

# Cancer **Advances**

Cleveland Clinic Cancer Center | Summer 2016

Researchers Find  
**Genetic Basis** for Cancer's  
Varying Vulnerability to  
DNA Damage

**Also Inside:**

'Striking' Immunotherapy  
Results in Metastatic  
Urothelial Cancer

New Metastatic Colon  
Cancer Research Center

Predicting Aggressive  
Prostate Cancers

Staged Radiosurgery for  
Previously Untreatable  
Brain Metastases

## Table of Contents

.....

Researchers Find Genetic Basis for  
Cancer's Varying Vulnerability to DNA  
Damage...3

Immunotherapy Shows 'Striking'  
Results in Metastatic Urothelial  
Cancer...7

New Center Driving Collaboration to  
Combat Metastatic Colon Cancer...10

Study Reveals Poorer Malignant  
Melanoma Outcomes in Women  
Diagnosed During Pregnancy...12

New Cancer Building Will Enhance  
Multidisciplinary Care...14

Variation in Treatment of Cancer-  
Associated Thrombosis: Can  
Management Be Standardized?...16

Chairman's Q&A: Brian J. Bolwell,  
MD, FACP, Talks About the Cancer  
Moonshot...18

Patterns of DNA Methylation May  
Differentiate Indolent and Aggressive  
Prostate Cancers...20

Novel Urine Biomarker *PCA3* May  
Improve the Prediction of Aggressive  
Prostate Cancer...22

Highlights from the ASCO Annual  
Meeting...23

Case Study: Pioneering Use of  
Staged Radiosurgery for Previously  
Untreatable Brain Metastases...24

Save the Date: Continuing Medical  
Education...26

Dale Shepard, MD, PhD, Earns NCI  
Team Leadership Award...26

New Staff...27

Resources for Physicians...28

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**On the cover:** A team including Cleveland  
Clinic Cancer Center researchers has  
identified a variety of genetic determinants  
that enable cancer cells to survive after  
exposure to radiation, setting the stage  
for predictive radiation susceptibility  
biomarkers and targeted radiotherapies.

Photo: © Russell Lee

## Welcome to *Cancer Advances*.

Regular readers of this biannual publication, which highlights research and clinical developments at Cleveland Clinic Cancer Center, may notice a slight name change from past issues of *Cancer Consult*.

We think *Cancer Advances* better reflects our emphasis on high-impact, translational cancer research and innovative therapies. We are transforming how we care for cancer patients, and greatly improving the setting for and efficiency of that care with the opening of our new \$276 million cancer facility next spring. (See P. 14 to learn how the new building enhances multidisciplinary lung cancer collaboration.) *Cancer Advances* signifies our constant quest to break boundaries.

The research that Cleveland Clinic Cancer Center radiation oncologist **Mohamed Abazeed, MD, PhD**, is conducting is a good example. In the past decade, genomic insights have helped us better understand, predict and modify individual patients' response to chemotherapies. Until now, that sort of progress has been absent from radiation therapy, which is applied without a fundamental understanding of the genetic complexities that may cause varied outcomes among patients. Our cover story describes groundbreaking work by Dr. Abazeed and colleagues to uncover a genetic basis for cancer's varying vulnerability to radiation-induced DNA damage. The research sets the stage for predictive radiation-susceptibility biomarkers and targeted radiotherapies that exploit the genetic alterations present in a patient's tumor.

Also inside, you can read about:

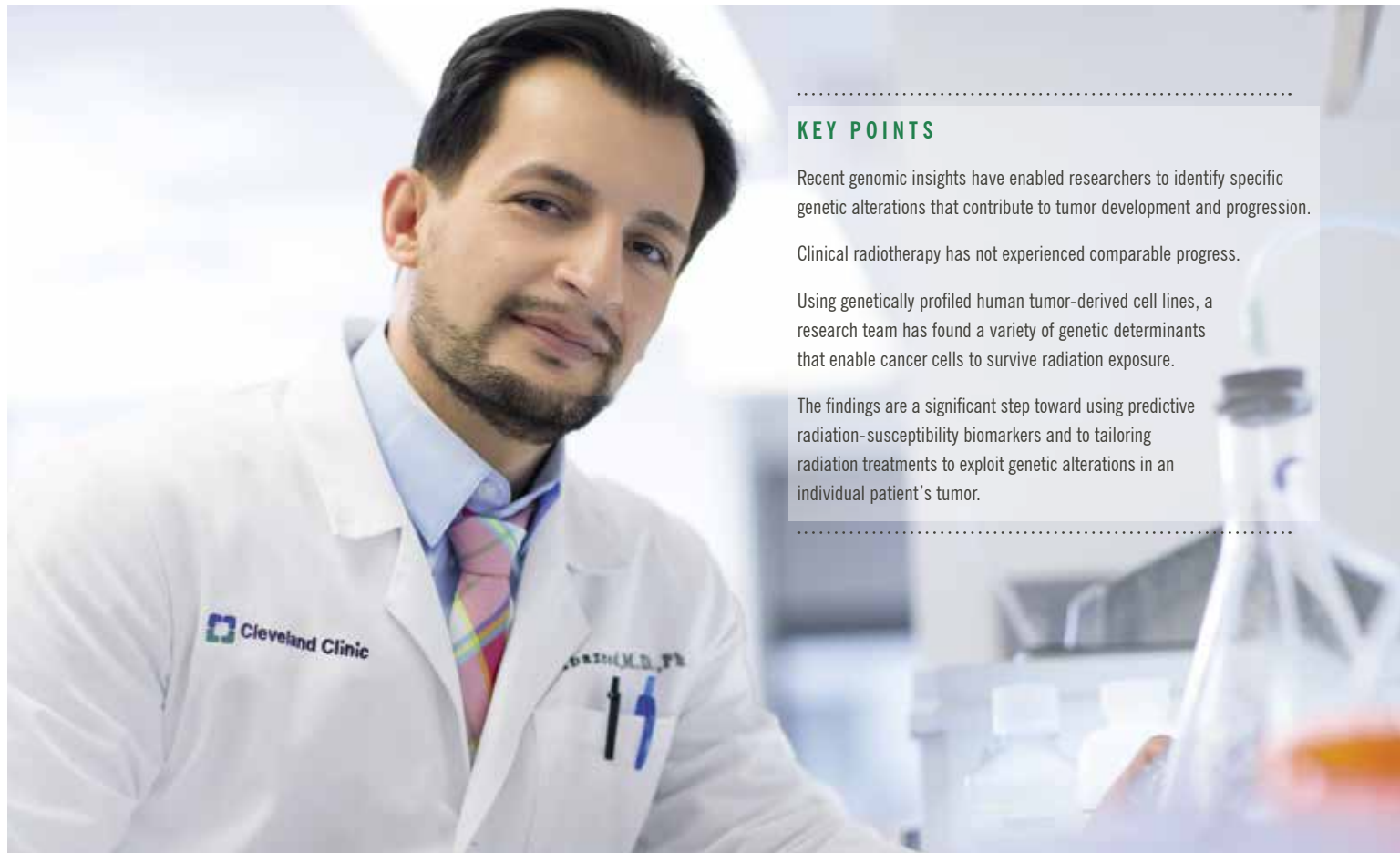
- Results of a phase II trial of atezolizumab, an immune checkpoint inhibitor that shows the first significant improvement in the systemic treatment of metastatic urothelial cancer in 30 years
- A Cleveland Clinic study confirming a troubling association between pregnancy and poor malignant melanoma outcomes
- The launch of our new Research Center of Excellence in Colon Cancer Metastasis, which unites basic, translational and clinical researchers in the search for new treatments and technologies
- My conversation about Cleveland Clinic Cancer Center's input in Vice President Biden's cancer moonshot initiative
- The development of a new predictive tool to identify patients at risk for prostate cancer, especially high-grade cancer, at initial biopsy, based on expression of the prostate cancer antigen 3 gene
- More prostate cancer research involving the use of advanced molecular techniques to reveal DNA methylation patterns that may help clinicians differentiate between indolent and aggressive disease
- Research that documents substantial nationwide variation in cancer-associated thrombosis anticoagulant care and suggests how to address it
- An informative case study about a resilient osteosarcoma patient and our pioneering use of staged radiosurgery to treat his brain metastases

Congratulations are in order for **Dale Shepard, MD, PhD**, the Director of our Phase I Clinical Trials Program, whose dedicated work to expand that effort has earned him the National Cancer Institute's 2016 Cancer Clinical Investigator Team Leadership Award.

As always, I welcome the chance to discuss the research projects and treatment initiatives underway at Cleveland Clinic Cancer Center and the possibilities for collaboration. Our Cancer Answer Line staff at 866.223.8100 is ready to help you with patient appointment referrals, clinical issues and other information. And our blog for cancer clinicians, *Consult QD/Cancer*, ([clevelandclinic.org/ConsultQDCancer](http://clevelandclinic.org/ConsultQDCancer)) provides timely oncology insights and perspectives from our experts.

Sincerely,

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## KEY POINTS

Recent genomic insights have enabled researchers to identify specific genetic alterations that contribute to tumor development and progression.

Clinical radiotherapy has not experienced comparable progress.

Using genetically profiled human tumor-derived cell lines, a research team has found a variety of genetic determinants that enable cancer cells to survive radiation exposure.

The findings are a significant step toward using predictive radiation-susceptibility biomarkers and to tailoring radiation treatments to exploit genetic alterations in an individual patient's tumor.

# Researchers Find **Genetic Basis** for Cancer's Varying Vulnerability to DNA Damage

A team including Cleveland Clinic researchers has identified a variety of genetic determinants that enable cancer cells to survive after exposure to radiation.

*Dr. Abazeed is an associate staff member of Cleveland Clinic Cancer Center's departments of Radiation Oncology and Translational Hematology and Oncology Research. He is also an Assistant Professor of Medicine at Cleveland Clinic Lerner College of Medicine. He can be reached at [abazeem@ccf.org](mailto:abazeem@ccf.org) or 216.445.0061.*

The groundbreaking research, which utilized a collection of 533 genetically profiled human tumor-derived cell lines, found that the cells' sensitivity to ionizing radiation results from significant underlying biological diversity within and across lineages.

"Our team's research helps explain why individual tumors may vary in their susceptibility to DNA-damaging radiation and drugs," says Cleveland Clinic radiation oncologist Mohamed Abazeed, MD, PhD, the lead author of the study published in *Nature Communications*.

The researchers showed that overall and individual somatic copy number alterations, gene mutations, and the expression of individual genes and gene sets correlated with cancer cells' ability to survive radiation exposure.

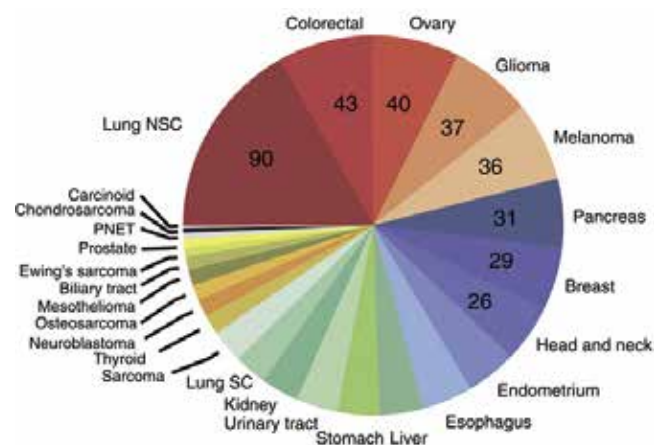
Characterizing genetic factors that dictate cellular response to radiation is a fundamental step toward using biomarkers to predict individual cancer patients' radiotherapy outcomes, and to tailoring radiation treatments to exploit the genetic alterations present in a patient's tumor.

Although cancer genomes can be diverse, the researchers found that relevant alterations were frequent and spanned multiple cancer types. This suggests that combinations of only a limited number of functionally relevant alterations can confer resistance to therapeutic radiation within and across cancer types. Accordingly, this makes the task of personalization substantially less daunting since patients can be binned into more homogenous groups. "The findings suggest that the promising strategies of personalized,

(continued on page 4)

RESEARCHERS FIND GENETIC  
BASIS FOR CANCER'S VARYING  
VULNERABILITY TO DNA DAMAGE  
(CONTINUED)

**Figure 1. Variation in cancer cell line survival after radiation-induced damage.**



Distribution of cancer types profiled by lineage.

genetically targeted cancer therapies can be extended to radiation therapy, and that we can develop predictive tools to guide clinical decision-making with improved patient selection and more precise drug-radiation combinations,” Dr. Abazeed says.

#### Seeking to Optimize Radiotherapy

Recent advances in genomic sequencing and analysis have enabled researchers to identify specific genetic alterations that contribute to tumor development and progression. These biomarkers have begun to serve as predictive tools that can indicate which patients may benefit from drugs targeting specific mutations and affected molecular pathways.

Clinical radiotherapy has not experienced comparable progress from these genomic insights. While radiotherapy contributes significantly to the curative and palliative cancer treatments, it is presently targeted based on the origin of the cancer and does not take into account the genetic complexity that may influence therapeutic response. The effectiveness of radiotherapy is tempered by a lack of biomarkers that can reliably predict tumors' varying sensitivity to ionizing radiation and inform treatment decisions.

Dr. Abazeed and his collaborators studied the genetic determinants of cancer cells' survival after irradiation using large-scale, high-throughput profiling of 533 genetically annotated human

tumor cell lines encompassing 26 cancer types. The research was conducted by investigators at Cleveland Clinic, Case Western Reserve University, Korea's Seoul National University College of Medicine, the Broad Institute at MIT and Harvard, the Dana-Farber Cancer Institute, Harvard University, and the Howard Hughes Medical Institute.

The researchers assessed clonogenic survival in the cell lines as a function of radiation dose and found significant survival variation across and within lineages — as large as five- to sevenfold in the latter (Figure 1).

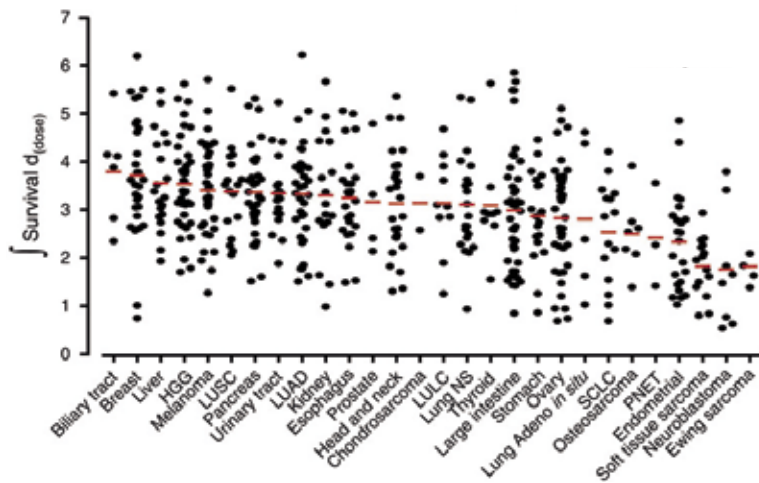
“We found that the responses of cancers to DNA-damaging therapy are incredibly diverse,” Dr. Abazeed said. “Although oncologists have anecdotally appreciated the diversity of cancer's response to radiation treatments, our study formalizes this diversity across 26 cancer types.”

The researchers next investigated the ability of several genetic factors to impact post-radiation cellular survival.

#### Probing the SCNA/Radiation Relationship

Somatic copy number alterations (SCNAs) are common in cancer and promote oncogenesis, but their relationship to cellular irradiation response has been unclear. Dr. Abazeed and his colleagues measured the fraction of each tumor genome that contained an SCNA ( $f$ SCNA) and found a positive correlation between  $f$ SCNA and radiation survival.





Integral survival is displayed by column scatter plot separated by lineage and histology where appropriate.

## Reference

Yard BD, Adams DJ, Chie EK, Tamayo P, Battaglia JS, Gopal P, Rogacki K, Pearson BE, Phillips J, Raymond DP, Pennell NA, Almeida F, Cheah JH, Clemons PA, Shamji A, Peacock CD, Schreiber SL, Hammerman PS, Abazeed ME. A genetic basis for the variation in the vulnerability of cancer to DNA damage. *Nat Commun.* 2016 Apr 25;7:11428.

They surmised that this could be due to either:

- Tumor cells having increased capacity to repair radiation-induced DNA double-strand breaks using the same mechanisms that create SCNAs, or
- Individual SCNAs changing the expression of specific genes within structurally altered chromosomal segments to regulate survival

By correlating radiation survival with gene expression within altered segments, the researchers determined that SCNAs regulate cellular radiation-damage response in part through direct gene expression changes.

SCNA frequency and distribution varied across tumor lineages, the investigators found, with colorectal, uterine and ovarian cancers showing a positive correlation between *f*SCNA values and cellular survival.

Further, in the uterine and colorectal cell lineages they discovered a correlation between radiation survival and SCNA, an anti-correlation between radiation survival and mutation frequency, and correlations between mutations in individual genes and radiation sensitivity. Collectively, these indicate a relationship between low SCNA, high mutation frequency, gene disruption of DNA repair and radiation sensitivity in uterine and colorectal cancer cell lines.

## Looking at Genes and Gene Pathways

The researchers then identified gene mutations associated with radiation sensitivity. A majority of the 19 most strongly correlated genes had not previously been implicated in radiation-induced damage response. Further analysis revealed that certain mutations directly regulated cellular radiation response rather than merely having an association with radiation sensitivity. For example, mutations in *KEAP1* confer radiation resistance by regulating oxidative damage response.

The investigators also found that genetic pathways are differentially correlated with radiation response. Top pathways correlated with radiation sensitivity included DNA damage response, cell cycle, chromatin organization and RNA metabolism, while pathways correlated with radiation resistance included cellular signaling, lipid metabolism and transport, stem-cell state, cellular stress, and inflammation.

This diversity of pathways across tumor lineages suggests that extensive cellular processes play a role in survival after irradiation, and reveals several cellular receptors that may be targetable for radiosensitization.

## An In Vivo Testbed for Radiosensitivity

Breast cancer provides a good example of the potential therapeutic benefits of identifying predictive biomarkers for radiation therapy.

(continued on page 6)

RESEARCHERS FIND GENETIC  
BASIS FOR CANCER'S VARYING  
VULNERABILITY TO DNA DAMAGE  
(CONTINUED)

Although breast-conserving surgery and mastectomy can eliminate detectable macroscopic cancer, tumor foci can remain in local and regional tissue. Radiotherapy significantly reduces the odds of recurrence and mortality, but some patients are more likely than others to fail treatment. Determining who is at risk is a priority.

Analyzing breast cancer cell lines, Dr. Abazeed and colleagues looked for genetic determinants of cellular radiation survival in breast cancer. They found multiple genetic pathways associated with radiation resistance. One of the most strongly correlated gene sets was linked to androgen signaling.

Androgen receptor (AR) expression has been found to promote radiation resistance in prostate cancer, and the combination of androgen blockage and radiotherapy is the standard of care for locally advanced disease. Abnormally high AR expression has been detected in most breast cancers but its role in breast oncogenesis is unclear.

Using various testing methods, the researchers demonstrated for the first time that AR expression plays a pivotal role in protecting breast cancer cells from DNA damage, and that the suppression of androgen signaling in breast cancer cells that express AR results in increased DNA damage.

To test AR's radioprotective role in vivo, the researchers created orthotopic xenografts by injecting AR-positive breast cancer-derived cells into the inguinal mammary glands of female immunodeficient mice. When tumors developed, the mice were randomized to receive one of four treatments: mock; the potent AR agonist enzalutamide (ENZ); ionizing radiation; or ENZ and radiation. The combined ENZ/radiation therapy more effectively suppressed tumor growth than either modality separately.

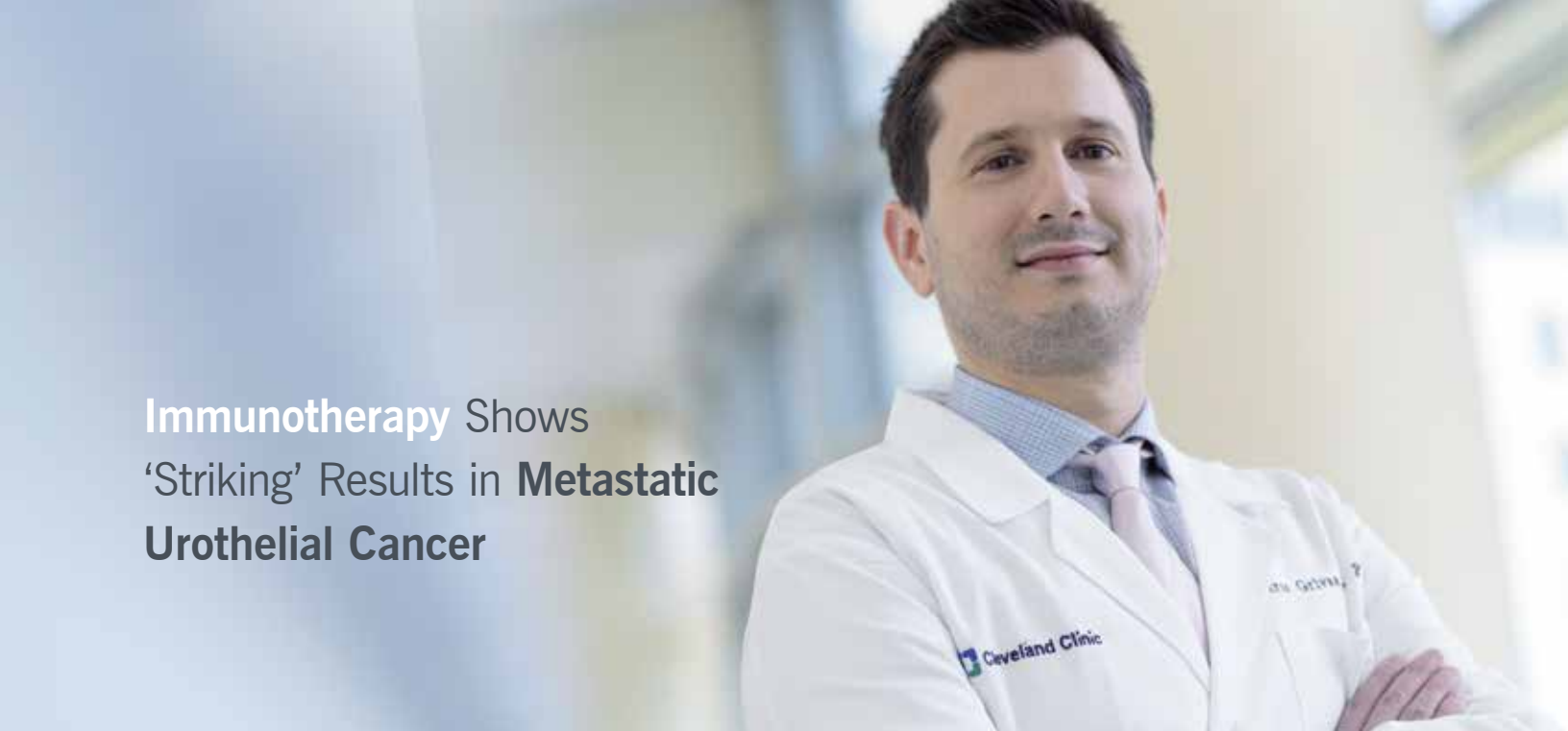
Using Findings to Develop Predictive Tests and  
Guide Treatment

The researchers' determination that there is a genetic basis for cancer cells' variable vulnerability to radiation has both diagnostic and therapeutic implications. Genetic alterations that dictate cellular response to DNA damage could be used predictively to assess individual patients' likely response to radiotherapy, to suggest possible combinatorial therapy strategies, and to indicate opportunities for precision targeting of molecular pathways that confer radioresistance.

"We can potentially bin patients into more homogeneous categories that are likely to maximize their ability to respond to our therapies," Dr. Abazeed said. "Our initial work has spawned several confirmatory studies in multiple cancer types. We are actively working on developing certified genetic tests that are destined to be incorporated into clinical practice. These tests are designed to assist the oncologist in identifying patients who are more or less likely to respond to these treatments."

The findings may help shift the use of radiotherapy and DNA-damaging drugs from the current generic, population-based approach to a much more personalized application guided by the genetic alterations present in an individual patient's tumor.

"Cancer treatments are currently guided by population studies of genetically heterogeneous patients," Dr. Abazeed said. "We and others believe that grouping patients in this manner is a suboptimal strategy, namely because it does not reflect the uniqueness of individual patients. Our work to date represents the construction of a critical scaffold that will serve as a basis for future studies."



## Immunotherapy Shows 'Striking' Results in **Metastatic Urothelial Cancer**

The immune checkpoint inhibitor atezolizumab showed promising, lasting efficacy in patients with locally advanced or metastatic urothelial cancer, according to results of a phase II clinical trial<sup>1,2</sup> conducted by an international team including Cleveland Clinic oncologist Petros Grivas, MD, PhD.

The findings represent the first significant improvement in the systemic treatment of metastatic urothelial cancer in 30 years — a very encouraging development for patients whose prognosis after relapse has been dismal.

"These are practice-changing results that confirm data from the phase I trial of atezolizumab," Dr. Grivas says. "Although the overall response rate was lower compared to what was noted in the phase I trial,<sup>3</sup> it still compares favorably to historical second-line cytotoxic chemotherapy. The Food and Drug Administration's approval of atezolizumab on May 18, 2016, provides a new standard treatment option for platinum-resistant advanced/metastatic urothelial cancer."

### Trying to Break a Therapeutic Logjam

Urothelial carcinoma is by far the most common type of bladder cancer, and the ninth most common cancer worldwide. It kills more than 165,000 people each year, including an estimated 15,000 Americans in 2015. It causes significant morbidity and healthcare expenses.

There have been no major advances in the systemic treatment of urothelial cancer since the development of combination platinum-based chemotherapy three decades ago. Median

overall survival in previously untreated patients with metastatic urothelial cancer who receive platinum-based chemotherapy is approximately 15 months. Prognosis for patients who relapse is grim, with median survival of 5 to 7 months.

Response rates to cytotoxic chemotherapy are low in patients with platinum-resistant advanced urothelial cancer, and side effects may reduce patients' quality of life and may make treatment intolerable. There is no FDA-approved second-line chemotherapy agent.

Immunotherapy offers the potential to overcome this therapeutic impasse. Immune checkpoint inhibitors that enhance anti-tumor immunity already have shown breakthrough results in treating metastatic renal cell carcinoma, melanoma, non-small cell lung cancer and Hodgkin lymphoma.

Dr. Grivas and colleagues at 70 academic medical centers in the United States, Canada and Europe sought to determine the safety and efficacy of atezolizumab, a humanized monoclonal antibody against programmed death ligand 1 (PD-L1), in patients with advanced urothelial carcinoma whose disease had progressed after

(continued on page 8)

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*Dr. Grivas has consulting agreements with Genentech and has participated as a speaker in an unbranded, non-product-related educational program for the pharmaceutical company, which is the developer of atezolizumab.*

# IMMUNOTHERAPY SHOWS ‘STRIKING’ RESULTS IN METASTATIC UROTHELIAL CANCER (CONTINUED)

platinum-based chemotherapy (cohort 2) or who were ineligible for cisplatin (cohort 1).<sup>4</sup> The FDA’s approval of atezolizumab was based on published results from cohort 2.<sup>1</sup>

## Negating Tumor-Mediated Immunosuppression

Urothelial carcinoma has high rates of somatic mutations, which should enhance the host immune system’s ability to identify tumor cells as foreign due to increased numbers of neoantigens. However, these cancers also possess the ability to evade immune surveillance and eradication through the overexpression of PD-L1.

PD-L1’s presence in the tumor microenvironment is an immune checkpoint that negatively regulates T-cell function, leading to decreased T-cell proliferation and survival. PD-L1 binds to

programmed death 1 (PD-1) and B7-1 receptors on activated T lymphocytes and other immune cells, delivering an inhibitory signal that enables tumors to avoid destruction.

Atezolizumab selectively binds to PD-L1, preventing its interaction with PD-1 and B7-1 and thereby negating tumor-mediated immunosuppression. Atezolizumab has demonstrated durable responses in patients with metastatic urothelial cancer in a phase I trial,<sup>3</sup> with higher response rates in patients with elevated PD-L1 expression levels on tumor-infiltrating immune cells.

To assess atezolizumab’s anti-tumor activity in advanced urothelial carcinoma, researchers at Cleveland Clinic and the phase II study’s 69 other sites enrolled patients with inoperable locally advanced or metastatic tumors whose disease had progressed after platinum-based therapy (cohort 2). Many had adverse prognostic indicators such as visceral or liver metastasis and baseline hemoglobin < 10 g/dL.

Between May and November 2014, 310 patients were treated with at least one dose of atezolizumab. At data cutoff in September 2015, 202 (65 percent) had discontinued treatment. Of those, 193 had died, eight had withdrawn and one had stopped for other reasons. Patients’ tumors were evaluated with cross-sectional computed tomography every nine weeks for a year and every 12 weeks thereafter. Tumor tissue obtained by surgical resection or biopsy was assayed for PD-L1 expression, assessing the percentage of PD-L1-positive immune cells in the tumor microenvironment.

## Durable Responses and Few Adverse Events

The researchers reported that treatment with atezolizumab produced “striking” and durable responses as determined by primary investigator-assessed analysis and longer-term independent radiological review. Responses were noted even in patients with poor prognostic features, though at a lower rate than patients who lacked unfavorable indicators.

For all evaluable patients, the objective response rate as independently assessed was 15 percent (95 percent confidence interval [CI] 11-19) compared with an overall response rate of 10 percent among historical controls. A complete response was recorded in 15 (5 percent) of 310 patients.

*Cancer Advances* provides information from Cleveland Clinic cancer specialists about innovative research and diagnostic and management techniques.

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Cleveland Clinic Cancer Center annually serves thousands of cancer patients. More than 450 clinicians, scientists and other cancer specialists are committed to researching and applying the latest, most effective techniques for diagnosis and treatment to achieve long-term survival and improved quality of life for all cancer patients. Cleveland Clinic Cancer Center is part of Cleveland Clinic, an independent, nonprofit, multispecialty academic medical center.

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## KEY POINTS

The systemic treatment of urothelial cancer has not advanced since the development of combination platinum-based chemotherapy three decades ago.

Immune checkpoint inhibitors that enhance anti-tumor immunity may help break this logjam.

Atezolizumab shows promising and durable efficacy in patients with locally advanced or metastatic urothelial cancer, according to a recent phase II clinical trial.

More research is needed to further understand the immunologic mechanisms and potential treatment combinations and sequences, and to develop prognostic and predictive biomarkers to aid in optimal patient selection.

With a median follow-up of 11.7 months (95% CI, 11.4–12.2), ongoing responses were recorded in 38 (84 percent) of 45 responders.

Increased levels of PD-L1 expression on immune cells (IC) measured by immunohistochemistry were associated with increased response. In addition to PD-L1 expression levels, patients' mutation load of cancer-related genes and luminal II molecular (TCGA) subtype were strongly indicative of their response to atezolizumab.<sup>5</sup>

The median treatment duration was 12 weeks. Median progression-free survival was 2.1 months. Median overall survival was 11.4 months in patients with IC2/3 PD-L1 expression, 8.8 months in patients with IC1/2/3 PD-L1 expression and 7.9 months in the entire cohort. Twenty (17 percent) of 121 patients treated beyond progression experienced reductions of at least 30 percent of the size of their tumors.

Atezolizumab was generally well-tolerated. Treatment-related serious (grade 3/4) adverse events occurred in 16 percent of patients. There were no treatment-related deaths. Most treatment-related adverse events were mild to moderate (primarily fatigue). Only 5 percent of patients had serious (grade 3/4) immune-related adverse events. This low incidence is encouraging, since patients with metastatic urothelial cancer often have renal dysfunction and/or other conditions that could be exacerbated by an adverse treatment reaction.

## The Need for More Clinical and Translational Research

More research is needed to evaluate the predictive value of patients' PD-L1 immune cell expression levels, to better determine which patients will benefit from atezolizumab treatment and to develop future treatment strategies. The associations between PD-L1 expression, molecular subtype, mutation load and response to atezolizumab suggest that the presence of additional neoantigens may correlate with immune system response, and that combination immunotherapies may further enhance therapeutic effects. More clinical trials are needed to define further new therapies in this challenging cancer; trial accrual is critical.

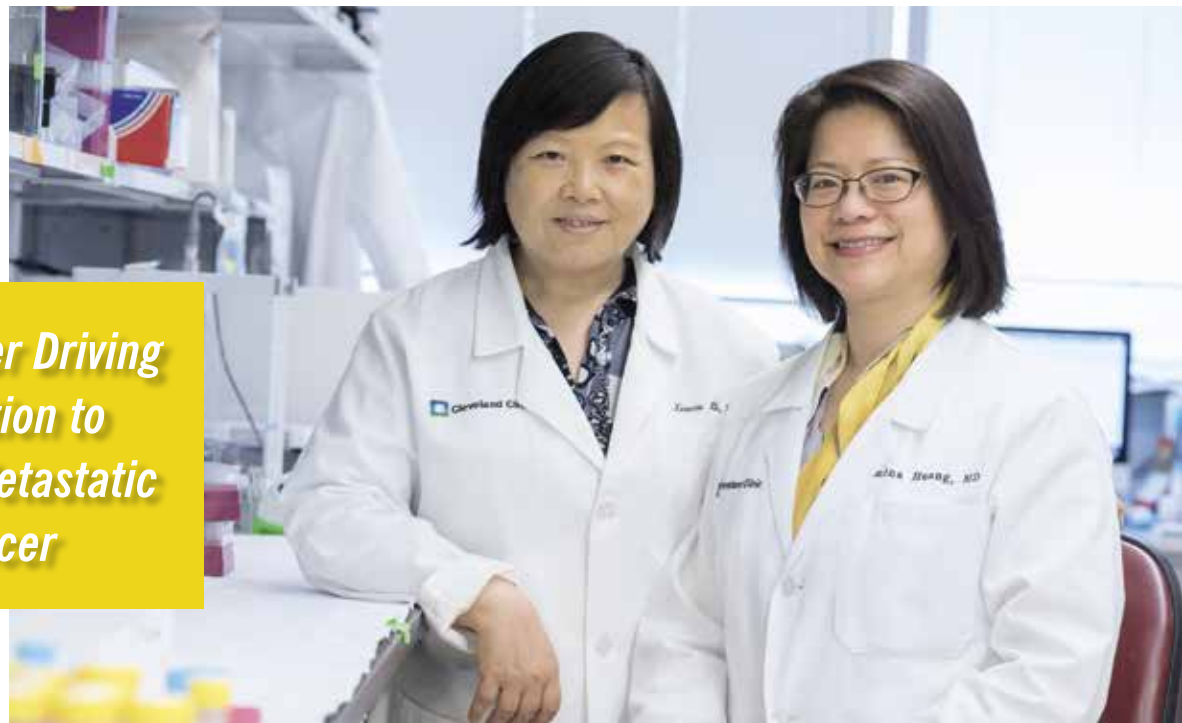
“The prior absence of a standard-of-care treatment option in patients with platinum-resistant advanced urothelial cancer, in conjunction with the shown efficacy and relatively favorable toxicity profile of immune checkpoint inhibitors, contributed to the recent FDA approval that rendered atezolizumab the new standard of care for patients with platinum-resistant advanced urothelial cancer,” Dr. Grivas says. “More clinical and translational research is critical to further understand the immunologic mechanisms and potential treatment combinations and sequences, and to develop prognostic and predictive biomarkers that can aid in optimal patient selection.”

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**Xiaoxia Li, PhD**  
(left), and **Emina**  
**Huang, MD**

## *New Center Driving Collaboration to Combat Metastatic Colon Cancer*



Bringing together expert scientists and clinicians with a singular focus — to develop new and effective treatments to improve a bleak prognosis — is the aim of Cleveland Clinic's new Research Center of Excellence in Colon Cancer Metastasis.

*Dr. Huang is a staff member of the departments of Colorectal Surgery and Stem Cell Biology and Regenerative Medicine, and a Professor of Surgery at Cleveland Clinic Lerner College of Medicine.*

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*Dr. Li is a staff member of the Department of Immunology. She holds the Paul L. Fox, PhD, Endowed Chair in Molecular Medicine and is a Professor of Molecular Medicine at Cleveland Clinic Lerner College of Medicine.*

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"We have very poor treatments for metastatic colon cancer, basically variations on 5-fluorouracil. That was discovered 50 or 60 years ago," said Emina Huang, MD, a colorectal surgeon and Co-Director of the center. "We haven't had that many advances since that have been successful."

Colorectal cancer is the third most common cause of cancer deaths in the United States. The five-year relative survival rate for stage IV colon cancers is approximately 11 percent, and 12 percent for stage IV rectal cancers, according to the National Cancer Institute's Surveillance, Epidemiology, and End Results database.

"We saw the need nationwide, and internationally, to try to address this deadly form of colon cancer," Dr. Huang said. So she, her colleague and Co-Director Xiaoxia Li, PhD, an immunology researcher, and others sought support from Cleveland Clinic to launch the new center.

The Research Centers of Excellence program, administered by Lerner Research Institute, matches basic, translational and clinical researchers at various Cleveland Clinic institutes who share common interests and goals. The

intent is to foster team-based, innovative research that challenges existing paradigms and produces new products, methods or technologies. Funding of up to \$300,000 a year for three years is available and is shared evenly by the partnering institutes. Centers are expected to use funds to build a team that will be competitive for external funding, producing high-impact publications and invention disclosures.

### **Empathy and Expertise**

The colon cancer metastasis center's staffing aligns with Cleveland Clinic Cancer Center's overall mission to promote interdisciplinary collaboration among the various institutes whose clinicians, surgeons and researchers are involved in cancer treatment.

"We have a really expert, multidisciplinary team that is trying to address this problem from all different angles," Dr. Huang said. But in addition to uniting specialists, the center's goal is to cultivate the infrastructure, resources and shared enthusiasm to explore the most promising research advances, she said.

Colorectal surgeons, medical oncologists, a liver surgeon, a pathologist and others will contribute their clinical acumen. Dr. Li's work on cancer immunology, Angela Ting, PhD's research on tumor epigenetics, and Paul Fox, PhD's work on angiogenesis are just a few of the initial, promising research avenues.

The center secured initial funding in February 2016, so it is still too early to know which prevention or treatment avenues will pan out, Dr. Huang said. "Our hope is that one, two or three of our approaches will translate to the bedside. Hopefully we'll have multiple effective strategies coming out of this."

### Exploring Multiple Avenues

Metastatic colorectal cancer's complexity warrants a multipronged search for targeted treatments that will work for individual patients. Immunology holds great promise, but more work is needed to identify effective applications in metastatic colon cancer, Dr. Li said. Dr. Ting will continue to explore tumor epigenetics, including significant differences between primary colon cancer and metastatic tumors. Dr. Fox recently discovered a novel, potent antiangiogenic factor, vascular endothelial growth factor-Ax (VEGF-Ax), which could be a therapeutic agent and whose unintended diminution by VEGF-A-targeted therapies may exacerbate the growth of metastatic colorectal tumors.

Dr. Huang plans to explore the potential role of inflammation in the stroma and how stem cell therapy could improve treatment of metastatic colon cancer patients. Other research will assess how to manipulate the tumor microenvironment and/or the colon microflora to prevent or suppress the development of metastatic disease. The center's additional team members include Matt Kalady, MD, Cristiano Quintini, MD, Alok Khorana, MD, and Thomas Plesec, MD.

"This team comprises the best of the best in colorectal cancer research at Cleveland Clinic. We have multiple approaches to attack this," said Dr. Huang, who is both a researcher and a clinician. She spends an estimated 40 percent of her time caring for patients. "I see this disease, and that is what really tugs at me," she said.

### Picking up the Pace

The center aims to accelerate research so that it translates more quickly to the bedside. Having expertise and resources in a single setting "means we can act immediately and investigate all promising leads," Dr. Li said. Previously, researchers had to wait for external funding for most projects, which can add months or years to the discovery process. "Now we can develop these new research directions right away," she said.

Another benefit of blending the research and clinical worlds is that researchers gain easier access to patient tissue samples to facilitate their work. For example, Cleveland Clinic surgeon Federico Aucejo, MD, maintains a liver tissue biobank whose inventory includes tumor samples of liver metastases from colorectal cancer. The hope is that a greater understanding of both primary and metastatic tumors will emerge from investigations involving patient epithelial cells, organoids, xenograft modeling and more.

"We have some preliminary data on expression profiles between normal and colon cancer tissues," Dr. Li said. "We have some exciting candidates that we want to pursue."

### Paying It Forward

Referring physicians can counsel patients with metastatic colon cancer that the new center aims not only to help them, but to advance the entirety of knowledge about metastatic colon cancer to help others as well.

"In three to five years we'd like to have a defined goal and a number of projects ready to attract funding from the National Institutes of Health, cancer societies or other funding sources at the national level," Dr. Li said. "Hopefully we can develop some new therapeutic approaches for the treatment of metastatic colon cancer. That's the goal."

"I would love it if we can be at phase I with one of our discoveries by then," Dr. Huang said. "We're really enthusiastic and energized by this center's formation. Together we'll be able to do something amazing."

## Study Reveals **Poorer Malignant Melanoma Outcomes** in Women Diagnosed During Pregnancy

By Brian D. Gastman, MD

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Women diagnosed with cutaneous malignant melanoma while pregnant or within a year of giving birth have a significantly worse prognosis than their nonpregnant counterparts, according to the key findings of a retrospective study my co-authors and I recently published in the *Journal of the American Academy of Dermatology*.

After adjusting for age, tumor location and American Joint Committee on Cancer stage, we determined that women with pregnancy-associated malignant melanoma were five times more likely to die, nearly seven times more likely to experience metastasis and nine times more likely to have the cancer recur than were melanoma patients who were not pregnant.

To our knowledge, this is the first study to document reduced survival and poor prognosis in pregnancy-associated malignant melanoma patients, despite adjusting for patient age, tumor

location and cancer stage. The magnitude of negative outcomes was a surprise to my colleagues and me. Our findings highlight the importance of melanoma screening and post-treatment surveillance in pregnant and recently pregnant women.

### **Documenting the Pregnancy-Melanoma Association**

The incidence of malignant melanoma in women has rapidly increased in recent decades. Our initial intent was to investigate the histopathology, staging, risk factors and outcomes of cutaneous melanoma in women younger than 50 years of age. Although pregnancy-associated melanoma is rare, the number of cases can be expected to grow, concomitant with the overall rise. Pregnancy's impact on malignant melanoma patients' prognosis has been unclear and subject to debate.

### **KEY POINTS**

The incidence of malignant melanoma in women has rapidly increased in recent decades, and although pregnancy-associated melanoma is rare, the number of cases can be expected to grow along with the overall rise.

Pregnancy's impact on malignant melanoma patients' prognosis has been unclear.

A retrospective study conducted by Cleveland Clinic confirmed an association between pregnancy and poor malignant melanoma outcomes, including increased risk of death, metastasis and recurrence.

More research is needed to determine the pathophysiology underlying these reduced outcomes, but the study's findings heighten the need for awareness of and counseling about melanoma's risks, particularly during and soon after pregnancy.





Cleveland Clinic's early adoption of electronic medical records technology provided us the opportunity not only to review oncology and surgery notes, but to examine any type of medical history, including family practice and Ob/Gyn appointment records, dating back to 1998. As a result, we collected detailed diagnostic and outcomes data for 462 women younger than 50 years of age treated for biopsy-confirmed cutaneous malignant melanoma between 1998 and 2012.

Through this research, we confirmed an association between pregnancy and poor malignant melanoma outcomes. Forty-one women in our study cohort were diagnosed with melanoma while pregnant or within one year of giving birth. The mortality rate for pregnancy-associated malignant melanoma patients was 20 percent, compared with 10 percent for nonpregnant women ( $p = 0.06$ ).

The incidence of metastasis was 25 percent among women with pregnancy-associated malignant melanoma compared with 12.7 percent for nonpregnant women ( $p = 0.03$ ). Our research also found 12.5 percent of women diagnosed with melanoma during or soon after pregnancy experienced recurrence within the next 7.5 years, compared with 1.4 percent of their nonpregnant counterparts ( $p < 0.001$ ).

#### Possible Reasons for Poor Prognosis

Although our research did not investigate the pathophysiology of pregnancy-associated malignant melanoma, there are several possible explanations for the poorer outcomes this study revealed. Detection of malignant melanoma may be delayed in some patients due to the common belief that pigmented lesions typically darken during pregnancy and thus are not a cause for concern. A biologic aspect of pregnancy — elevated estrogen levels, heightened immunosuppression and/or enhanced lymphangiogenesis — may

contribute to tumor aggressiveness or invasiveness. Further research is needed.

Previous studies examining melanoma prognosis and pregnancy have produced inconsistent results, possibly due to limitations in available patient data, methodological differences and the exclusion of women diagnosed with melanoma during the postpartum period.

#### Spurring Skin Cancer Awareness, Prevention

Our hope is that this study creates greater awareness of melanoma's risks, particularly during and soon after pregnancy, and that our findings will inform the assessment, treatment and counseling of these patients.

Women should be encouraged to talk with their physician if they are considering becoming pregnant and have obvious melanoma risk factors, such as excessive ultraviolet light exposure or a personal or family history of skin cancer. They should be counseled to perform a skin self-examination every month. Patients should be instructed to seek medical evaluation of any new or changing lesion noted during or soon after pregnancy.

As physicians, we should work to better educate the public about the dangers of excessive sun exposure. Frequent sunburns, especially during childhood, are associated with the development of melanomas on the trunk and legs. Ultimately, the best prevention originates with parents who are vigilant about their child's exposure.

Finally, my co-authors and I hope our work leads to larger studies that will further explore the science underlying this link between pregnancy and melanoma prognosis, so that we can tailor therapies and prevention strategies.

# New Cancer Building Will Enhance Multidisciplinary Care

Providing multidisciplinary care for patients is the norm at Cleveland Clinic Cancer Center, but the new cancer building opening in March 2017 will make that process far more efficient for patients and physicians.

Currently, cancer patients getting outpatient treatment must travel to multiple locations within the existing Cancer Center building and among other Cleveland Clinic buildings to see specialists, undergo tests and procedures, and receive medical and social services. Sometimes those appointments are spread over more than one day.

With consolidated offices and clinical facilities and advanced scheduling, the new Cleveland Clinic Cancer Center will minimize transit and wait times and maximize convenience. "All of the services we need are set up to happen in the same place," says Nathan Pennell, MD, PhD, Director of the Thoracic Malignancies Program. "The patients are in one place that's tailored to their needs and everyone comes to them."

## A Concentration of Providers and Services

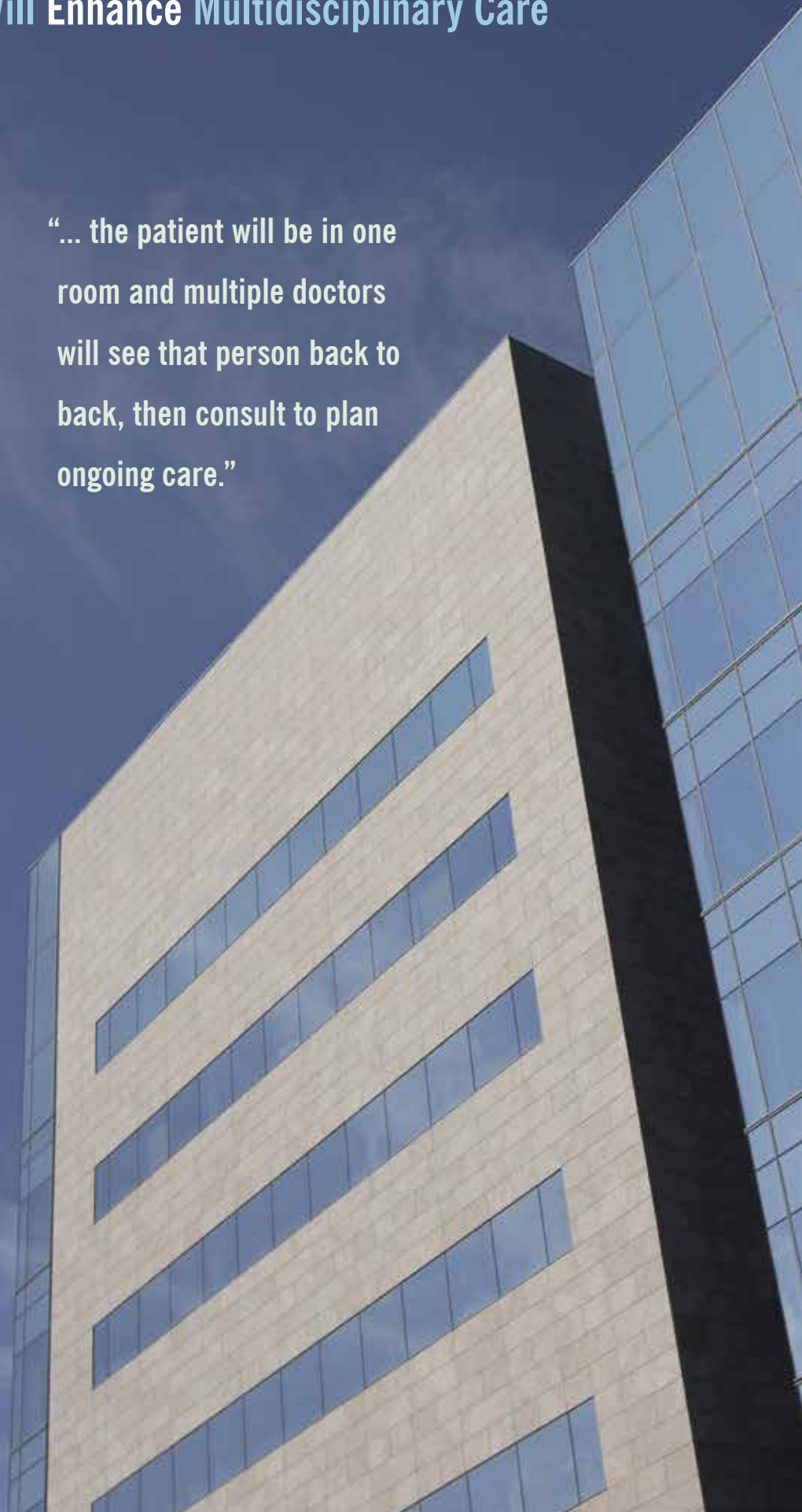
Lung cancer care provides a good example of how the new seven-floor, 385,000-square-foot building will streamline operations.

Lung cancer patients who need diagnostic imaging or radiotherapy will access those services in the basement — a skylighted, high-ceiling space that will contain six linear accelerators, a Gamma Knife® stereotactic radiosurgery unit and a diagnostic imaging suite.

The building's first floor houses the patient reception and check-in area, an expansive hematology laboratory and blood-drawing stations to eliminate waiting lines, a retail pharmacy, and patient services including a café, wellness center, spiritual area, wig boutique and art and music therapy facilities.

Lung cancer patients will see clinical specialists and receive chemotherapy on the third

**"... the patient will be in one room and multiple doctors will see that person back to back, then consult to plan ongoing care."**







floor. There, examination rooms surround a meeting/working area where members of the lung cancer multidisciplinary team, including oncologists, surgeons, radiologists, palliative care providers, oncology nurses and advanced practice providers, can discuss therapeutic decisions and treatment plans. Private and semiprivate chemotherapy infusion rooms a short walk from the examination area have floor-to-ceiling windows overlooking a tree-lined lawn.

The second floor will contain a dedicated area where patients with lung cancer or other malignancies who are participating in phase I clinical trials will receive chemotherapy infusion while monitored by specially trained

nurses and research assistants. The space and staffing reflects Cleveland Clinic Cancer Center's aggressive efforts to expand phase I clinical trials access for patients.

#### **A More Efficient Process**

"We already have good multidisciplinary care, but I think it's a bit disjointed from the patient perspective," Dr. Pennell says. "While the patient may see a surgeon and radiation and medical oncologists and a palliative medicine physician all in the same day, those visits are often spread out — seeing different people and walking back and forth to different places.

"The idea of the multidisciplinary clinic is that the patient will be in one room and multiple doctors will see that person back to back and then consult to plan ongoing care," Dr. Pennell says. At present those discussions often take place at weekly tumor board meetings.

"From a care standpoint, it will definitely be much more efficient for us to discuss the patient while working in the same space and sitting next to each other, Dr. Pennell says, "so that by the end of the day when the patient is ready to leave, he or she will have a plan for treatment."

To learn more about our new cancer facility, visit [clevelandclinic.org/newcancerbuilding](http://clevelandclinic.org/newcancerbuilding).



## Variation in Treatment of Cancer-Associated Thrombosis: Can Management Be Standardized?

By Alok A. Khorana, MD

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Cancer-associated thrombosis is very prevalent in patients with cancer, with some estimates suggesting that one-fifth of all patients are affected.

Multiple randomized trials have addressed best options for treatment, with a general consensus that treatment with low-molecular-weight heparins (LMWHs) is most efficacious. Therefore, current guidelines recommend anticoagulation with LMWH monotherapy for as long as six months, and possibly indefinitely, for patients with active cancer.

However, there are issues with these agents, particularly that they require injection and may be more expensive than newer anticoagulants, and that patient preference issues may lead to non-compliance.

### Documenting Variation from Treatment Guidelines

In research<sup>1</sup> presented at the most recent American Society of Hematology (ASH) annual meeting, my colleagues and I analyzed medical

### KEY POINTS

For patients with cancer-associated thrombosis, current guidelines recommend anticoagulation with low-molecular-weight heparin (LMWH) monotherapy.

In an analysis of a national medical and pharmacy claims database, Cleveland Clinic researchers and their colleagues found substantial variation in anticoagulant care and therapy persistence.

Despite guideline recommendations, warfarin and rivaroxaban are utilized nearly as often as LMWH for the treatment of cancer-associated thrombosis (CAT), and patients are less likely to persist on LMWH therapy.

In a related study, the researchers found that standardized management of CAT reduces variation in care and appears to improve patient-related outcomes, including the need for venous thromboembolism (VTE)-related hospitalizations and recurrent VTE.

With increased understanding of the risk of recurrent VTE, it may be possible to develop risk-adapted treatment approaches that improve patients' experience and reduce recurrence and hospitalization.

and pharmacy claims from the Humana Database to identify national patterns and variation in cancer-associated thrombosis care between Jan.1, 2013, and Dec. 31, 2014. Based on the first anticoagulant agent received, patients were classified in one of the following cohorts: LMWH, LMWH/warfarin, warfarin, or rivaroxaban. Use of other anticoagulants, including fondaparinux, heparin, apixaban and dabigatran, was low and therefore could not be appropriately evaluated.

Among 2,941 newly diagnosed cancer patients who developed venous thromboembolism (VTE) and received anticoagulation, agents used included LMWH (N = 735; 25 percent), LMWH/warfarin (N = 550; 18.7 percent), warfarin (N = 853; 29 percent) and rivaroxaban (N = 709; 24.1 percent). This suggests a substantial variation in care, with only a quarter of patients receiving guideline-recommend therapy.

In addition, there was variation in anticoagulant therapy persistence. The median treatment



durations for LMWH, LMWH/warfarin, warfarin, and rivaroxaban users were 3.29 months, 7.76 months, 8.12 months and 7.92 months, respectively. LMWH/warfarin, warfarin, and rivaroxaban users were significantly more likely to remain on their initial therapy compared with LMWH patients, with hazard ratios (HRs; 95 percent confidence interval) of 0.38 (0.32-0.45), 0.40 (0.34-0.46) and 0.42 (0.36-0.50), respectively (all  $p$  values < 0.0001).

#### Testing a Standardized Care Management Approach

Thus, this real-world analysis shows that despite guideline recommendations, warfarin and rivaroxaban are utilized nearly as often as LMWH for the treatment of cancer-associated thrombosis and that patients are less likely to persist on LMWH therapy. It is unclear whether these findings are related to patient preference, cost of medication or provider preference.

Can this variation in the care of cancer-associated VTE be reduced? In another abstract<sup>2</sup> presented at ASH, we provided results from Cleveland Clinic's experience. In 2014 we instituted a centralized service for care of cancer patients with suspected deep venous thrombosis (DVT) and/or pulmonary embolism (PE) at Cleveland Clinic Cancer Center. We hypothesized that a cancer-associated thrombosis (CAT) clinical service that provides standardized management would reduce variation in care and lower rates of recurrence, bleeding and hospitalization in this patient population.

The study population comprised 221 patients with suspected VTE seen by the CAT clinical service between August 2014 and July 2015. VTE was diagnosed in 51 patients (23 percent). Hospitalization for VTE was necessary in only 24 percent (N = 13 of 51) of cases. The mean and median costs of hospitalization for VTE (all costs) were \$7,656 and \$2,842, respectively, whereas the mean and median costs of outpatient VTE treatment were \$1,160 and \$824, respectively.

The initial treatment for 94 percent (N = 48 of 51) of patients was enoxaparin. Other treatments included warfarin (2 percent, N = 1 of 51), heparin (2 percent, N = 1 of 51) and apixaban (2 percent, N = 1 of 51). Of patients started on enoxaparin, 71 percent (N = 34 of 48) remained on it for the duration of their care. Common

causes for transitioning to warfarin were financial considerations (50 percent, N = 4 of 8), patient preference (38 percent, N = 3 of 8) and poor renal function (13 percent, N = 1 of 8).

VTE recurred in 14 percent (N = 7 of 51) of patients with a median follow-up of 3.5 months. Recurrences occurred in 9 percent (N = 3 of 34) of patients on enoxaparin monotherapy, in 22 percent (N = 2 of 9) of patients started on or bridged to warfarin and 33 percent (N = 2 of 6) of patients taken off anticoagulation. A total of 10 recurrent VTE events occurred in seven patients. Of these, four required hospitalization. The mean and median costs of hospitalization for recurrence (all costs) were \$19,528 and \$18,627, respectively. The mean and median costs of initial outpatient care (excluding drug costs) for recurrent VTE were \$998 and \$728, respectively.

#### The Benefits of Centralized CAT Care

Thus, our experience suggests that centralizing care of CAT reduces treatment variation and appears to improve patient-related outcomes, including the need for VTE-related hospitalizations and recurrent VTE. Substantial cost savings can be achieved by avoiding unnecessary hospitalization for appropriate patients and by reducing recurrence and bleeding rates with appropriate therapy.

As greater knowledge regarding risk of recurrent VTE emerges, it may be possible to develop risk-adapted approaches in which higher-risk patients are treated with LMWH and lower-risk patients with oral anticoagulants, thereby improving patients' experience and reducing the risk of recurrence and hospitalization.

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## CHAIRMAN'S Q&A

### Brian J. Bolwell, MD, FACP, Talks About the **Cancer Moonshot**



Earlier this year, the White House announced plans for a \$1 billion “cancer moonshot,” led by Vice President Joe Biden, that aims to accelerate progress toward a cure.

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#### Why is the timing appropriate for this initiative?

It is a combination of the fact that there are so many promising therapies today to try to help cancer patients, and that this subject is obviously near to the vice president's heart because of the death of his son.

#### There have been previous initiatives, such as President Nixon's war on cancer in the early 1970s. How will this be different?

I think the organizers are still figuring that out. As recently as late April, they asked for input as to what cancer leaders and people active in the cancer community think should be the moonshot agenda. Most of us think that the vast majority is going to be research-related, and that's fine. The more funding we have to conduct cancer research, the better. There is a huge opportunity to improve screening in the United States, a huge opportunity for community outreach, and a lot of other initiatives. Another issue that clearly is important to the moonshot organizers is information technology and data sharing. Ultimately it would be great if we could get electronic medical records to become databases, but that's not easy to do.

#### How do you feel about the moonshot being framed as an effort to cure cancer?

It is probably more than a little aspirational to think that we can make 10 years of progress in five years, which is how the moonshot is being described. Everybody in this field welcomes more funding. The timing is great because our knowledge of immunologic and genomic therapies is so much greater today than it was a decade ago. The FDA approved 16 new targeted drugs in 2015, all of which look very promising. But to think that we're going to cure 50 percent more people in a short period

of time is probably unrealistic. Scientific advancements are generally step by step. Stretch goals are great, but for people who have these diseases, it is very important that they receive honest and accurate messaging about their current state.

#### You and Case Comprehensive Cancer Center Director Stan Gerson, MD, met with Vice President Biden's staff recently. What role might Cleveland Clinic and its partners in the Case Comprehensive Cancer Center play in the moonshot?

We met with three leaders of the initiative, including the person who's in charge of it and who happens to be a cancer survivor. We talked about things that we think make Cleveland somewhat unique and provide certain opportunities. We talked about the fact that the Case Comprehensive Cancer Center services about 70 percent of the population of Northeast Ohio, which is significantly greater than any other comprehensive cancer center. But there are more opportunities, especially to help underserved populations. Patient navigation can be extraordinarily important, and we have adopted the Harold P. Freeman model that has proved to be so successful. We are poised to do more good work. So I talked about that with the vice president's team. It is the sort of thing that, if we had some more funding, has immediate, very tangible benefits to help people today.

#### If you were in charge of moonshot funding, how would you apportion it?

Increasing the number of dollars available for cancer research is very important. The bedrock for federal funding for a long time has been to support individual investigators through R01 funding. The percentage of

RO1 grants that have been funded has decreased steadily over the past decade until the past 18 months or so. It got down to less than 10 percent but is back up a little. There is a lot of very good research that depends on RO1 funding. I think if we simply increase the percentage — especially if we directed it toward certain areas such as genomics or immunologic therapies — that would be very important. The economic challenges faced by cancer patients are really important too. Several studies show that a small percentage of patients receiving therapy for cancer actually go bankrupt. Part of their challenge is the cost of new cancer therapies, which these days can be a quarter of a million dollars a year for targeted or precision-based therapies. That continues to escalate unchecked. That must be addressed, because it simply is not a sustainable economic model. These sorts of issues are potentially opportunities that moonshot funding can at least start to address.

### Should improving cancer patients' access to care, particularly to clinical trials, be a moonshot goal?

Access is as important a priority of mine as any. We are very concerned about quality and safety, but at the end of the day, we have to get people in. That is one of the reasons we are focused on time to treat. It is not just getting people in; it is trying to relieve their fear and anxiety by treating them in a timely way. We have navigation programs. Probably the best-developed is at our South Pointe Hospital, whose population is largely underserved, and it has tangible benefits — we have detected patients with cancers that otherwise wouldn't have been detected early, which is a big win. That is one of the reasons why Cleveland Clinic Cancer Center has the strategy of having many different locations, to offer services to people who may not be able to come to our main campus or who would rather not. We are increasingly exploring affiliations at more distant locations. And clinical trials are how we make scientific progress for patients, and we have an enormous clinical trial portfolio. It is a major priority and we are very proud of the work that we do with clinical research.

### What about preventive care and cancer screening?

The best results are for cervical cancer screening, but I think participation is around 78 percent. If people don't have insurance, screening levels fall into the 50s. Colon cancer screening goes well under 50 percent if you don't have insurance. Screening for colon cancer clearly saves lives. If we made screening a major public health priority, we would save thousands of lives. And it isn't just those cancers. There is clear evidence now that screening for lung cancer is effective. That gets into preventive things like smoking cessation. The biggest single thing that

could be done in the United States to reduce the risk of cancer is to end smoking, and there are all sorts of ways to try to do that, which also could be resourced. HPV vaccines are not only for cervical cancer, but also to prevent head and neck cancers, and yet the adherence to that isn't anywhere near 100 percent. Those are examples of initiatives that, in terms of return on investment, are hard to beat.

### Are you concerned that the moonshot program might not last beyond the current presidential administration?

Our hope is that it is sustainable and that the vice president makes this kind of his career. If he does, then the goal is that he becomes a magnet for some funding outside of the federal government. The example that's been kicked around is Al Gore and the environment. That would be one way to make the moonshot sustainable. Federal funding does crest and trough, depending on how the economy goes, depending on if a Republican or a Democrat is elected, depending on the status of the House and the Senate — there are all sorts of variables. But it certainly would be unfortunate if the moonshot was a one-year thing.

### You mentioned nongovernmental funding. Web entrepreneur Sean Parker recently donated \$250 million for collaborative immunotherapy research, and this summer Cleveland Clinic holds the third annual VeloSano cycling event to raise money for cancer research. What role does philanthropy play in cancer research?

Philanthropy is incredibly important. One of the first things I did when I became Chairman of Taussig Cancer Institute was to make philanthropy part of the agenda at our standing meetings, along with patient experience, quality and clinical research. The reason is that philanthropy equals research. They are directly linked, and it would be impossible for us or any academic medical center to execute the sort of research initiatives and priorities that exist without philanthropic dollars. I think it is fabulous that an individual has dedicated a quarter of a billion dollars to try to enhance immunologic therapies. VeloSano is not quite to that dollar amount yet, but it is an aspirational goal. VeloSano is a bike ride modeled after the Pan-Mass challenge, which started many years ago in Boston to support the Dana-Farber Cancer Institute very successfully. Last year we raised \$3 million and 100 percent of that is going to cancer research, and that is going to be our plan going forward. It is a very inspirational event.

## Patterns of DNA Methylation May Differentiate Indolent and Aggressive Prostate Cancers

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Prostate cancer continues to be a serious health-care problem, with approximately 220,800 new cases reported in the United States in 2015. The disease course of prostate cancer is heterogeneous and ranges from slow-growing, indolent forms to aggressive, potentially life-threatening forms. Distinguishing between indolent and more aggressive prostate cancers is difficult with currently available biomarkers.

A recently conducted Cleveland Clinic study used advanced molecular techniques to characterize differences between indolent and more aggressive forms of prostate cancer. The results, published in the journal *Cell Reports*, not only advance understanding of the development of prostate cancer, but may eventually lead to diagnostic tools to

identify patients with the most aggressive forms of cancer, according to co-author Angela H. Ting, PhD, of Cleveland Clinic Cancer Center and the Genomic Medicine Institute.

DNA methylation is an epigenetic alteration that plays a role in prostate cancer. Both genetic mutations and epigenetic alterations (i.e., chemical changes to tumor DNA, such as DNA methylation) are believed to be important in carcinogenesis.

“DNA methylation was selected for study based on the observed low mutation rate in prostate cancers relative to other cancers,” Dr. Ting says. “The low mutation rate suggests that mechanisms other than genetic mutations are involved, which motivated us to investigate the role of epigenetic changes in the biology of prostate cancers.”

### KEY POINTS

Distinguishing between indolent and more aggressive prostate cancers is difficult with currently available biomarkers.

Cleveland Clinic researchers used advanced molecular techniques to study DNA methylation as a potential differentiator of tumor progression.

The researchers observed distinctive, identifiable patterns of DNA methylation for the different tumor groups studied.

Pervasive focal hypermethylation was the most common and statistically robust difference between indolent and aggressive prostate cancer.

Accurate determination of aggressive prostate tumors could guide treatment decisions, while improved understanding of DNA methylation patterns of aggressive cancers could lead to new therapies.





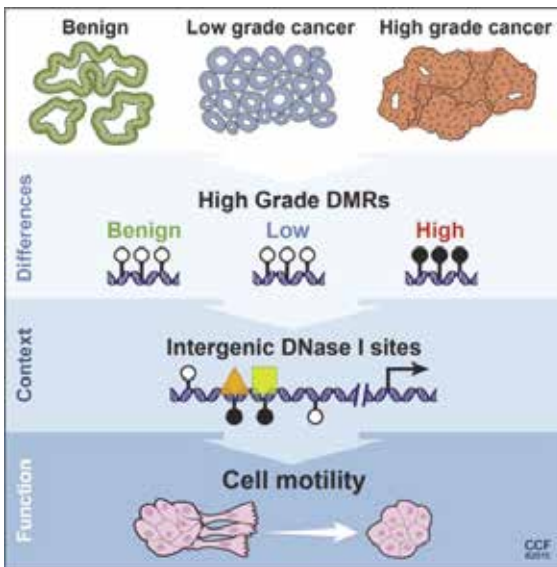


Figure 1. **Hypermethylated DNA is indicated by black circles and unmethylated DNA is represented by white circles.** High-grade differentially methylated regions (DMRs) occurred more frequently at intergenic regions and gene bodies than in other genomic contexts. In addition, the intergenic DMRs appear highly enriched for DNase I hypersensitivity sites, which are markers for regulatory DNA regions. Genes near the DMRs regulate cellular activities, such as cellular motility, that are purported to play a role in aggressive disease.

### Differences in DNA Methylation Patterns

Dr. Ting and her collaborators, including Eric A. Klein, MD, Chairman of the Glickman Urological & Kidney Institute, and Cristina Magi-Galluzzi, MD, PhD, Director of Genitourinary Pathology, chose to stratify the prostate tumors studied by histology classified by Gleason scores. The samples were divided into three groups: benign prostatic tissue, low-grade (indolent, Gleason score 6) prostate cancer and high-grade (aggressive, Gleason score 8 to 10) prostate cancer.

“By stratifying prostate cancer samples using Gleason scores derived from radical prostatectomy, our results relate to biological criteria, as opposed to stratifications using recurrence that are influenced by stage of disease at presentation,” says Dr. Ting.

The researchers observed distinctive, identifiable patterns of DNA methylation for the different tumor groups studied. Pervasive focal hypermethylation was the most common and statistically robust difference between indolent and aggressive prostate cancer.

“Our study revealed a very unique signature of differentially methylated regions (DMRs) for aggressive disease,” Dr. Ting says. High-grade DMRs occurred more frequently at intergenic regions and gene bodies than in other genomic contexts. The intergenic DMRs appear highly enriched for regulatory elements in the genome.

In addition, shared DMRs were more commonly located over CpG islands and shores than high-grade DMRs. Furthermore, genes near the DMRs regulate cellular activities, such as cellular motility and extracellular structure organization, which are highly relevant biological processes for aggressive disease.

More importantly, the high-grade DMRs target genes known to be associated with aggressive tumor types.

### Hope for New Cancer Therapy Targets

The overall goal in distinguishing slow-growing tumors from aggressive forms is to improve patient care and outcomes. A validated and clinically useful diagnostic test would be a valuable tool for clinicians.

“Accurate determination of aggressive prostate tumors could have important implications for treatment options,” Dr. Ting says. “Patients with aggressive tumors that threaten life expectancy could be offered potentially curative treatments. Conversely, patients with indolent prostate cancers could avoid unnecessary treatment and associated side effects.”

Finally, enhancing understanding of DNA methylation patterns of aggressive cancers could pave the way for development of new treatments, Dr. Ting says. Targeting pathways that are epigenetically reshaped in aggressive prostate cancer could offer hope as a treatment approach.



**J. Stephen Jones, MD (left), and Ahmad El-Shafei, MD, PhD**

## Novel Urine Biomarker *PCA3* May Improve the Prediction of Aggressive Prostate Cancer

By J. Stephen Jones, MD, and Ahmad El-Shafei, MD, PhD

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A new prostate cancer prediction tool developed and validated by Cleveland Clinic investigators achieves high accuracy, especially for high-grade tumors, by incorporating the prostate cancer antigen gene 3 (*PCA3*) as a biomarker.

The newly developed nomogram is biopsy protocol-specific and is based on a large cohort of men who underwent initial prostate biopsy.

Although further validation is needed, the *PCA3*-based nomogram has potential clinical utility to identify patients at risk for harboring prostate cancer, especially high-grade cancer, at initial biopsy.

Accurate and reliable early-detection methods for prostate cancer are needed. The prostate-specific antigen (PSA) protein, which is the most frequently used biomarker for prostate cancer, lacks specificity, often resulting in potentially unnecessary biopsy.

The *PCA3* gene, formally known as the *DD3* gene, is a noncoding gene located at chromosome 9q21-22 whose expression is restricted to prostate tissue. *PCA3* is overexpressed in at least 94 percent of prostate tumors.

The goal of using *PCA3* as a biomarker is to reduce the number of unnecessary biopsies. The literature supports the predictive accuracy of *PCA3* over PSA for early detection of prostate cancer.

Prior *PCA3*-based predictive models were not biopsy protocol-specific as they included men who underwent initial and repeat prostate biopsy.

The goal of our retrospective study was the development and internal validation of a *PCA3*-based nomogram for prediction of overall prostate cancer and high-grade prostate cancer in a large North American cohort of patients who underwent initial prostate biopsy.

### Study Details

Our cohort consisted of 3,675 patients from a single institution (Western New York Urology Associates) who had undergone transrectal ultrasound-guided prostate biopsy of at least 10 cores after detection of an elevated PSA level ( $\leq 20$  ng/mL) and/or abnormal findings on digital rectal examination (DRE). After prostate massage, 20 to 30 mL of voided urine was collected and analyzed for *PCA3* prior to biopsy.

Biopsy results confirmed prostate cancer in 44 percent of the 3,675 patients, and high-grade prostate cancer was present in 19.1 percent.

The variables whose predictive values were tested for inclusion in our nomogram were age, PSA level, *PCA3* score, race, family history of prostate cancer, DRE findings and prostate volume.

We calculated subjects' *PCA3* score using the formula (*PCA3* mRNA/PSA mRNA)  $\times$  1,000.

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## KEY POINTS

Accurate and reliable early-detection methods for prostate cancer are needed.

The prostate cancer antigen 3 (*PCA3*) gene's expression is restricted to prostate tissue, and *PCA3* is overexpressed in nearly all prostate tumors, suggesting its prognostic usefulness.

Cleveland Clinic researchers used a retrospective study to develop and validate a *PCA3*-based nomogram for prediction of overall prostate cancer.

Including *PCA3* in multivariate models predicting prostate cancer and high-grade prostate cancer improves the predictive accuracy of the models, making it a useful tool to identify patients at risk of prostate cancer at initial biopsy.

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We constructed two logistic regression models to predict overall prostate and high-grade prostate cancer, defined as Gleason score  $\geq 7$ .

### Nomogram Predictive Accuracy

The multivariate logistic regression models showed that age, PSA level, *PCA3* score, prostate volume, family history of prostate cancer and abnormal DRE were independent predictors for prostate cancer overall. Age, PSA level, *PCA3* score, prostate volume and abnormal DRE were independent predictors for high-grade prostate cancer.

We built a *PCA3*-based logistic regression nomogram using the risk factors from the logistic regression models that predicted overall prostate cancer and high-grade prostate cancer.

The *PCA3*-based nomogram demonstrated a predictive accuracy (concordance index) of 0.742 for prostate cancer overall and a c-index of internal validation of 0.768 when applied for the prediction of high-grade prostate cancer. The base model without *PCA3* showed a decline in the c-index from 0.742 to 0.700 for the prediction of prostate cancer overall, and from 0.768 to 0.753 for the prediction of high-grade prostate cancer.

Agreement (calibration) of the two nomograms for prediction of overall prostate cancer and high-grade prostate cancer was excellent.

### A Useful Tool

Including *PCA3* in multivariate models predicting prostate cancer and high-grade prostate cancer improves the predictive accuracy of the models. *PCA3* is a useful tool to identify patients at risk of prostate cancer at initial biopsy.

HIGHLIGHTS  
from the

ASCO  
ANNUAL MEETING

Cleveland Clinic Cancer Center physicians and investigators made major contributions to the 2016 American Society of Clinical Oncology Annual Meeting in Chicago, reporting results from a number of notable studies. Here are the titles and authors/co-authors/presenters of eight of those research projects.

To read more about these projects, visit our blog for physicians at [consultqd.clevelandclinic.org/cancer](http://consultqd.clevelandclinic.org/cancer).

For a complete listing of ASCO abstracts, see [meetinglibrary.asco.org/abstracts](http://meetinglibrary.asco.org/abstracts).

### Manmeet Ahluwalia, MD

Graded Prognostic Index for Gastroesophageal Cancer with Brain Metastases

Impact of EGFR and ALK Mutation on the Outcomes of Non-Small Cell Lung Cancer Patients with Brain Metastases

### Petros Grivas, MD

PD-L1 Expression, Cancer Genome Atlas Subtype and Mutational Load as Independent Predictors of Response to Atezolizumab in Metastatic Urothelial Carcinoma (IMvigor210)

### Halle Moore, MD

Prevalence, Risk Factors and Attenuators of Patient-Reported Concerns among Breast Cancer Survivors

### Brian Rini, MD

Overall Survival in METEOR, a Randomized Phase 3 Trial of Cabozantinib versus Everolimus in Patients with Advanced Renal Cell Carcinoma

### Davendra Sohal, MD, MPH

SWOG S1505: A Randomized Phase II Study of Perioperative mFOLFIRINOX vs. Gemcitabine/Nab-Paclitaxel as Therapy for Resectable Pancreatic Adenocarcinoma

### Vamsidhar Velcheti, MD

Meta-Analysis of Tumor PD-L1 Expression as a Predictive Biomarker of Benefit from PD-1/PD-L1 Axis Inhibitors in Solid Tumors

### Michael Vogelbaum, MD, PhD

Results of the Interim Analysis of the EORTC Randomized Phase III CATNON Trial on Concurrent and Adjuvant Temozolomide in Anaplastic Glioma without 1p/19q Co-Deletion: An Intergroup Trial



## Case Study:

# Pioneering Use of **Staged Radiosurgery** for Previously Untreatable Brain Metastases

By Liliyana Angelov, MD,  
FRCS(C)

*Dr. Angelov is a neurosurgeon in Cleveland Clinic's Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center and a staff member of Cleveland Clinic Cancer Center. She performs brain tumor surgical procedures and Gamma Knife radiosurgery and is the Head of the Section of Spinal Radiosurgery.*

*She can be reached at [angelol@ccf.org](mailto:angelol@ccf.org) or 216.444.4253.*

### **Presentation: Painful Mass in the Lower Right Leg**

Leg pain in a 19-year-old football player is typically no cause for alarm. But this patient's pain in his lower right leg persisted and was associated with a mass, so his primary care physician referred him to Cleveland Clinic's Orthopaedic & Rheumatologic Institute in 2007. So began a journey involving multidisciplinary, multimodality care over nearly a decade in which providers across several of the institutes that are part of Cleveland Clinic Cancer Center partnered with this brave young man to beat the odds.

### **Evaluation Reveals High-Grade Osteosarcoma**

A biopsy was performed and the mass was diagnosed as a high-grade osteosarcoma. This is the most common type of malignant primary bone cancer, and it most often affects children and young adults. Bone and soft tissue cancers represent less than 1 percent of cancer cases and are difficult malignancies to treat. Their associated pain typically occurs at nighttime and with sports, as was the case with this active teen.

### **Treatment: Deploying a Full Arsenal Against Extensive Metastases**

Because of the patient's young age, he received aggressive treatment. Before surgery, he had 18 cycles of chemotherapy to shrink the tumor. Subsequently, his leg was amputated below the knee.

Unfortunately, osteosarcoma is among the pediatric tumors with the worst prognosis, even when aggressive chemotherapy and local resection are used. The poor prognosis is related to both recurrence and distal metastases.

Soon after his limb amputation, the patient was diagnosed with bilateral lung metastases, and a Cleveland Clinic thoracic surgeon resected these tumors as a

component of his crucial salvage therapy. The patient then restarted chemotherapy in April 2008, which has been an ongoing part of his treatment during these past nine years. Lung metastases are known to be a common complication of osteosarcoma, and the patient has repeatedly developed lung lesions, which have been treated with surgery and/or chemotherapy. Such aggressive management of these lesions has meaningfully prolonged his survival.

Over the years, metastases in this patient have involved multiple other organs and body parts: stomach, ascending colon, ribs and diaphragm. These too were resected, and the patient carried on with chemotherapy and working, as tolerated, in an attempt to pursue a normal life for a young adult.

### **Metastasis to the Brain**

Then a new obstacle arose: a brain metastasis near the part of his brain that controls one side of his body.

In March 2014, the patient unexpectedly developed a nosebleed. As part of the workup for this seemingly innocuous event, an MRI was performed and revealed a 1.6-cm metastatic osteosarcoma-related tumor in the right precentral gyrus. Although this was a concerning location, he had not yet developed neurological symptoms. Brain metastases are uncommon in sarcoma patients (developing in only 8 percent of cases), yet rare presentations appear to be the norm for this young man who had already endured so much.

The patient was sent to Cleveland Clinic's Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center and the Department of Radiation Oncology to co-manage the new brain metastasis. Our goal was to provide effective local treatment to the tumor while minimizing his time off chemotherapy, which was keeping the various other sites of metastases under reasonable control.



Gamma Knife® radiosurgery was the treatment of choice in this patient, as it delivers high-intensity, targeted radiation, typically in a single session, to effectively control even radioresistant brain metastases such as those from osteosarcoma. Further, Gamma Knife surgery is an outpatient procedure requiring no meaningful recovery time, so it allowed resumption of his chemotherapy immediately following treatment.

### A New Approach to Gamma Knife Radiosurgery

Unfortunately, while the brain metastasis was stable for a year, it began growing again. The Gamma Knife treatment had transiently controlled the brain tumor but had not ablated all of the cancer cells within it, and they appeared to emerge from their dormant state and grow again.

Fortunately, we were able to offer this patient staged Gamma Knife radiosurgery, a new approach that involves two treatments one month apart, each with a medium-high dose of radiation that intensifies delivery of radiation without injuring the brain. This “1 + 1 = 3” approach serves to better protect the surrounding normal brain tissue from excessive radiation while giving an even higher than normal dose to the brain metastasis, in hope of eradicating it with higher radiation dosing.

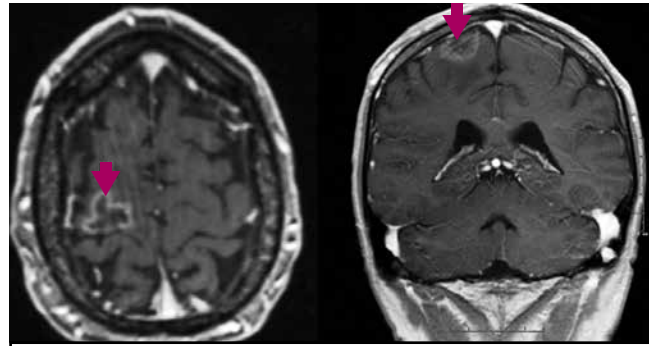
Staged Gamma Knife radiosurgery is a novel treatment first performed in Japan within the past few years and recently reported by Yomo and Hayashi.<sup>1</sup> In 2015, Cleveland Clinic became the first site outside Japan to provide this pioneering therapy. It offers new hope for patients with very large or radioresistant brain tumors that don't respond to standard Gamma Knife radiosurgery.

### Promising Outcomes in This Patient and Others

Since we began performing staged Gamma Knife radiosurgery for large and/or radioresistant tumors, this patient and many others with equally challenging brain metastases have responded well to it. At Cleveland Clinic, staged Gamma Knife radiosurgery for large brain metastases has been shown to be feasible, safe and effective. Preliminary results have demonstrated significant ( $p = 0.002$ ) reduction in the size of the metastasis after the second Gamma Knife treatment and a 90.5 percent response rate (data being prepared for publication).

While early results are excellent, it will take time to know whether this approach can offer durable control of the most therapeutically challenging category of brain metastases while minimizing short- and intermediate-term effects of our interventions.

For now, however, the case patient remains fully functional and is able to live independently and work. The amount of swelling around his brain tumor has decreased and the tumor has not enlarged. He has no neural deficit, and no



**Figure 1.** Axial and coronal brain images of the patient at a recent examination following staged Gamma Knife radiosurgery. Arrows point to his lesion.

new metastatic sites have appeared in his brain or spine. Figure 1 presents axial and coronal images showing the size of his lesion at a recent follow-up appointment.

Each time the patient looks at us with his gentle, smiling eyes and shakes our hands with his own hand calloused from hard work as a carpenter, there is no doubt about the huge impact on his life made by this pioneering treatment approach and all the care received from his multidisciplinary management team.

In a highly complicated case like this, when a patient develops metastases throughout the body, Cleveland Clinic Cancer Center's multidisciplinary approach is especially important. This patient's many providers have worked together closely to ensure prompt interventions (often with aggressive therapies) and meticulous integration of his many concomitant treatments through careful monitoring. When that collaborative approach has yielded as much as it can, we have been ready to try novel approaches as necessary.

Advances in genomics, immunotherapy and other areas are extending cancer patients' survival. As patients live longer, they will require ongoing systemic treatments. To help patients take full advantage of their additional time, it is imperative that we develop therapies that are not only effective but physiologically minimally invasive and minimally intrusive on quality of life. Staged Gamma Knife radiosurgery has the potential to meet all of those criteria, creating an opportunity for patients who previously would have succumbed to their disease to continue meaningful, productive activities.

We are honored to help this young man maintain his excellent quality of life, and we are committed to helping him continue to beat the odds against a tremendously tenacious malignancy.

### Reference

1. Yomo S, Hayashi M. A minimally invasive treatment option for large metastatic brain tumors: long-term results of two-session Gamma Knife stereotactic radiosurgery. *Radiat Oncol*. 2014 Jun 10;9:132.

## Save the Date

### CONTINUING MEDICAL EDUCATION

**August 3-6, 2016**

#### **Palliative Medicine and Supportive Oncology 2016 Symposium**

Marriott Key Center, Cleveland

[ccfcme.org/pallmed16](http://ccfcme.org/pallmed16)

**Oct. 22-23, 2016**

#### **18th Annual Brain Tumor Update and 7th Annual International Symposium on Long-Term Control of Metastases to the Brain and Spine**

The Cosmopolitan of Las Vegas

Las Vegas, Nevada

[ccfcme.org/brainmets16](http://ccfcme.org/brainmets16)

**Oct. 28, 2016**

#### **Third Annual Multidisciplinary Colorectal Oncology Course**

InterContinental Hotel and Conference Center, Cleveland

[ccfcme.org/colorectal16](http://ccfcme.org/colorectal16)

**Nov. 10, 2016**

#### **Multidisciplinary Genitourinary Oncology Course**

InterContinental Hotel and Conference Center, Cleveland

[ccfcme.org/genitourinary16](http://ccfcme.org/genitourinary16)

**March 10-11, 2017**

#### **2017 Multidisciplinary Head and Neck Cancer Update**

Loews Portofino Hotel, Orlando, Florida

Contact Sheryl Krall at [kralls2@ccf.org](mailto:kralls2@ccf.org) or 216.444.7924.

#### **Cleveland Clinic Tumor Board Series**

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#### **Dale Shepard, MD, PhD, FACP, Earns NCI Team Leadership Award**

Cleveland Clinic Cancer Center oncologist Dale Shepard, MD, PhD, FACP, is a 2016 recipient of the National Cancer Institute's Cancer Clinical Investigator Team Leadership Awards (CCITLAs).

Dr. Shepard, who directs Cleveland Clinic Cancer Center's phase I clinical trials and sarcoma programs, is one of 13 cancer researchers nationwide to be honored with this year's CCITLAs. The grant awards recognize and support outstanding mid-career clinical investigators at NCI-designated cancer centers.

The awards, established in 2009, are presented to academic clinical researchers who have extensive involvement in NCI-funded collaborative clinical trials and who promote clinical trials and research. Candidates are nominated by the director of their cancer center and must be board-certified physicians or other oncology clinicians, be full-time faculty members and have practiced medicine three to 10 years post-fellowship.

CCITLAs provides partial salary support for two years for the recipient to take part in activities related to the award. Dr. Shepard plans to work to further expand Cleveland Clinic Cancer Center's phase I clinical trials program, which has increased fourfold in annual accrual to disease-nonspecific trials under his leadership since 2014.

He also will increase his participation in the Case Comprehensive Cancer Center's (Case CCC) Developmental Therapeutics Program, which identifies and evaluates innovative new anti-cancer agents, and will work with regional oncology practices to expand awareness of phase I trials availability and enroll new patients. Cleveland Clinic is a partner in the Case CCC along with Case Western Reserve University and University Hospitals Case Medical Center.

"Dr. Shepard is an excellent leader and a talented, dedicated clinician, educator and colleague who makes numerous contributions to the Cleveland Clinic Cancer Center and the Case CCC," says Brian J. Bolwell, MD, FACP, Chairman of Taussig Cancer Institute and Associate Director of the Case CCC. "His efforts to grow the phase I program are producing real benefits for our patients while helping our researchers gain valuable knowledge. This well-deserved award will help Dr. Shepard continue to improve access and enrollment."

Dr. Shepard also is Cleveland Clinic Cancer Center's principal investigator for a newly awarded NCI grant to fund collaborative phase I/II cancer clinical trials. The UM-1 supplemental grant will support an alliance among the Case CCC, the Ohio State University Comprehensive Cancer Center and the University of Kentucky's Markey Cancer Center to conduct early-phase NCI-sponsored research that combines pharmacology-focused (phase I) and disease-focused (phase II) investigators in the same program. The grant will provide another important source of clinical trials access for Cleveland Clinic Cancer Center and the Case CCC.

Dr. Shepard is a staff member of the Department of Hematology and Medical Oncology and the Center for Geriatric Medicine. He is an Assistant Professor of Medicine at Cleveland Clinic Lerner College of Medicine.

## New Staff

**Aneel Chowdhary, MD**  
Regional Oncology



**Joel Marcus, PsyD**  
Psychosocial Oncology



**Ravi Verma, MD**  
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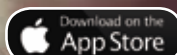
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The Cancer Center's more than 450 physicians, researchers, nurses and technicians care for thousands of patients each year and provide access to a wide range of clinical trials. Cleveland Clinic Cancer Center unites clinicians and researchers based 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, and at Cleveland Clinic Florida. Cleveland Clinic is a nonprofit academic medical center ranked as the No. 2 hospital in the country (*U.S. News & World Report*), where more than 3,400 staff physicians and researchers in 140 specialties collaborate to give every patient the best outcome and experience.