical investigations. He will be responsible for the Clinical Research Office, the Protocol Review and Monitoring Committee, and the Data and Safety Monitoring Committee, which collectively oversee therapeutic cancer clinical trials. He has been a member of the CCCC Executive Committee since 2014 as Deputy Associate Director for Clinical Research, where he oversaw the Clinical Research Operations Committee and was responsible for development and maintenance of policies and procedures that govern clinical research across the consortium. Dr.

Sekeres is Director of Cleveland Clinic Cancer Center's Leukemia Program and Vice Chair for Clinical Research. His book, *When Blood Breaks Down: Life Lessons from Leukemia*, was recently published by MIT Press. He is a regular medical columnist for the *New York Times*.

ERIC KLEIN, MD, RECEIVES PRESTIGIOUS PROSTATE CANCER RESEARCH AWARD

Eric A. Klein, MD, Chairman of Cleveland Clinic's Glickman Urological & Kidney Institute, is the recipient of the Urology Care Foundation's 2020 Richard D. Williams, MD, Prostate Cancer Research Excellence Award. The award is presented annually to recognize outstanding and impactful work in prostate cancer research during the past 10 years.

Throughout his career, Dr. Klein has made significant contributions to elevate clinical, genomic and preventive aspects of prostate cancer treatment. He has authored more than 600 scientific papers and book chapters and is a frequent lecturer and visiting professor at national and international universities. Dr. Klein also serves as editor-in-chief of *Urology*.

More recently, he has led clinical efforts to develop and validate IsoPSA™, a prostate-specific antigen assay designed to detect high-grade, clinically significant prostate cancers and reduce unnecessary prostate biopsies. His expertise in liquid biopsy positioned him to lead several high-profile clinical trials examining the effectiveness of this approach in screening for other types of cancer — a modality that could shift the diagnostic paradigm for cancer.

Dr. Klein was nominated for this honor by the Society of Urologic Oncology and was selected by a review committee. "I am deeply humbled and honored to be recognized with this award by my esteemed colleagues," he says. "My research accomplishments are all done in service of our patients. That includes the patients I have the privilege of caring for — and those whom I will never meet."

Dr. Klein holds the Glickman Urological & Kidney Institute's Andrew C. Novick Distinguished Professor Chair and has joint appointments in the Taussig Cancer Institute and Lerner Research Institute.

LET'S TALK ABOUT FEAR

Addressing anxieties is a key to managing during the pandemic



BRIAN J. BOLWELL, MD, FACP

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Fear is an inevitable part of cancer care — for patients facing a life-threatening disease, and for oncologists who manage difficult cases and often have to deliver bad news.

We all develop ways of coping, imperfect though they may be.

The coronavirus pandemic has added a new dimension of fear. Many caregivers are afraid to physically be with patients, and patients needing care are afraid to visit a doctor or hospital. As a leader, I have never dealt with anything so challenging. I am no expert at managing fear. But I want to share what has seemed to work well for us at Cleveland Clinic Cancer Center.

First, we have created the safest possible healthcare environment. We have greatly expanded our telemedicine capabilities, to accommodate patients who do not require in-person care. We have modified our clinical areas to reduce infection risk, with visitor restrictions, social distancing, and masks, temperature scans and health status checks for caregivers and patients. We have reached out to cancer patients to stress the importance of ongoing care.

Second, we have strived to communicate regularly, directly and honestly with our caregivers about the COVID-19 situation.

That starts with me showing up and being accessible every day in the cancer center. I also write a daily email update to our staff, summarizing institutional, national and international data and developments on the pandemic.

In this email and in my other contacts with my colleagues, I also share my own feelings and experiences regarding COVID-19. I have confessed my worries about handling mail, my search for a good moisturizer after frequent hand-washings, and my less-than-stellar attempts at home cooking.

I recount these things not because my situation is unique or deserves special attention; it is precisely the opposite. Everyone has similar concerns. Everyone can relate. Making these human connections reduces fear and reminds us that we are all in this together — that we need each other to get through.

Revealing vulnerabilities does not make a leader weak. It is a sign of authenticity, of humanity. Our shared humanity is stronger than fear. It is the bond that holds our cancer center together.

VIRTUAL VELOSANO

Due to the COVID-19 pandemic, VeloSano, the fundraising initiative to support cancer research at Cleveland Clinic Cancer Center, has created virtual fundraising activities in lieu of its flagship July *Bike to Cure* event. There are no registration fees or fundraising minimums, and participation extends to Oct. 1, 2020. To learn more, visit velosano.org. To date, VeloSano has raised more than \$21 million, with 100% of the funds going to research projects to develop new cancer diagnostics and therapeutics.

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ABOUT CLEVELAND CLINIC

Cleveland Clinic is a nonprofit, multispecialty academic medical center integrating clinical and hospital care with research and education for better patient outcomes and experience. More than 3,900 staff physicians and researchers in 180 medical specialties provide services through 26 clinical and special expertise institutes. Cleveland Clinic comprises a main campus, 11 regional hospitals and more than 150 outpatient locations, with 19 family health centers and three health and wellness centers in northern Ohio, as well as medical facilities in Florida, Nevada, Toronto and Abu Dhabi. Cleveland Clinic is currently ranked as one of the nation's top hospitals by *U.S. News & World Report*.

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UPCOMING CONTINUING MEDICAL EDUCATION EVENTS

(Information is subject to change. Please visit clevelandclinicmeded.com for latest updates and registration.)

August 21 – 22

22nd Annual Brain Tumor Update and 11th Annual Symposium on Brain and Spine Metastases Course (*virtual*)

October 19 – 23

Leksell Gamma Knife® Icon Training Course (*virtual*)

November 12 – 14

Cleveland Clinic Microscopic and Endoscopic Skull Base Surgery Workshop – Weston, FL

December 14 – 18

Leksell Gamma Knife® Icon Training Course (*virtual*)