

Cancer Advances

Cleveland Clinic Cancer Center | Winter 2019

Harnessing the
Power of Precision
Oncology



The diagram illustrates the progression of cancer through three stages, represented by ovals containing cells. The first oval shows a diverse population of cells in various colors (blue, red, green, yellow, purple, brown). The second oval shows a population where most cells are red, with a dashed circle highlighting a subset of red cells labeled n_1 . The third oval shows a population almost entirely composed of red cells, with a dashed circle also labeled n_1 . Arrows indicate the progression from the first to the second, and then to the third stage. In the bottom left corner, the mathematical formula $\sum_{i=1} n_i \sim \mu$ is displayed.

$$\sum_{i=1} n_i \sim \mu$$

Dear colleagues,

Welcome to this issue of *Cancer Advances*. Our cover story features a sampling of our work in genetics and genomics, which is shifting the focus of questioning in oncologic research and care from tumor location to genetic mutation. Our researchers are approaching questions of cancer genetics from across the continuum, including detecting cancers at an earlier stage (p. 4), best practices in testing for non-small cell lung cancer (p. 6), expanding the use of predictive assays (p. 7), treatments targeting individual tumor DNA (p. 8) and a new National Cancer Institute grant to study response prediction in radiation oncology (p. 10).

Our leadership in developing the accreditation program for rectal cancer (p. 22) and the continued relevance and utility of the Khorana score (p. 14) showcase our ability to determine the line of inquiry at the national level.

Our multidisciplinary Sarcoma Program continues to investigate better treatments for this rare cancer while providing patients with a level of expertise matched by few centers in the United States (p. 16). Our work on potential new therapies for acute myeloid leukemia (p. 20) and breast cancer (p. 13) demonstrates the promising results of the continued pursuit of inquiry for our patients.

Finally, we demonstrate our ability to ask complex questions with the work we're pursuing on laser interstitial therapy with colleagues in the Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center (p. 24).

I hope this issue of *Cancer Advances* sparks new insights into your research and clinical questions, and I welcome the opportunity to collaborate, to discuss new ideas and to answer your questions, from bench research to clinical trials to operations and strategies for optimal clinical alignment. If we can help you with a patient's care or a clinical issue, please let me know.

Sincerely,

Brian J. Bolwell, MD, FACP

Chairman, Taussig Cancer Institute
Cleveland Clinic Cancer Center
bolwelb@ccf.org | 216.444.6922
On Twitter: @BrianBolwellMD

Advancing Precision Oncology

**from Risk Prediction
to Treatment Response**

Cancers are increasingly seen as diseases of the genome. The characterization of genetic and protein abnormalities now often determines how cancers are diagnosed and treated. Precision oncology uses genetic information from an individual's cancer to determine the most effective treatment, and allows the use of an agent targeted to that specific genetic abnormality.

This increasingly complex and variable picture of cancer further underscores the need for innovative responses. Novel approaches are essential in every realm of cancer care: genomic data collection and analysis; drug development; clinical trial design; surgery, radiation and chemotherapeutics; cost reimbursement strategies; research funding.

Fortunately, there is no shortage of inventive work underway when it comes to cancer care. Cleveland Clinic's strong clinical genomics program, housed in the Center for Clinical Genomics, enhances the Cancer Center's efforts to harness precision oncology for the benefit of patients. Many tumors undergo testing for genomic alterations, which are then reviewed by the Genomics Tumor Board, a regular meeting with various oncologists, translational scientists, pathologists and genetic counselors.

Experts then alert each patient's physician to recommended, individualized treatment options, as well as to clinical trials for which the patient might be an appropriate candidate. Every eligible patient is offered tumor genomic profiling.

"It's a very exciting time. Personalized cancer medicine is real," says Brian Bolwell, MD, Chair of Cleveland Clinic's Taussig Cancer Institute. "It's not theoretic; it's happening today in clinic. In some cancers for which we didn't have much to offer patients 10 to 15 years ago, we now have targeted therapies that are extending their lives and giving them a good quality of life as well."

The following projects demonstrate a sampling of Cleveland Clinic's expertise across the continuum, from prediction and prevention to diagnosis and treatment.



Cleveland Clinic's Charis Eng, MD, PhD, and former Vice President Joe Biden receive the 2018 Medal of Honor from the American Cancer Society...11

Table of Contents

ADVANCING PRECISION ONCOLOGY

Detecting Early-Stage Cancers

Circulating Cell-Free Genome Atlas Substudy Demonstrates Project's Potential to Map Cancer Genetics...4

Best Practices in Testing

Next-Generation Sequencing Saves Time and Money for Treatment of Metastatic Non-Small Cell Lung Cancer...6

Expanding the Use of Predictive Assays

Multigene Assay Holds Prognostic Promise for Renal Cell Carcinoma...7

Treatments Targeting Individual Tumor DNA

ALLELE: Guiding Glioblastoma Treatment with Tumor Genetics...8

Predicting Responses to Therapy

Abazeed Receives \$2 Million Grant to Study Role of Genetic Composition in Predicting Radiation Therapy Efficacy...10

.....
T-DM1 + Neratinib's Safety and Efficacy in Women with Metastatic *HER2*+ Breast Cancer...13

The Khorana Score, 10 Years Later...14

Sarcoma: Rare, Complex, Approachable with Appropriate Care...16

VeloSano: 100% for the Cure...19

How Nucleophosmin Mutation Causes Acute Myeloid Leukemia...20

Developing the National Accreditation Program for Rectal Cancer...22

Tumor Ablation with Chemo-Radiotherapy Consolidation Yields Rare Durable Remission of Glioblastoma...24

New Staff...26

Chairman's Q&A: Cultivating Emotional Intelligence Through Asking Questions...26

Resources for Physicians...28

Cover image: The work of researcher and radiation oncologist Mohamed Abazeed, MD, PhD, explores whether the genetic composition of lung cancer cells can predict response to radiotherapy. Dr. Abazeed recently received a \$2 million grant from the National Cancer Institute for this research.

ADVANCING PRECISION ONCOLOGY

Detecting Early-Stage Cancers

Circulating Cell-Free Genome Atlas Substudy
Demonstrates Project's Potential to Map Cancer Genetics

Dr. Klein is Chair of Cleveland Clinic Glickman Urological & Kidney Institute and Professor of Surgery at Cleveland Clinic Lerner College of Medicine.

He can be reached at kleine@ccf.org or 216.444.5591.

On Twitter: @EricKleinMD

Cleveland Clinic researchers are helping build a database that could lead to the development of a blood test for early-stage cancer and promises to shed new light on the biology of cancer at its initial stages. Results of a preplanned substudy of this multicenter clinical trial — the Circulating Cell-Free Genome Atlas (CCGA) — were presented at the 2018 American Society of Clinical Oncology (ASCO) meeting.

NCT02889978 at a glance

The observational study, funded by GRAIL Inc., has so far enrolled > 11,000 of 15,000 planned participants (70 percent with cancer, 30 percent noncancer) in order to characterize the population variation in cancer and noncancer subjects. The research team will use deep sequencing of cell-free nucleic acids in the blood, an emerging biomarker for earlier cancer detection, to develop a detailed atlas of cancer genetics.

The Center for Clinical Genomics team, along with primary investigators Eric A. Klein, MD, Chair of Cleveland Clinic Glickman Urological & Kidney Institute, and Mikkael Sekeres, MD, MS, Director of Cleveland Clinic Cancer Center's Leukemia Program, will help recruit more than 1,000 Cleveland Clinic patients over the age of 20.

"The complex nature of cancer makes it difficult to identify biomarkers for detection of early-stage cancer before symptoms appear," says Dr. Sekeres. "The CCGA study will expand our knowledge about genomic profiles in cancer patients."

Substudy methods and results

The preplanned substudy of 1,627 participants collected blood from 878 participants with newly diagnosed, untreated cancer (20 tumor types, all stages) and 749 participants with no cancer diagnosis (controls) for plasma cell-free DNA (cfDNA) extraction. The team performed three prototype sequencing assays: paired cfDNA and white blood cell (WBC) targeted sequencing (507 genes, 60,000X) for single nucleotide variants/indels, cfDNA whole genome bisulfite sequencing (30X) for methylation, and paired cfDNA and WBC whole-genome sequencing (30X) for copy number variation. WBC sequencing identified the contribution of clonal hematopoiesis.





Dr. Sekeres is Director of Cleveland Clinic Cancer Center's Leukemia Program and Professor of Medicine at Cleveland Clinic Lerner College of Medicine.

He can be reached at sekerem@ccf.org or 216.445.9353.

On Twitter: [@MikkaelSekeres](https://twitter.com/MikkaelSekeres)

Results from this first set of patients demonstrate that:

- Strong biological signals are present in unscreened cancers that are typically diagnosed at late stages.
- Signals correlate highly across assays. With specificity set at 98 percent, sensitivity ranged from 56 to 80 percent for a wide range of early-stage (I-III) cancers, many of which currently lack good screening tests.

"These exciting results suggest that these assays are sensitive and specific ways of detecting a variety of cancers at an early stage," says Dr. Klein. "The results demonstrate the power of current sequencing technology and add to the growing trend of personalized cancer medicine."

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

Please direct correspondence to:

Taussig Cancer Center / CA
Cleveland Clinic
9500 Euclid Ave.
Cleveland, OH 44195

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.

Cancer Advances Medical Editor

Brian I. Rini, MD, FACP
Director, Genitourinary Cancer Program

Managing Editor

Deborah Booth Summers

Designer

Amy Buskey-Wood

Photography

Russell Lee, Steve Travarca, Don Gerda, Yu Kwan Lee, Annie O'Neill, Matt Kohlmann

Cancer Advances is written for physicians and should be relied on for medical education purposes only. It does not provide a complete overview of the topics covered and should not replace the independent judgment of a physician about the appropriateness or risks of a procedure for a given patient.

© 2018 The Cleveland Clinic Foundation

ADVANCING PRECISION ONCOLOGY

Best Practices in Testing

Next-Generation Sequencing Saves Time and Money for Treatment of Metastatic Non-Small Cell Lung Cancer

Dr. Pennell is staff in the Department of Hematology and Medical Oncology and Associate Professor of Medicine at Cleveland Clinic Lerner College of Medicine.

He can be reached at pennelln@ccf.org or 216.445.9282.

On Twitter: @n8pennell

Biomarker-driven treatment strategies are advancing for metastatic non-small cell lung cancer (mNSCLC). In the past two years, the number of biomarkers has grown from one to four and could increase to six or seven in the next couple of years.

This presents a challenge for physicians as well as government and private insurance organizations: Does it make sense not just medically but also economically to test for each biomarker sequentially or to perform one test — next-generation sequencing (NGS) — for a complete picture of the cancer's DNA?

That was the question Nathan Pennell, MD, PhD, staff in the Department of Hematology and Medical Oncology, and colleagues sought to answer by creating a decision analytic model studying four genetic testing scenarios for patients with mNSCLC.

"Traditionally when we had one or two biomarkers, you would do a test and then wait for the results. If it came back positive, you would treat the patients, and if it came back negative, you would do the next test," says Dr. Pennell, who presented the results of the model at ASCO 2018.

"But now that we have a minimum of four biomarkers, it has become more difficult to justify doing these tests sequentially," he says. "Not only does it take time to do each test, you start running out of tissue from their biopsy. So then you have to get a new biopsy to perform more testing. And, of course, each test costs money."

Four testing approaches

Dr. Pennell and his colleagues created a decision analytic model to illustrate which genetic testing approach was better in terms of cost and time. The model had four different testing arms, and the team built a variety of measures into the model, including turnaround time



for tests, unit costs and mNSCLC prevalence based on literature, public data and expert opinion. In addition, time to receive results and total cost (test plus rebiopsy) were calculated for each modality and compared with NGS.

The model estimated that for a hypothetical 1 million-member insurance plan, 2,066 mNSCLC patients with Centers for Medicare & Medicaid Services (CMS) insurance and 156 mNSCLC patients with private insurance would need to be tested for genomic alterations. NGS testing saves CMS payers between \$1.4 and \$2.1 million, with proportionate savings for commercial payers. With NGS and hotspot panel testing, patients start therapy 2.8 and 2.7 weeks faster than with the sequential and exclusionary options, respectively. The authors concluded that NGS testing in mNSCLC patients saves time and money for patients and payers, and more quickly identifies the appropriate treatment for an individual patient.

Dr. Pennell says part of the impetus for creating the model was to help insurers understand that using NGS will save both time and money. "Historically, insurers have resisted covering new technology to do tests," he says. "We wanted to illustrate that not only is this the right thing to do because patients get timely results to help guide treatment, but ultimately it will cost the insurers less."

ADVANCING PRECISION ONCOLOGY

Expanding the Use of Predictive Assays

Multigene Assay Holds Prognostic Promise for Renal Cell Carcinoma

Approximately 30 percent of patients with stage I-III renal cell carcinoma (RCC) will relapse. The lack of accurate methods for estimating the true risk of recurrence in RCC has made it difficult for clinicians and patients to make informed decisions regarding treatment options. Standard risk classification systems — tumor, node, metastasis (TNM) staging; Fuhrman grade and ECOG performance status — which analyze clinicopathologic parameters only, have limited prognostic value. A new study validating a multigene assay hopes to change that landscape.

In other tumor types, such as breast, prostate and colon, multigene assays that reveal unique tumor biology have been extensively validated and shown to provide prognostic, and sometimes predictive, information beyond traditional parameters that can guide the selection of adjuvant therapy.

Over the past decade, a 16-gene recurrence score (RS) assay, consisting of 11 cancer-specific and five reference genes, has been developed and validated in one study of

RCC patients with stage I-III disease. Cleveland Clinic participated in a second study to confirm the assay's validity and provide the required level 1B evidence needed for the assay's inclusion in treatment guidelines.

Study analyzes patient data

The first validation study was based on an observational cohort of untreated stage I-III RCC patients.¹ The latest study analyzed primary RCC tumor tissue from 212 participants, with a focus on 193 with stage III RCC, from the randomized prospective trial S-TRAC (Sunitinib as Adjuvant Treatment for Patients at High Risk of Recurrence of Renal Cell Carcinoma Following Nephrectomy).² In S-TRAC, one-year adjuvant treatment with sunitinib, a multitargeted kinase inhibitor, prolonged disease-free survival versus placebo in patients with locoregional, high-risk RCC following nephrectomy. Based on the trial results, the U.S. Food and Drug Administration (FDA) recently approved sunitinib for adjuvant treatment for this category of RCC patients.

With the introduction of kinase inhibitors like sunitinib and the immune checkpoint inhibitor nivolumab, the RCC treatment landscape has rapidly evolved over the past decade. Having a validated multigene assay may enable more astute selection of adjuvant therapy for locoregional and metastatic RCC.

The recent study's primary objectives were to validate the prognostic ability of the RS assay to differentiate recurrence risk in untreated RCC patients with

Dr. Rini leads Cleveland Clinic Cancer Center's Genitourinary Program and is Professor of Medicine at Cleveland Clinic Lerner College of Medicine.

He can be reached at rini2@ccf.org or 216.444.9567.

On Twitter: @brian_rini

(continued on page 8)

References

1. Rini B, Goddard A, Knezevic D, et al. A 16-gene assay to predict recurrence after surgery in localised renal cell carcinoma: development and validation studies. *Lancet Oncol.* 2015;16(6):676-685.
2. Rini BI, Escudier B, Martini JF, et al. Validation of the 16-gene recurrence score in patients with locoregional, high-risk renal cell carcinoma from a phase III trial of adjuvant sunitinib. *Clin Cancer Res.* 2018;24(18):4407-4415.



(continued)

locoregional, high-risk T3, and to evaluate the potential association between RS result and benefit from sunitinib treatment.

Results validate prognostic value

The study showed that the RS assay was able to identify patients with low and high risk of recurrence, based on overexpression of certain genes, and provide independent prognostic information beyond the parameters of standard systems. The results were prognostic for time to recurrence (TTR), disease-free survival (DFS) and renal cancer-specific survival (RCSS) in both the placebo and sunitinib arms. The performance of the RS result in the placebo arm was similar to the first study with a hazard ratio (HR) for a 25-unit increase in RS result of 4.24 versus 3.91 for TTR and 7.21 versus 5.55 for RCSS. When the high and low groups were compared, the HR for recurrence was 9.18 in the placebo arm; interaction with RS results and treatment was not significant.

The assay has now been validated in more than 830 patients across RCC stages I-III. “The study confirmed the prognostic value of the gene signature. Patients will have more useful information to understand the true risk of recurrence,” says Brian Rini, MD, lead study author and Leader, Genitourinary Program, Cleveland Clinic Cancer Center.

Next step: studying predictive value

While the study showed that the RS assay was able to predict recurrence, it did not include enough samples to determine whether the assay could predict the benefit of sunitinib treatment. The next step is applying the RS assay to a larger data set; conducting another study is currently under consideration. “The data indicate that the gene signature might have predictive value,” says Dr. Rini.

ADVANCING PRECISION ONCOLOGY

Treatments Targeting Individual Tumor DNA

ALLELE: Guiding Glioblastoma Treatment with Tumor Genetics

Despite improvements in surgeries, medical therapies and radiation, the outlook for patients with glioblastoma (GBM) remains dismal. Patients live an average of just 15 months after being diagnosed with this aggressive brain tumor.

GBM’s bleak prognosis is due in large part to the heterogeneous nature of the tumor’s DNA. Tumors often have unique genetic signatures, so what works for one patient may not work for another. Researchers now are exploring whether targeting treatment based on an individual tumor’s DNA could result in better outcomes for patients with GBM.

“We’d like to know the genetic driver of the patient’s tumor before we treat them,” says Manmeet Ahluwalia, MD, Director, Brain Metastasis Research Program, Cleveland Clinic. “The genomics of glioblastoma are very diverse, and if we use targeted therapy that focuses on the genetic alterations of the tumor, the chances of success increase.”

Dr. Ahluwalia and investigators from several leading institutions are part of ALLELE, a new consortium to generate prospective clinical genomics and inform treatment decisions in patients with GBM.

Clinical trial with biomarker groups

Patients enrolled in ALLELE undergo extensive genetic testing to determine the feasibility of genotyping their tumors in a time frame that would support real-time use in clinical trials. So far, the researchers have enrolled 46 patients with GBM at five sites. The median time between surgery and biomarker analysis completion was 51 days, a clinically acceptable timeframe for patients with newly diagnosed GBM.

Of those 46 patients, 26 with MGMT-unmethylated GBM were subsequently enrolled in INSIGHt, a companion randomized multiarm trial comparing the standard of care, temozolomide, with three other experimental



Dr. Ahluwalia is Director of Cleveland Clinic's Brain Metastasis Research Program and Professor of Medicine at Cleveland Clinic Lerner College of Medicine.

He can be reached at ahluwam@ccf.org or 216.444.6145.

On Twitter: @BrainTumorDoc

adjuvant treatments — CC-115, neratinib or abemaciclib. Predefined biomarker groups EGFR, PI3K and CDK-positive will be evaluated for their ability to predict outcomes in each arm.

The first is the standard-of-care arm, in which patients receive temozolomide orally on a daily dosing schedule approximately two to three hours before daily radiotherapy. Temozolomide is administered post radiation for up to six cycles (five days/cycle). Radiation occurs for a maximum of 49 days.

In the second arm, patients receive temozolomide orally on a daily dosing schedule approximately two to three hours before daily radiotherapy. Patients receive abemaciclib post radiation in a twice-daily predetermined oral dose. Radiation occurs for a maximum of 49 days.

Patients in the third arm receive twice-daily oral dosing of CC-115 along with daily radiation for a maximum of 49 days.

In the fourth arm, patients receive temozolomide orally on a daily dosing schedule approximately two to three hours before daily radiotherapy. Patients receive neratinib post radiation in daily predetermined oral dose. Radiation occurs for a maximum of 49 days.

Hope for better outcomes

INSIGHt, which is currently enrolling patients, will look at overall survival in the experimental arms compared with the standard temozolomide arm. It will also look at secondary incidence of treatment-emergent adverse events and progression-free survival.

Eligible patients must have evidence that their tumor MGMT promoter is unmethylated and must be immunohistochemically negative for *IDH1* R132H mutations. Traditionally, the use of temozolomide is associated with just a one-month survival benefit in these patients. Hence researchers such as Dr. Ahluwalia are hopeful that the tumor-DNA tailored trial may result in improved outcomes.

“We are hoping this precision medicine-based approach is more likely to be successful compared with treating the whole group with one therapy in a heterogeneous tumor.”



ADVANCING PRECISION ONCOLOGY

Predicting Responses to Therapy

Abazeed Receives \$2 Million Grant to Study Role of Genetic Composition in Predicting Radiation Therapy Efficacy

Dr. Abazeed is associate staff in the departments of Radiation Oncology and Translational Hematology and Oncology Research, and Assistant Professor of Medicine at Cleveland Clinic Lerner College of Medicine.

He can be reached at abazeem@ccf.org or 216.445.0061.

On Twitter: [@mohamed_abazeed](https://twitter.com/mohamed_abazeed)

Researcher and radiation oncologist Mohamed Abazeed, MD, PhD, has been awarded a \$2 million grant from the National Cancer Institute (NCI) to explore whether the genetic composition of lung cancer cells can predict response to and perhaps guide strategy for radiotherapy.

Dr. Abazeed's overall objective for this award is to identify new genetic markers calibrated on the basis of radiation therapy effectiveness, and new drug-radiation therapy strategies that more precisely and effectively target the most radiation-resistant lung tumors.

"Current radiation therapy regimens use a one-size-fits-all approach, not taking into account the genetic content of individual tumors," says Dr. Abazeed. "There is an urgent need to identify genetic markers that can recognize tumors that are more or less likely to respond to radiotherapy and translate these markers for clinical use. This more personalized approach not only can improve treatment responses, but it can also potentially reduce toxicity, resulting in an improved quality of life for survivors who receive these treatments."

Efforts thus far to predict the response to radiotherapy have been limited in large part because the genetic features that regulate tumor survival — and their frequency

across and within individual cancer types — had not been studied on a large scale. In 2016, Dr. Abazeed's lab published results of the largest profiling effort of cancer cell survival after radiation, comprising a collection of 533 genetically annotated tumor cell lines from 26 cancer types.¹ Results showed significant biological diversity in the survival of cancer cells after exposure to ionizing radiation, and offered evidence that new genetic features regulating cellular response to these treatments can be identified.

Dr. Abazeed's new NCI-funded investigation aims to advance the clinical translation of a short list of the most important regulators of radiation resistance in lung cancer. The molecular pathways implicated in their studies are found in as many as approximately 30 percent of patients or as few as 7 percent. His preliminary work suggests that specific mutations in these pathways confer a strong phenotype of radiation resistance in cells, human-derived mouse xenografts and patients with non-small cell lung cancer.

Dr. Abazeed's profiling efforts have also demonstrated that some mutations that cause resistance to radiation can be subclonal. Dr. Abazeed contends that these subclones can become dominant during the course of radiation. This treatment-associated subclonal evolution may have significant implications for radiation's ability to completely eradicate tumors. On the basis of these studies, Dr. Abazeed seeks to advance a genetically guided radiosensitization strategy that makes tumor cells more sensitive to radiation therapy.

"If these hypotheses are correct, our results will demonstrate that radiotherapeutic sensitizers can be selected based on both the identity and type of genetic alterations identified in a patient's cancer, prompting an evolution in the use of radiation from a generic approach to one that is guided by the genetic composition of individual tumors," adds Dr. Abazeed.

Reference

1. Yard BD, Adams DJ, Chie EK, et al. A genetic basis for the variation in the vulnerability of cancer to DNA damage. *Nat Commun.* 2016;7:11428.





Dr. Eng Receives Prestigious **Medal of Honor** from American Cancer Society

Charis Eng, MD, PhD, Chair of the Genomic Medicine Institute and Director of the Center for Personalized Genetic Healthcare at Cleveland Clinic, received the American Cancer Society's Medal of Honor, the organization's highest award, on Oct. 18, 2018, in Washington, D.C. She was honored alongside four others who also "have made advances of unique magnitude in the understanding, diagnosis, treatment, cure and prevention of cancer and whose professional careers have engendered widespread feelings of admiration and respect."

This year's recipients include former Vice President Joe Biden. Past recipients include former President George H.W. Bush, Senator Ted Kennedy, cancer researcher Judah Folkman and U.S. Surgeon General C. Everett Koop.

Dr. Eng, an internationally renowned pioneer in cancer genomic medicine, was honored for her clinical research, which has significantly improved patient outcomes.

"I am honored and humbled to receive this award," she says. "To receive it on stage with the Honorable Joe Biden as well as Jennifer Doudna and Emmanuelle Charpentier, co-discoverers of CRISPR-Cas9 gene editing, is overwhelming."

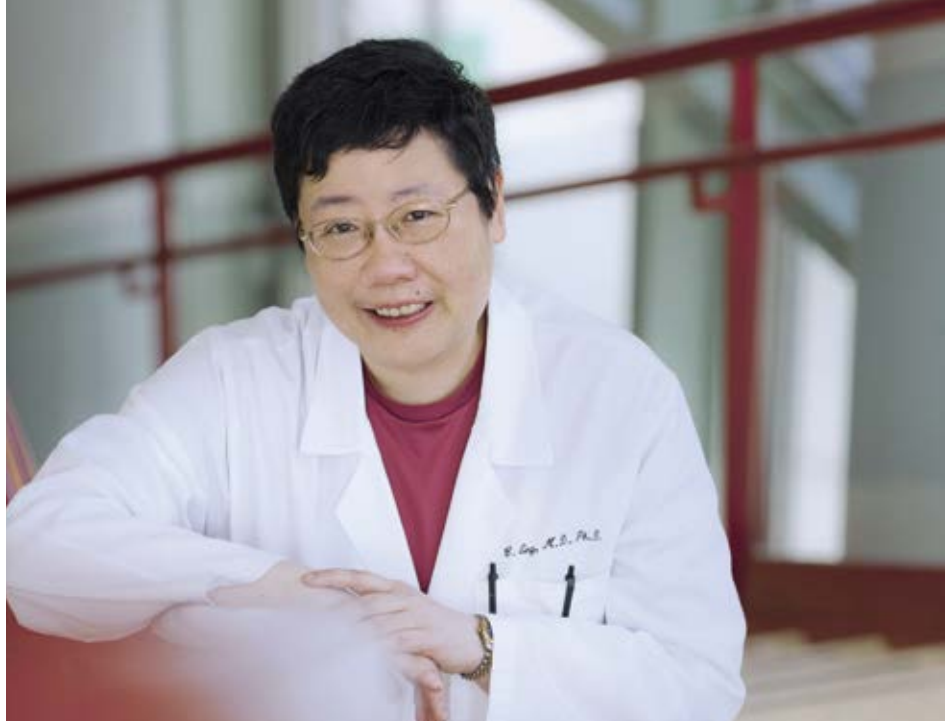
Michael Thun, MD, Emeritus Vice President of Epidemiological Research at the American Cancer Society, also received a 2018 Medal of Honor.

"Our Medal of Honor recipients embody what the American Cancer Society is all about," says Gary M. Reedy, Chief Executive Officer of the American Cancer Society. "We bestow this highest honor on these individuals for their significant contributions to the advancement and impact of our collective efforts to save more lives from cancer."

Connecting genetic mutations to cancer

Dr. Eng has dedicated her career to understanding the genes that play a role in heritable cancers and translating those findings into improved patient care.

Her research revealed the relationship between certain germline *PTEN* mutations and Cowden syndrome, which carries high risks of breast, thyroid and other cancers. Since then, she and her colleagues have linked other gene mutations for Cowden and Cowden-like syndromes as well as pheochromocytoma. These discoveries are helpful for examining the pathogenesis of common cancers, as well as for diagnosis, prognosis, therapy and prevention — building the foundation of precision oncology.



About Dr. Eng

Dr. Eng grew up in Singapore and the United Kingdom and entered the University of Chicago at age 16. After earning an MD and PhD there, she specialized in internal medicine at Beth Israel Hospital in Boston and completed a fellowship in medical oncology at Harvard's Dana-Farber Cancer Institute. She then trained in clinical cancer genetics at the University of Cambridge and the Royal Marsden NHS Trust, and completed postdoctoral research training in human cancer genomics at the University of Cambridge.

When she returned to Dana-Farber Cancer Institute in 1995, she was one of only two formally trained clinical cancer geneticists in the U.S.

Dr. Eng joined Cleveland Clinic in 2005, where she founded and leads the Genomic Medicine Institute and its clinical arm, the Center for Personalized Genetic Healthcare. She holds the Sondra J. and Stephen R. Hardis Endowed Chair in Cancer Genomic Medicine and has published more than 500 peer-reviewed articles.

Among her numerous accolades, Dr. Eng has been elected to the American Society for Clinical Investigation, the Association of American Physicians and the National Academy of Medicine. She served on the U.S. Department of Health and Human Services Secretary's Advisory Committee on Genetics, Health and Society, and has been named one of the most influential biomedical researchers in the world.

"We currently can predict a group's risk of getting specific cancers, but my long-term goal is to predict individuals' risk," says Dr. Eng. "We are looking at various modifying factors that interact with germline mutations. The time is ripe to identify and deliver targeted therapies for patients with heritable gene mutations."

Most recently, Dr. Eng's work has focused on exploring the microbiome of cancers, which could offer a new perspective in the battle against the disease.

"My hope is to find a biomarker that would help us diagnose breast cancer early and easily," she says. "In our wildest dreams, we hope we can use microbiomics right before breast cancer forms, and then prevent cancer with probiotics or antibiotics."

SAVE THE DATE

CONTINUING MEDICAL EDUCATION

For a full list of CME events, please visit ccfcme.org.

Feb. 13, 2019

Breast Cancer Update: Review of Breast Cancer Symposia

Embassy Suites Hotel

Independence, OH

ccfcme.org/breastcancerupdate

Feb. 22-24, 2019

12th Annual International Symposium on Stereotactic Body Radiation Therapy and Stereotactic Radiosurgery

Grand Floridian Hotel

Orlando, FL

Visit ccfcme.org as registration information becomes available.

March 8-9, 2019

2019 Multidisciplinary Head and Neck Cancer Update

Marriott Harbor Beach Resort & Spa

Fort Lauderdale, FL

ccfcme.org/headandneck19

April 1-5, 2019; May 13-17, 2019; June 24-28, 2019;

Aug. 19-23, 2019; Oct. 7-11, 2019; Dec. 2-6, 2019

Leksell Gamma Knife® Perfexion™ Course

Cleveland Clinic Gamma Knife Center

Cleveland, OH

Visit ccfcme.org as registration information becomes available.

April 5, 2019

14th Annual Contemporary Issues in Pituitary Disease:

Update on Significant Challenges

Cleveland, OH

Visit ccfcme.org as registration information becomes available.

Aug. 22-23, 2019

2019 Cleveland Breast Cancer Summit

Cleveland, OH

Visit ccfcme.org as registration information becomes available.

Nov. 2-3, 2019

21st Annual Brain Tumor Update and 10th Annual Symposium on Brain and Spine Metastases Course

Cosmopolitan Hotel

Las Vegas, NV

Visit ccfcme.org as registration information becomes available.

TUMOR BOARD SERIES

Complimentary CME-certified webcasts offer expert opinions and discussion based on case presentations of patients seen at Cleveland Clinic Cancer Center.

ccfcme.org/tumorboardseries

SPEAKERS BUREAU

Cleveland Clinic Cancer Center Speakers Bureau offers presentations by leading experts on a full range of oncology topics. Educational sessions are available to physicians, nurses and other healthcare professionals. Experts in hematology, medical oncology, radiation oncology, blood and marrow transplant, palliative medicine, and translational hematology and oncology research are available. Recent topics have included management of late effects of cancer treatment, circulating tumor cells and renal cell carcinoma advancements. To customize a speaker's program for your organization's specific needs or to learn more, contact Sheryl Krall at kralls2@ccf.org or 216.444.7924.

Search Our Cancer Clinical Trials Database

Stay up to date on Cleveland Clinic's more than 200 active clinical trials for cancer patients.

.....

Search a database of open clinical trials by disease, phase, physician or location.

.....

Browse real-time information on each trial's objective, eligibility criteria, phase(s) and more.

.....

Connect to our Cancer Answer Line for more information about a trial or to enroll patients.

.....

To search the database, go to clevelandclinic.org/cancerclinicaltrials

T-DM1 + Neratinib's Safety and Efficacy in Women with Metastatic *HER2+* Breast Cancer

Phase 1b trial shows good response rate

Despite improvements in surgery, radiation and chemotherapy, 40,000 women still die each year from breast cancer, many from its most aggressive form, *HER2+* breast cancer.

Results of a phase 1b study demonstrate that a new drug combination offers a promising regimen to attack *HER2*.

"About 25 percent of breast cancers are *HER2+*, and they tend to be more aggressive," says Jame Abraham, MD, Director of the Breast Oncology Program at Cleveland Clinic Cancer Center. "Fortunately, in the past 10 to 15 years, we have developed several new treatment options for *HER2+* breast cancer that specifically target the *HER2* protein. One is trastuzumab emtansine, T-DM1. Unfortunately, not all patients respond to it."

Dr. Abraham is the principal investigator of a multi-institutional phase 1b clinical trial sponsored by the National Surgical Adjuvant Breast and Bowel Project (NSABP). The trial, called NSABP FB-10, combines T-DM1 and neratinib to treat women with metastatic *HER2+* breast cancer who relapsed or progressed after trastuzumab- and pertuzumab-containing regimens. Dr. Abraham presented data from the trial at the 2018 American Society of Clinical Oncology annual meeting.

"Neratinib was recently approved for treatment in early *HER2+* breast cancer but not metastatic breast cancer," he says. "This particular trial is testing this drug in combination with T-DM1 in women who have *HER2+* metastatic breast cancer."

T-DM1 is a conjugated antibody that targets the extracellular domain of *HER2*. With T-DM1, trastuzumab is armed to deliver the potent cytotoxic payload of DM1, a maytansinoid antimicrotubule agent, selectively to antigen-expressing *HER2+* cells.

Neratinib, on the other hand, targets tumors from within the cell. It is an irreversible tyrosine kinase inhibitor (TKI) that interrupts signaling across the ErbB family by inhibiting phosphorylation and activity of *HER2*, as well as epidermal growth factors, *HER1* and *HER4*.

Trial characteristics

In the trial, patients received concurrent therapy with T-DM1 (3.6 mg/kg IV) on day 1 of a 21-day cycle and neratinib as a continuous daily oral dose. The neratinib dose-escalation included four dose levels — 120 mg, 160 mg, 200 mg and 240 mg — and used a 3+3 design.

Twenty-four patients were evaluable for toxicity, and 20 were evaluable for efficacy. Dose-limiting toxicity occurred in six patients during cycle 1. Treatment-related grade 3 toxicities included diarrhea (five patients), thrombocytopenia (four patients) and ALT elevation (one patient).

The response lasted from 42 days to 600-plus days. There was not a correlation of dose and peak or steady-state levels; responses were seen at all doses.

High response rate

Overall, Dr. Abraham says, the combination of full-dose T-DM1 and neratinib at 160 mg/d was well-tolerated. The overall response rate was 64 percent, with four patients experiencing a complete response and nine experiencing a partial response.

"That's actually pretty high, and we're really happy with that," he says. "We have some patients going on almost two years on this regimen."

A phase 2 trial to further test the safety and effectiveness of the drug combination has already started. Depending on the results, Dr. Abraham says, a phase 3 trial may compare patients treated with T-DM1 versus those treated with T-DM1 and neratinib.

Dr. Abraham is Director of the Breast Oncology Program at Cleveland Clinic Cancer Center, Co-Director of the Cleveland Clinic Comprehensive Breast Cancer Program and Professor of Medicine at Cleveland Clinic Lerner College of Medicine.

He can be reached at abrahamj5@ccf.org or 216.445.0150.

On Twitter: [@jamecancerdoc](https://twitter.com/jamecancerdoc)



The Khorana Score, 10 Years Later

Since its introduction in 2008, the Khorana score has helped clinicians worldwide calculate the risk of venous thromboembolism (VTE) for individual cancer patients.

Dr. Khorana is Vice Chair for Clinical Services and Director of the Gastrointestinal Malignancies Program at Cleveland Clinic Cancer Center. He is also Professor of Medicine at Cleveland Clinic Lerner College of Medicine.

He can be reached at khora@ccf.org or 216.636.2690.

On Twitter: [@aakonc](https://twitter.com/aakonc)

The Khorana score uses readily available clinical information like the type of cancer, the complete blood count and a person's body mass index. Part of its advantage lies in its ease of use.

Since Alok Khorana, MD, Vice Chair for Clinical Services at Cleveland Clinic Cancer Center, and colleagues introduced this tool a decade ago, it has been validated multiple times in different countries and incorporated into a number of society guidelines. "At Cleveland Clinic, we've incorporated the score into the electronic medical record for early detection of potential clots," says Dr. Khorana.

Though subsequent investigators dubbed it the Khorana score, Dr. Khorana credits its utility and longevity to the team of colleagues that helped develop this risk stratification and prediction tool, including Charles W. Francis, MD; Gary H. Lyman, MD, MPH; Nicole M. Kuderer, MD; and Eva Culakova, PhD.

Updating the score

"Despite the score's persistent relevance over the past decade," says Dr. Khorana, "it is time to find new biomarkers to refine the score and increase its accuracy."

Part of the tool's popularity is its simplicity, so Dr. Khorana and his team are proceeding carefully with

updates to avoid adding unnecessary complexity. They address this balancing act between precision and practicality in an editorial published in *The Lancet Haematology*.¹

The team also wants to ensure that any update provides a very high positive predictive value — 70 percent or greater.

Simplicity versus complexity

For example, in the same issue of *The Lancet Haematology*, a new VTE prediction model is proposed based on two factors: tumor site risk (low or intermediate versus high or very high) and D-dimer concentrations.²

D-dimer assays are widely used in hospitals for other indications. "The test itself is not hard to order, and you can get results very quickly," says Dr. Khorana. "However, D-dimers need to be ordered in most cases — it is not a test routinely done for people with cancer. So it's an extra step, which can be a challenge because you're asking oncologists to add more to their workflow."

This raises a question: If the new tool is more accurate, is it going to be more widely used? Dr. Khorana and the team seek to strike a careful balance between clinical applicability and improved prediction.

Over the past decade, some investigators have suggested adapting the Khorana score to specific cancer types. However, the score is only designed to look at a general cancer population. "We could certainly develop a better score for each type of cancer, but we could end up with 25 different scores that no one uses," says Dr. Khorana.

References

1. Khorana AA. Simplicity versus complexity: an existential dilemma as risk tools evolve. *Lancet Haematol*. 2018;5(7):e273-e274.
2. Pabinger I, van Es N, Heinze G, et al. A clinical prediction model for cancer-associated venous thromboembolism: a development and validation study in two independent prospective cohorts. *Lancet Haematol*. 2018;5(7):e289-e298.
3. Khorana AA, Francis CW. Risk prediction of cancer-associated thrombosis: Appraising the first decade and developing the future. *Thromb Res*. 2018;164(Suppl 1):S70-S76.

Multiple applications over time

In a report in the journal *Thrombosis Research*, Dr. Khorana reviews more details of how clinicians and researchers have used the Khorana score over the past decade.³ Initially, research was focused on discovering risk factors for VTE in people receiving outpatient chemotherapy. This research led to an appreciation that VTE is multifactorial and identifying risk factors is insufficient. Thus, the team developed a risk stratification score.

Expanded uses for the score have emerged over the past decade. Examples include predicting VTE risk in inpatient cancer settings, designing subsequent thromboprophylaxis studies, targeting education about VTE to high-risk individuals and identifying a subgroup of cancer patients at risk for early mortality.

Also in this report, Dr. Khorana addresses the score's possible future. A potential adaption of the tool would involve identifying innovative biomarkers that contribute to precision medicine. "We would also like to address the knowledge gap regarding the risk of bleeding in patients treated with thromboprophylaxis, as well as learn more about how arterial events can lead to stroke and myocardial infarction in a cancer population," says Dr. Khorana.

Future studies

Dr. Khorana and the team are currently studying whether the Khorana score can be used to identify patients who might benefit from prophylaxis. Dr. Khorana is co-leading a trial with approximately 800 patients worldwide, assigning patients with a higher risk score to prophylaxis with an oral anticoagulant and comparing them with a placebo group.

They also are investigating genomics in lung cancer patients to try to improve risk prediction as well as evaluating circulating small RNA as a biomarker. Dr. Khorana just received a five-year grant from the National Heart, Lung, and Blood Institute to assess these plasma biomarkers to improve cancer risk prediction. Keith McCrae, MD, staff in Cleveland Clinic's Department of Hematology and Medical Oncology, is co-principal investigator on this grant.

Not only would identifying a plasma biomarker for cancer be less invasive than taking tumor tissue for a biopsy, it could also be easier for monitoring treatment response or disease progression over time.

The first decade of the Khorana score brought clinicians an easy-to-use prediction tool to assess their patients' risk of VTE. With ongoing refinements, conversations and research, the tool should continue to help clinicians help their patients for years to come.

Researchers Receive \$4.7M NIH Grant to Prevent Cancer-Associated Thrombosis

News BRIEFS

The National Heart, Lung, and Blood Institute (NHLBI), part of the National Institutes of Health, awarded a \$4.7 million grant to Cleveland Clinic to study the prevention of life-threatening, cancer-associated thrombosis.

The new funding will support a Cleveland Clinic-led research consortium that will focus on developing strategies to prevent cancer-associated thrombosis.

The five-year grant, led by Keith McCrae, MD, and Alok Khorana, MD, supports the creation of a new risk assessment tool to better predict which cancer patients will develop blood clots during treatment. The project, led by Cleveland Clinic's Taussig Cancer Institute and Lerner Research Institute, will coordinate a consortium of three sites involved in this NHLBI program. Other sites are Beth Israel Deaconess Medical Center (Harvard Medical School) and the University of Cincinnati.

"About 20 percent of cancer patients develop blood clots, which can cause stroke, hospitalization and delays in treatment. In fact, cancer-associated

thrombosis is the second-leading cause of death in patients with cancer," says Dr. Khorana. "This grant will help us address the challenge of identifying who will develop blood clots and enable us to treat them proactively with blood thinners to prevent this complication."

The study will incorporate data from more than 5,000 patients with colorectal, lung and pancreatic cancer enrolled in clinical trials at various research centers. Researchers will use this robust biobank to identify coagulation-related and genetic biomarkers associated with abnormal blood clotting. They will build on research that suggests that activation of a specific blood-clotting pathway may contribute to thrombosis, and that biomarkers related to that pathway may identify patients at particularly high risk of blood clots, before they happen.

The team ultimately plans to synthesize these data to develop a comprehensive risk calculator by incorporating the identified biomarkers and statistical modeling. The online risk assessment tool would be available for clinical use.

"Cancer-associated blood clots are a critical clinical problem, and we urgently need better ways to predict which patients are at greatest risk," says Dr. McCrae. "This NHLBI grant will provide new information that will greatly improve the management of patients with cancer, arming physicians with an advanced statistical tool to better identify who may develop this common and harmful side effect."

The new grant builds on important work initiated through Cleveland Clinic's Center of Excellence in Cancer Thrombosis Research, which focuses on novel approaches to the management and prevention of cancer-associated thrombosis. Since the center's establishment in 2016, a multidisciplinary team of researchers across Cleveland Clinic, with collaborators at Case Western Reserve University, have worked to study the efficacy of novel therapies, develop new preclinical models, and create and expand biorepositories. Dr. Khorana's work is supported by the Sondra and Stephen Hardis Chair in Oncology Research.



Sarcoma: Rare, Complex, Approachable with Appropriate Care

Dr. Shepard is Co-Director of the Sarcoma Program and Assistant Professor of Medicine at Cleveland Clinic Lerner College of Medicine.

He can be reached at shepard@ccf.org or 216.445.5670.

On Twitter: @ShepardDale

Dr. Mesko is Co-Director of the Sarcoma Program, Director of the Musculoskeletal Tumor Program and Assistant Professor of Surgery at Cleveland Clinic Lerner College of Medicine.

He can be reached at meskon@ccf.org or 216.444.4603.

On Twitter: @NMeskoMD

Sarcoma is a rare form of malignancy, accounting for 1 percent of all adult malignancy diagnoses. Despite long-standing educational efforts to increase recognition and improve practice patterns surrounding sarcoma care, the literature shows persistently high rates (19 to 60 percent) of unrecognized soft tissue sarcomas that undergo inappropriate, margin-positive surgical excision.

Because of its complexity and rarity, sarcoma requires a tremendous amount of very specialized expertise and care coordination. Cleveland Clinic's comprehensive Sarcoma Program better serves patients by streamlining care across multiple disciplines, which enables physicians to diagnose and treat patients with great efficiency.

"As soon as a patient is seen in clinic, the medical oncology, surgery and radiation oncology teams discuss the case," says Dale Shepard, MD, PhD, Co-Director of Cleveland Clinic Cancer Center's Sarcoma Program. "We also incorporate psycho-oncology and supportive care services from the beginning."

The Sarcoma Program includes medical oncologists (adult and pediatric), radiation oncologists, orthopaedic surgeons, other surgical subspecialists, pathologists, radiologists, palliative medicine specialists, psychosocial oncologists and other practitioners. Each discipline plays a vital role in the care of the sarcoma patient. The multidisciplinary Sarcoma Tumor Board, which meets weekly, facilitates optimal communication and patient care. All core disciplines are present, submit cases and contribute to the discussion.

Care paths and clinical trials

An additional Sarcoma Program initiative involves developing specific care paths structured around certain bone and soft tissue sarcoma diagnoses. The care paths reflect the team's agreement about how best to evaluate patients, structure timing of multidisciplinary treatments and determine frequency and type of disease surveillance. Care paths help reduce unnecessary tests and decrease time to treatment as well as streamline processes in a way that is beneficial to patients and clinicians.

Definitive care administered at high-volume institutions with a functioning multidisciplinary sarcoma team leads to lower complication and mortality rates and better functional outcomes.¹ Dr. Shepard and colleagues see more than 175 newly diagnosed sarcoma patients each year. They receive requests for their expertise on more than 2,000 pathology consults annually from clinicians across the country.

"We also offer a wide spectrum of clinical trials, including surgery, radiation and chemotherapy studies," says Nathan W. Mesko, MD, orthopaedic surgeon, Co-Director of the Sarcoma Program and Director of the Musculoskeletal Tumor Program. Examples include trials led by Lukas Nystrom, MD, Orthopaedic Surgery, who is studying wound healing in radiated soft tissue sarcoma using transcutaneous oxygen; several clinical trials from Peter Anderson, MD, Pediatric Hematology Oncology and Blood and Marrow Transplantation, who specializes in pediatric sarcoma; and sarcoma chemotherapy trials led by Dr. Shepard, including a trial for a rare subtype of sarcoma.

Reference

1. Ogura K, Yasunaga H, Horiguchi H, et al. Impact of hospital volume on postoperative complications and in-hospital mortality after musculoskeletal tumor surgery: analysis of a national administrative database. *J Bone Joint Surg Am.* 2013;95(18):1684-1691.



Left to right: Chirag Shah, MD; Jacob Scott, MD, DPhil; Dale Shepard, MD, PhD; and Nathan W. Mesko, MD

Innovative treatment options for retroperitoneal sarcomas

Two Cleveland Clinic radiation oncologists are developing unique treatments for retroperitoneal sarcoma, an aggressive disease often presenting close to vital tissues. Chirag Shah, MD, and Jacob Scott, MD, DPhil, radiation oncologists and sarcoma specialists, generally target retroperitoneal sarcomas in one of two ways:

Brachytherapy. In this strategy, physicians place one or more catheters in the area surrounding the tumor or its resection bed to deliver radiation therapy directly to the sarcoma. Brachytherapy can often deliver a higher dose of radiation faster and in a more conformal/targeted way as compared with standard external beam radiation. Radioactive implants in these cases are temporary.

Interstitial brachytherapy is one of the unique treatments for retroperitoneal sarcoma offered by Drs. Shah and Scott. Very few centers in the U.S. offer this treatment, and Drs. Shah and Scott were recently co-authors on national guidelines regarding this technique.

External beam radiation therapy. In external beam radiation, a linear accelerator device directs beams of high-energy radiation at the tumor from outside the body (Figure 1).

An advantage of this external delivery is flexibility — physicians can target the tumor from any angle. Most people receive a series of treatments, typically five days a week for five to six weeks.

(continued on page 18)

Dr. Shah is Director of Clinical Research and Breast Radiation in the Department of Radiation Oncology and Associate Professor of Medicine at Cleveland Clinic Lerner College of Medicine.

He can be reached at shahc4@ccf.org or 216.445.8180. On Twitter: @CShahMD

Dr. Scott is associate staff in the departments of Translational Hematology and Oncology Research, and Radiation Oncology.

He can be reached at scottj10@ccf.org, 216.445.5962 or online at lerner.ccf.org/thor/scott/lab.

On Twitter: @CancerConnector



Figure 1. A 3D surface representation showing external beam radiation therapy to treat retroperitoneal sarcoma.

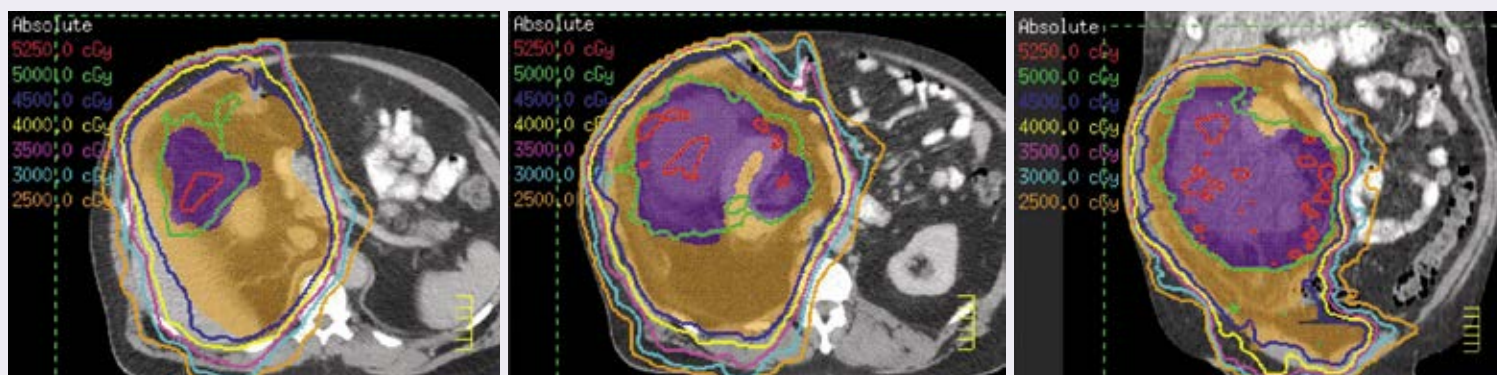


Figure 2. Images of radiation treatment plan for retroperitoneal sarcoma sparing normal tissue structures.

(continued)

“We also perform image-guided radiation therapy where we can perform daily tracking of the patient’s tumor with a CT scanner attached to a linear accelerator during external beam radiation therapy,” Dr. Shah says. This helps ensure radiation accurately targets the changing tumor throughout the series of treatments.

In conjunction with external beam, Cleveland Clinic is one of the few centers nationally that offers patients an intraoperative radiation therapy boost following external beam radiation therapy for cases that require additional treatment.

The importance of precision

Retroperitoneal sarcomas often arise very close to healthy, vital tissue and organs. Dr. Shah and colleagues are evaluating new radiation therapy strategies for retroperitoneal sarcomas that further refine their ability to minimize risk to nearby organs (Figure 2). In so doing, they also hope to minimize some of the side effects patients experience. For example, they are using techniques such as simultaneous integrated boost and differential dose per fraction that deliver higher doses to areas away from tissues at risk while rapidly reducing doses near critical structures.

Coordinated care in international guidelines

To maximize the likelihood of a successful outcome, international guidelines recommend referral of patients to a high-volume center with a collaborative, multidisciplinary team of physicians adept at addressing retroperitoneal sarcomas.

The European Society for Medical Oncology (ESMO) and the European Network for Rare Adult Solid Cancer (EURACAN), for example, support coordinated, expert care for retroperitoneal sarcomas in new guidelines released in May 2018.

Advancing care through clinical trials

Ultimately, each patient and each retroperitoneal sarcoma presentation is unique. “The most important things to know are that these sarcomas can be quite aggressive locally, and they can recur,” says Dr. Shah. When a physician sees a mass in the retroperitoneum, he or she should refer the patient to a high-volume sarcoma team right away, he adds.

VELOSANO

100% for the cure

VeloSano 5 Draws Nearly 26,000 Donations

This past July, 3,500 riders, virtual riders and volunteers from 28 states, the District of Columbia, England, New Zealand and Spain made VeloSano 5 a success, raising over \$4.5 million to support cancer research at Cleveland Clinic. More than 26,000 donations were received from all 50 states and 39 countries.

Every dollar directly benefits Cleveland Clinic in the research areas of cancer genomics, immunotherapy and clinical trials. The research VeloSano 5 will support will be announced in early 2019.

Since 2014, VeloSano has raised more than \$17 million in the fight against cancer.

VeloSano 6 weekend is scheduled for July 19-21, 2019. Get involved today at velosano.org.



How Nucleophosmin Mutation Causes Acute Myeloid Leukemia

Groundbreaking study paves way for targeted therapy

Dr. Sauntharajah is staff in the Department of Hematology and Medical Oncology and Professor of Medicine at Cleveland Clinic Lerner College of Medicine.

He can be reached at saunthy@ccf.org or 216.444.8170.

On Twitter: @Sauntharajah

Nucleophosmin (*NPM1*) is the most frequently mutated gene in de novo acute myeloid leukemia (AML). But just how this mutation causes leukemia has been unknown, until now.

A new study has revealed how *NPM1* mutation disrupts the master circuit that makes granulocytes and monocytes, thereby stalling myeloid precursor cells at inherently proliferative points in their maturation course.¹

“We are most excited because we show how we can turn this information into nontoxic treatment that reverses the mechanism of leukemogenesis. By understanding how myeloid differentiation is blocked, we can unblock it,” says the study’s team lead Yogen Sauntharajah, MD, staff in the Department of Hematology and Medical Oncology at Cleveland Clinic Cancer Center. “Our research was done in test tubes and mice, but the drug molecules we used to treat the mice are available for use in clinical trials, and we hope to move forward with such trials soon.”

What happens in myeloid cells with mutant *NPM1*

Using proteomic techniques including mass spectrometry, researchers identified the molecular machinery within myeloid cells in which *NPM1* participates. They found:

- ***NPM1* is a co-factor for PU.1 — the master transcription factor commander of monocyte lineage fates — and when *NPM1* is mutated, it drags PU.1 into cytoplasm with it.** PU.1 is notable because it commands other transcription factors



and hundreds of genes to determine cell fate. This “master transcription factor” drives the production of monocytes and contributes to the production of granulocytes. The dislocation of PU.1 from the nucleus to the cytoplasm causes it to malfunction.

- **Without PU.1 in the nucleus, its partner master transcription factors CEBPA and RUNX1 are unable to activate granulocyte lineage programs.** Large amounts of the master transcription factors CEBPA and RUNX1 are also present in AML cells (in the nucleus). These proteins collaborate with PU.1 to drive granulomonocytic differentiation. However, without PU.1, they turn off instead of turn on hundreds of granulocyte program genes.

“In brief, we discovered that mutant *NPM1* disrupts the PU.1/CEBPA/RUNX1 master circuit to repress instead of activate granulomonocyte lineage programs,” says Dr. Sauntharajah. “Maturation is the usual cue to stop replicating. Because these cells don’t mature, they continue to replicate, causing AML.”

Reversing leukemogenic actions

Can these leukemogenic actions of mutant *NPM1* somehow be reversed? That was the next step for the research team. Using in vitro and in vivo models, they discovered that:

- Mutant *NPM1* causes PU.1 to be dislocated to the cytoplasm, but moving mutant *NPM1* and PU.1 back to the nucleus activates the genes that trigger terminal monocyte differentiation.
- Selinexor, which inhibits nuclear export, effectively locks mutant *NPM1* and PU.1 in the nucleus, activating terminal monocyte differentiation. Mice treated with low, noncytotoxic doses of selinexor that were readily administered for several months, had significantly lower bone marrow and especially spleen (extramedullary) AML burden than mice not receiving selinexor.

1. Gu X, Ebrahem Q, Mahfouz RZ, et al. Leukemogenic nucleophosmin mutation disrupts the transcription factor hub that regulates granulomonocytic fates. *J Clin Invest*. 2018;128(10):4260-4279.



News BRIEFS

Familial Melanoma Diagnosis Can Signal Higher Risk for Other Cancers

People with a higher incidence of cancer — multiple melanomas, melanoma and additional cancers, or a family history of melanomas and other malignancies — can carry a higher risk for breast, prostate, brain and other cancers.

Nearly 1 in 5 of 81 patients evaluated, 18.5 percent, had a germline mutation on multiplex genetic testing. In addition, almost half of these mutations were associated with other tumor types.

“These familial traits are not only in melanoma. It’s important for patients and their families to know which other cancers they may be at risk for,” says Pauline Funchain, MD, a hematologist and medical oncologist at Cleveland Clinic Cancer Center and lead author of the study.

For clinicians treating familial melanoma, these findings reinforce the importance of sending patients to genetic counseling, says Dr. Funchain, who presented these findings at the 2018 American Society of Clinical Oncology annual meeting in Chicago.

Melanoma may be ‘more genetic than not’

Dr. Funchain and colleagues assessed patients from Cleveland Clinic’s Melanoma Program. In previous research, they found approximately 75 percent of these patients had some family history of cancer.

“Then we drilled down to find out how many have more than three people in their family with cancer — because that’s a lot,” she says. “And that was almost 30 percent.”

In the meantime, a Nordic twin study looking at concordance revealed that melanoma and prostate cancers had the highest heritability.¹

“We started getting the sense that melanoma is more genetic than not,” Dr. Funchain says. “We knew we were on to something — now we actually had to show it.”

Using patients enrolled in the Gross Family Melanoma Registry, Dr. Funchain and colleagues focused on people with a personal or family history of multiple melanomas and/or other cancer diagnoses.

They tested participants with a multiplex genetic panel for 12 genetic alterations associated with melanoma and 69 associated with other cancers. “Not only did we get a decently high rate of people with positive germline mutations ... but half of them were found in genes not even believed to be associated with melanoma.”

Multiple melanoma types tested positive

Mutations were observed across melanoma subtypes, including 12 cutaneous, two uveal and one mucosal melanoma. “Uveal melanoma is definitely a different beast than cutaneous melanoma. But we also had a mucosal melanoma that was positive, and that hasn’t been associated with any genes.”

“I think we have enough data to say — regardless of what type of melanoma a patient has — that genetic testing should be considered.”

Going forward, Dr. Funchain would like to tease out the right criteria for which patients to send to genetic counseling, “and then start learning about these genes that have not been associated with melanoma in the past.”

Reference

1. Mucci LA, Hjelmborg JB, Harris JR, et al. Familial risk and heritability of cancer among twins in Nordic countries. *JAMA*. 2016;315(1):68-76.



- Decitabine, which depletes the corepressor DNA methyltransferase 1 from the interactomes of CEBPA and RUNX1 that remained in the nucleus, activated terminal granulocyte differentiation.
- The concentrations or doses of selinexor and decitabine used did not terminate the growth of normal bone marrow cells, and normal blood counts were not decreased by several months of these treatments.

“When used together, the clinical small molecules selinexor and decitabine extended survival of mice with leukemia by more than 160 days, compared with mice that didn’t receive the drugs,” says Dr. Sauntharajah.

Precision medicine could bring new hope

These findings open the door to noncytotoxic differentiation-restoring treatments for patients with *NPM1*-mutated AML, says Dr. Sauntharajah.

NPM1 mutation is present in approximately 30 percent of AML cases. With current antimetabolite/cytotoxic treatments, only about 50 percent of these patients have long-term survival, he notes.

“There have been no targeted therapies for *NPM1*-mutated AML because, until now, we didn’t fully understand how mutant *NPM1* was leukemogenic,” says Dr. Sauntharajah. “The results of our study can bring new hope of targeted or precision noncytotoxic treatments for the many patients with chemorefractory, *NPM1*-mutated AML.”

Developing the National Accreditation Program for Rectal Cancer



In October 2017, the American College of Surgeons' Commission on Cancer, the American Society of Colon and Rectal Surgeons, the College of American Pathologists and the American College of Radiology launched a new quality improvement initiative for rectal cancer care called the National Accreditation Program for Rectal Cancer (NAPRC). The NAPRC is the result of a concerted effort of an interdisciplinary team of experts, spanning the past seven years.



Dr. Wexner is Director of the Digestive Disease Center at Cleveland Clinic Florida and Chairman of Cleveland Clinic Florida's Department of Colorectal Surgery.

He can be reached at wexners@ccf.org or 954.659.5278.

On Twitter: @SWexner

Two Cleveland Clinic physicians lead the way

Together with his colleagues, Steven D. Wexner, MD, PhD, Chairman of Cleveland Clinic Florida's Department of Colorectal Surgery, played an instrumental role in launching the initiative and facilitating its early implementation. Matthew F. Kalady, MD, Co-Director of Cleveland Clinic's Comprehensive Colorectal Cancer Program, took the lead in verifying the importance of NAPRC standards in improving patient outcomes.

A multidisciplinary approach to rectal cancer care

"This initiative brings together a multi-institutional team of colorectal surgeons, medical oncologists, radiation oncologists, radiologists and pathologists on a common mission of improving rectal cancer care in the U.S.," says Dr. Kalady. "The NAPRC aims to achieve this goal through the application of specific standards for process measures, quality and performance indicators."

Dr. Kalady explains that one of the focal points of the NAPRC is a multidisciplinary approach to rectal cancer care.

"Rectal cancer is usually treated with different types of therapy used in combination or in sequence," he says. "It is really important not only that the specialists who are delivering care are experts at what they do, but also that they work to collaborate with all other physicians involved in caring for the patient."

The importance of colorectal cancer multidisciplinary conferences

One important aspect of a multidisciplinary approach to care outlined in the *NAPRC Standards Manual* is the colorectal cancer multidisciplinary conference (CRC-MDC) or tumor board. In an article in the *Journal of the American College of Surgeons*, Dr. Kalady and his colleagues reported the results of a study that assessed the impact of CRC-MDCs on the management of rectal cancer patients.





The study included 408 rectal cancer cases presented at a weekly CRC-MDC at Cleveland Clinic main campus between July 2015 and June 2016. Physician survey responses documenting a change in management plan were obtained for 371 patients.

“The CRC-MDC resulted in a change in management of 26 percent of patients,” Dr. Kalady says. “The change was categorized as a change in therapy, change in therapy sequence or recommendation for additional evaluation and was independent of the presenting surgeon’s years of clinical experience.”

Dr. Kalady says that the CRC-MDCs have been an important part of colorectal cancer care at Cleveland Clinic in the past 10 years by providing a forum for review and discussion of each case.

“After examining the key decision-making factors, which include the patient’s history and characteristics, pathology findings and imaging results, the physicians participating in the conference decide as a group on the best treatment plan,” he says. “This approach promotes discussion, is very efficient and allows for the implementation of standards and a quality check of the treatment plan.”

Implementing the NAPRC standards

Published in October 2017, the updated *NAPRC Standards Manual* outlines the current standards and performance indicators of rectal cancer care.

“The standards are divided into three main groups: process standards, performance standards and outcome measures,” says Dr. Wexner. “The first standard is institutional Commission on Cancer accreditation. Having a multidisciplinary rectal

cancer team in place is critical, as well as having all the specialists work through their respective societies to ensure participation in educational initiatives and use of synoptic reports. Synoptic reports, comprising pathology, radiology and surgery data, serve as checklists and ensure that none of the important information about the patient is missed.”

Cleveland Clinic was among the first medical centers to implement the NAPRC standards.

“Having implemented the NAPRC standards at Cleveland Clinic’s Ohio and Florida campuses throughout the past few years, we are confident that we will see our patients derive the same benefits as patients have achieved in similar programs in Europe,” says Dr. Wexner. “We anticipate some of these benefits to be lower rates of colostomy construction, lower rates of local tumor occurrence and greater tumor-free survival.”

Among the first to be accredited

In late 2018, Cleveland Clinic’s rectal cancer programs in Ohio and Florida became two of the nation’s first four to receive NAPRC accreditation. Each program underwent a rigorous evaluation of its compliance with NAPRC standards.

“Accreditation affirms that we are consistent with best practices and helps us ensure that every single patient gets this standard of care,” says Dr. Kalady. “We know outcomes are better at accredited centers for other conditions such as breast cancer, bariatric surgery and trauma. I think ultimately patients are going to seek care in centers that are accredited.”



Dr. Kalady is Co-Director of Cleveland Clinic’s Comprehensive Colorectal Cancer Program and Professor of Surgery at Cleveland Clinic Lerner College of Medicine.

He can be reached at kaladym@ccf.org or 216.445.2655.

On Twitter: [@MattKaladyMD](https://twitter.com/MattKaladyMD)

Tumor Ablation with Chemo-Radiotherapy Consolidation Yields Rare Durable Remission of Glioblastoma

No evidence of residual tumor or recurrence at 6.5 years of follow-up

By Gene Barnett, MD,
MBA, and Manmeet
Ahluwalia, MD

*Dr. Barnett is Director
of Cleveland Clinic's
Rose Ella Burkhardt
Brain Tumor and Neuro-
Oncology Center.*

*He can be reached at
barnetg@ccf.org or
216.636.0007.*

*Dr. Ahluwalia is the Dean
and Diane Miller Family
Endowed Chair in Neuro-
Oncology in the Burkhardt
Brain Tumor and Neuro-
Oncology Center.*

*He can be reached at
ahluwam@ccf.org or
216.444.6145.*

*On Twitter:
@BrainTumorDoc*

History/presentation

A 48-year-old right-handed man presented with recent onset of motor and cognitive dysfunction. He had begun to have vague symptoms of dizziness and unsteadiness about two weeks earlier. Initially these were attributed to a resolving sinus infection, but approximately one week before presentation his wife began to notice more significant cognitive symptoms. He then fell while in the shower and was taken to an outside emergency department, where a CT scan revealed a left medial parietal mass. He was placed on dexamethasone and levetiracetam and then sought a second opinion at Cleveland Clinic.

Evaluation

When he was seen at Cleveland Clinic, the patient's symptoms had resolved and he was neurologically intact. An MRI showed ring enhancement and extensive edema around the mass, which appeared to be situated in the cingulate gyrus, immediately below the left paracentral lobule and the primary motor and sensory fibers (Figure 1).

Management

Additional imaging, including diffusion tensor imaging for fiber tracking, was obtained. This led to the determination that any conventional surgical approach (including parafascicular surgery) would subject the patient to a very high risk of motor and/or sensory deficits in his right lower limb because of the sensitive and deep location of the tumor. He was offered stereotactic biopsy and what was at the time — i.e., autumn 2011 — a relatively new therapeutic surgical modality, laser interstitial thermal therapy (LITT), which involves a laser probe only a few millimeters wide.

Five days after his fall in the shower, he underwent the minimally invasive LITT procedure and, as had been predicted, had only mild dorsiflexion weakness of his right foot, which resolved within a few weeks.

The following week, his case was reviewed in one of the twice-weekly multidisciplinary brain tumor boards convened by Cleveland Clinic's Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center. The neuropathologist noted that the patient had a WHO grade IV astrocytoma (glioblastoma) without *IDH1* wild-type mutation and with a Ki-67 labeling index of 9 to 10 percent and chromosomes 1p- and 19q intact (at that time [2011], the *MGMT* gene promoter was not routinely assessed). The neuroradiologist confirmed that postoperative imaging showed a complete ablation of the enhancing portion of the tumor (Figure 2).

The brain tumor board recommendation was for external beam radiotherapy (60 Gy to the ablation bed + 2 cm) with concurrent temozolomide, followed by high-dose temozolomide for five days repeated at 28-day cycles. The patient elected to have the chemoradiation therapy performed at Cleveland Clinic.

Outcome

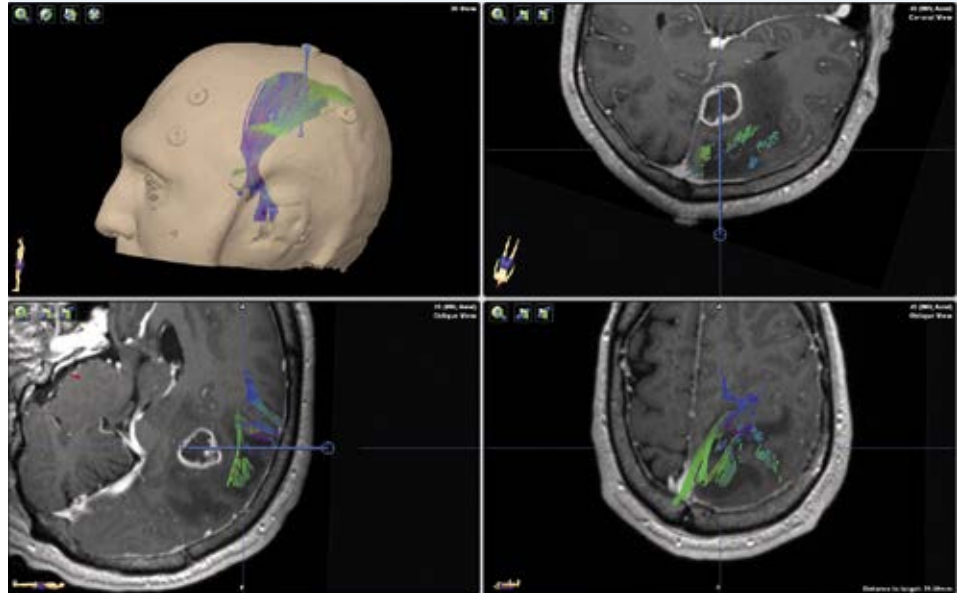
His first imaging after chemoradiation showed marked improvement in the appearance of the tumor, which was even better at six months (Figure 3). In view of this, his temozolomide therapy was continued for a full year. Serial imaging showed that the tumor remnant continued to decrease, and the patient remained neurologically normal more than six and a half years after his surgery, with no evidence of recurrent or residual tumor (Figure 4).

Discussion

Although stereotactic brain biopsy can provide accurate and safe diagnosis of deep brain lesions owing to the small diameter of the biopsy instrument, it does not provide meaningful cytoreduction. In some cases, a safe corridor can be devised via a minimally invasive craniotomy using neuronavigation (with or without



Figure 1. Neuronavigation planning for biopsy and laser ablation showing the relationship of the tumor in the cingulate gyrus to overlying motor and sensory projection fibers and the paracentral lobule. Blue lines indicate the surgical trajectory.



tubular retractors), but the location in this case was not accessible without a high risk of sustained functional morbidity for the patient's right lower limb. A non-invasive treatment such as stereotactic radiosurgery eliminates the access issue but has been shown not to improve prognosis as part of the initial management of glioblastoma.

LITT (also known as laser ablation) was a relatively new method of minimally invasive cytoreduction at the time of this case in 2011, with the first case of human tumor ablation using this system performed at Cleveland Clinic (by co-author Dr. Gene Barnett) in 2008. Nonetheless, early results in the multicenter clinical trial led by Dr. Barnett — along with subsequent clinical experience after LITT was cleared by the FDA for ablation of brain tissues — were very promising and prompted Dr. Barnett to offer this cutting-edge treatment to the case patient, whose prognosis otherwise looked bleak. Tumor ablation followed by consolidation using a multidisciplinary approach combining chemotherapy and radiotherapy has led to a rare, durable remission of the tumor with no evidence of viable residual tumor or recurrence.

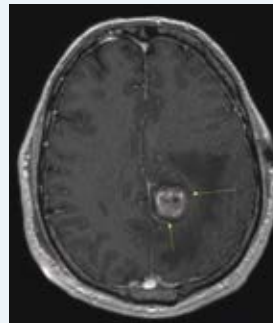


Figure 2. MRI taken 24 hours after ablation showing the extent of ablation (thin eggshell of enhancement indicated by arrows) and loss of contrast enhancement (hyperintensities are postablation blood and protein products).

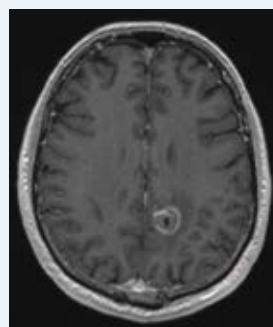


Figure 3. Six-month postoperative MRI with contrast showing decreasing rim of ablation enhancement and overall reduction in lesion size.

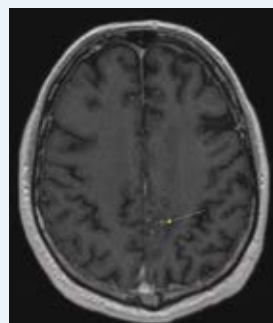


Figure 4. MRI with contrast taken 6.5 years after ablation showing a single speck of enhancement (arrow) and no clear evidence of residual or recurrent tumor. The patient has remained asymptomatic.

New Staff



Faiz Anwer, MD, is a new staff member in Cleveland Clinic's Department of Hematology and Medical Oncology. Before joining Cleveland Clinic, Dr. Anwer was Associate Professor of Medicine at the University of Arizona and served as Clinical Director of its adult blood and marrow stem cell transplantation program. His interests include multiple myeloma, clinical research on plasma cell disorders, malignant hematology, high-dose chemotherapy, immunotherapy, targeted therapy and stem cell transplantation.

Board certified in internal medicine, oncology and hematology, Dr. Anwer received his medical degree from Rawalpindi Medical College at the University of Punjab in Pakistan. He completed his internal medicine residency initially at Holy Family Hospital in Pakistan and later at University of Pittsburgh Medical Center. He completed a fellowship in hematology and medical oncology at the University of Arizona and received further training in blood and bone marrow transplantation at the University of Washington's Fred Hutchinson Cancer Research Center.



Brian Hobbs, PhD, is associate staff in Cleveland Clinic's Department of Quantitative Health Sciences and Section Head of Cancer Biostatistics. Before joining Cleveland Clinic in 2017, Dr. Hobbs was a tenured Associate Professor in the Department of Biostatistics at The University of Texas MD Anderson Cancer Center.

His work at Cleveland Clinic will involve working with clinical investigators, computer (data) scientists and translational scientists to better understand complex data through mathematical modeling. This quantitative analysis and pattern recognition is pivotal to precision medicine in oncology.

After earning his undergraduate degree at the University of Iowa, Dr. Hobbs completed an internship in biostatistics at Mayo Clinic. He then earned an MS/PhD in biostatistics from the University of Minnesota and completed a fellowship in biostatistics at The University of Texas MD Anderson Cancer Center.

CHAIRMAN'S Q&A

Cultivating Emotional Intelligence Through Asking Questions



Dr. Bolwell is Chairman of Taussig Cancer Institute, Cleveland Clinic Cancer Center. He can be reached at bolwellb@ccf.org or 216.444.6922. On Twitter: @BrianBolwellMD

What is emotional intelligence (EQ), and why is it important to you as leader of a major academic cancer center?

Emotional intelligence is the ability to see things from other people's perspectives, to walk in another person's shoes, to read nonverbal cues and in general to appreciate situations from perspectives beyond one's own. I believe that EQ goes hand in hand with empathy.

Our cancer center aspires to have a culture of compassion and empathy as well as clinical excellence, and EQ is necessary for all of these goals. My mission as a leader is to create that culture, to make sure that everyone who touches our patients does so with compassion and empathy.

How do you cultivate EQ?

I think there are many ways to build EQ. Here's one example: When I was in residency, I had a co-resident who later became a psychiatrist. She was magnetic, and everyone liked her. As I got to know her better, I discovered her simple secret — she asked questions. This skill, taught and learned, helped her break down social barriers. People opened up to her, and she created meaningful connections. I realized that asking questions was a powerful but simple way to engage others.

A recent article in *Harvard Business Review* highlights the power of questions in developing EQ. "The Surprising Power of Questions" by Alison Brooks and Leslie John claims that most of us don't ask enough questions and don't ask them in the best way, but "the good news is that by asking questions, we naturally improve our emotional intelligence, which in turn makes us better questioners — a virtuous cycle."

Growing EQ takes significant effort, and asking questions is a great way to learn the perspective of others and grow that skill.

How do we know which questions to ask?

Well, according to the authors, we ask four types of questions, and some of them are better than others for developing EQ.

1. Introductory questions ("How are you?")
2. Mirror questions ("I'm fine; how are you?")
3. Full-switch questions (those that change the topic of conversation entirely)
4. Follow-up questions (ones that solicit more information)

All of these are useful, but the power lies in follow-up questions. Studies show that these types of questions signal to others that you are listening actively and want to know more. People feel respected and heard. In general, studies show that asking questions is correlated with liking people, improved learning and interpersonal bonding.

How do you incorporate this skill into your leadership style?

Many leadership books talk about the importance of building relationships in the workplace. In fact, many of these authors claim that the workplace is entirely about relationship building. Asking questions, especially follow-up questions that show you are listening, is a fundamental way to build relationships, to show interest in another person and draw them in.

I try to create a culture of openness to diverse opinions by answering questions with "I don't know" a lot. This generally relaxes the room and invites more questions. I also like to ask questions of people during meetings and make sure they feel comfortable responding. Asking questions and earnestly listening communicates a culture of honesty, of welcoming many perspectives, of openness and transparency. It shows that I want to know what's going on and what we can do to improve. Questions are an essential part of this learning process.

What advice would you offer to physicians and leaders looking to incorporate this skill into their practices?

We must take time to listen to our patients. The best doctors know how to ask good questions, and they listen to the answers to inform a course of treatment. We have to let patients talk and give them the time and attention they deserve to share their stories.

Asking questions is also how you learn new things and grow. You may hear surprising answers or hear a story that impacts your career or your life.

In terms of advice for fellow physicians and leaders, this suggestion is pretty straightforward to implement. We can all ask more questions as a way to grow our EQ and become better doctors, leaders and people.



The Cleveland Clinic Foundation
Cleveland Clinic Cancer Center
9500 Euclid Ave. / AC311
Cleveland, OH 44195



CASE
COMPREHENSIVE
CANCER CENTER



Stay Connected with Cleveland Clinic Cancer Center

24/7 Referrals

855.REFER.123
(855.733.3712)

clevelandclinic.org/refer123

Outcomes Data

View Outcomes books at
clevelandclinic.org/outcomes.

CME Opportunities

Visit ccfme.org for offerings
from Cleveland Clinic's Center
for Continuing Education.

Consult QD — Cancer

News, research and perspectives from
Cleveland Clinic experts:
consultqd.clevelandclinic.org/cancer

Cancer Advances eNews

Sign up to receive our bimonthly
e-newsletter.
clevelandclinic.org/canceradvances



[Facebook.com/CMEClevelandClinic](https://www.facebook.com/CMEClevelandClinic)



[@CleClinicMD](https://twitter.com/CleClinicMD)



clevelandclinic.org/MDlinkedin



clevelandclinic.org/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 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 Cleveland Clinic Florida. Cleveland Clinic is a nonprofit academic medical center ranked as a top hospital in the country (*U.S. News & World Report*), where more than 3,400 staff physicians and researchers in 140 specialties collaborate to give every patient the best outcome and experience.