WINTER 2025

ASTRO news

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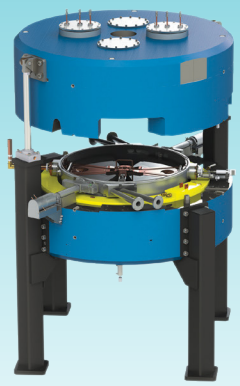

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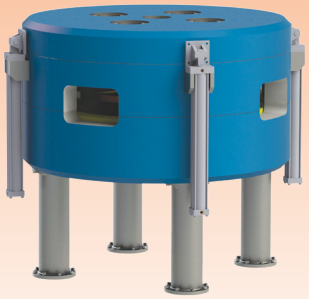

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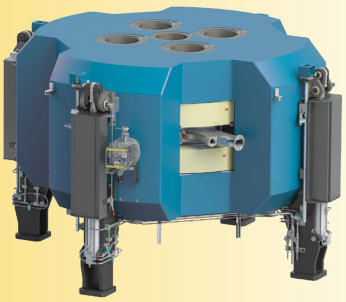

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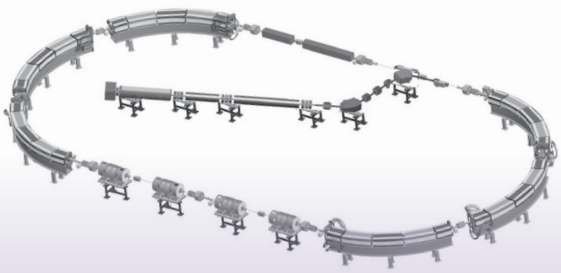
Installation of B70 MeV Cyclotron at INFN, Legnaro, Italy.



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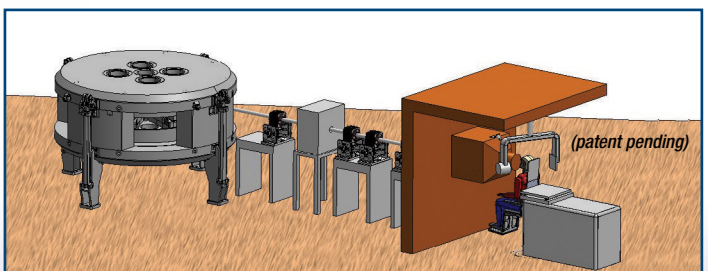

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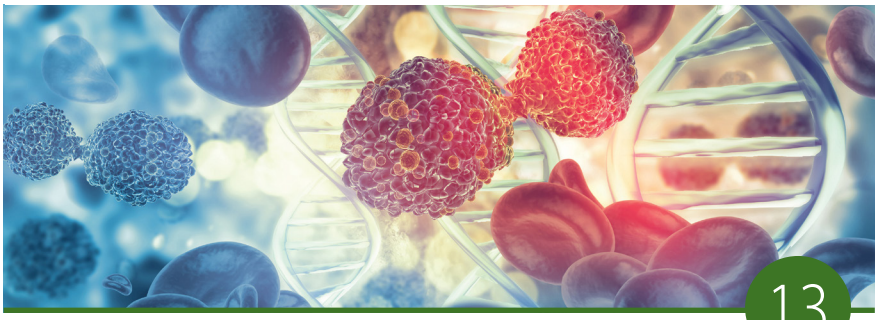

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VOLUME 28 • NUMBER 1

ASTRO news

AMERICAN SOCIETY FOR RADIATION ONCOLOGY

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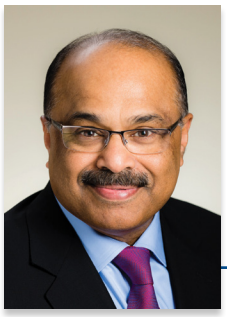

EDITORS' *notes*

BY NAJEEB MOHIDEEN, MD, FASTRO, AND BRIAN KAVANAGH, MD, MPH, FASTRO, *ASTRONEWS*

Biomarker is an elastic term

A HISTORY-OF-ONCOLOGY BUFF might argue that the granddaddy (grandmammy?) of all biomarkers is the estrogen receptor, which was discovered in the late 1950s. While it's true that by then, Charles Huggins had figured out a link between testosterone and prostate cancer, there wasn't much awareness of the cell surface interactions that were taking place in endocrine-driven tumors. Tamoxifen was synthesized not long after the estrogen receptor characterization in the early 1960s, initially with the intent to be used as a contraceptive pill. However, studies soon showed it to be ineffective — in fact, surprisingly counterproductive — for that indication. And so began its rebirth as the first targeted cancer therapy.[1]

A lot more has been learned about numerous other biomarkers in the last 60 years, and to some of us it feels like most of that knowledge has emerged in the last 60 minutes. There has been a head-spinning surge of new, clinically impactful scientific advances in this domain in the last decade. Hence the motivation for this issue's theme.

In this *ASTROnews*, we apply a broad definition, considering biomarkers to be genetic tests on tumor tissue that reveal information about its expected behavior beyond what is known from the microscopic appearance; imaging methods apart from routine initial staging studies that characterize a diagnosis or prognosis or guide treatment; artificial intelligence technologies that reveal histologic nuances too subtle to be appreciated by the human eye; circulating serum proteins or cellular fragments that offer screening or predictive knowledge, or any other nouveau "omics" that sheds new light on the nature of a neoplasm.

We enlisted a team of topic experts to highlight the status quo of biomarkers in their protean roles across a spectrum of common cancers. They were given license to let their imagination roam free to convey a sense of the creative intellectual undercurrents that keep moving the field forward.

The astute reader will notice a few omissions, for which we apologize. For example, space constraints did not allow us to delve into the evolution of glioma classification, where in recent years the World Health Organization (WHO) has effectively transmogrified diagnostic criteria from an older system based on microscopic morphology to a nouveau nomenclature predicated almost entirely on molecular features (IDH mutations, TERT promoter mutations, ATRX status, 1p19q deletions, etc.) not visible to the naked eye. In the realm of endometrial cancer, we are only just beginning to appreciate the extraordinary implications of polE mutations, which turn upside down traditional pathologic features associated with progression and have sweeping implications for adjuvant therapy.[2] And let's not forget about rectal cancer, where the provocative results of the NO-CUT trial presented at ESMO last year suggest that ctDNA can be a powerful tool to predict outcomes after non-operative management.[3]

Nevertheless, we hope that the issue's content offers a light-spirited look at the current implications of biomarker assays of all sorts and maybe a hint of what is to come, alongside maybe a few pearls here and there of value in weekly tumor boards for the practicing radiation oncologist.

And, as the outgoing Senior Editor, I pen my last note. It's been a pleasure to co-edit this issue with Brian Kavanagh, who takes over as *ASTROnews* editor from the next issue. I'm certain he will lead the magazine to even greater heights. My gratitude to the contributors who write for us, taking time out from their extremely busy schedules to help communicate with the wider community, the importance of which can't be overstated. My time here has been a truly rewarding experience, thanks in large part to the unstinting support of the Editorial Board and Staff, especially Diane Kean and Anna Arnone. Thanks to all of you — *ASTROnews* is testament to your dedication and talent.

Happy New Year from all of us.

GUEST EDITOR
Carmen Bergom, MD, PhD

The Biomarker-Driven Future of Personalized Radiation Therapy

THE FIELD OF RADIATION ONCOLOGY is on the verge of a biomarker-driven revolution. We could have dedicated a textbook to newly established biomarkers as well as those on the horizon in radiation oncology. Instead, we have highlighted key developments and upcoming areas of interest in a few types of cancers, providing a landscape of select biomarkers currently used in practice and promising future biomarkers. Any doubt about how biomarkers are already starting to shape clinical practice should be shattered after reading the summaries in this issue. Although gradual advancements characterize the current biomarker landscape, our field will likely undergo a fundamental shift with the upcoming wave of breakthroughs, led by more and more -omic data (e.g., genomics, transcriptomics, proteomics, metabolomics), AI- and machine learning-guided discoveries, and the maturation of lines of research such as how the microbiome may influence cancer treatment responses and how to more effectively enhance anticancer immunity. The current biomarker innovations, whose effects are still in their infancy, foreshadow a future where biomarker-driven personalized cancer treatments are commonplace.

In this issue, we have mainly focused on how biomarkers will help to guide more effective antitumor treatments. Another way in which biomarkers may guide our treatments in the future is by determining normal tissue sensitivities in patients. For example, biomarkers predictive of a critical organ's relative radiation sensitivity, such as the heart, may lead to altered dose-volume constraints for a patient with lung cancer, adjustments in radiation dose and fractionation, and/or the adoption of specialized techniques such as proton therapy. Conversely, biomarkers predicting radiation resistance in critical organs may provide clinicians with greater confidence to escalate doses if necessary. Furthermore, these biomarkers may inform survivorship surveillance guidelines, offering a more tailored approach to monitoring long-term outcomes.

While we have mostly focused on the immense promise of biomarkers in radiation oncology, the integration of biomarkers into clinical practice is not without difficulties. Chelain Goodman, MD, PhD, nicely summarized many of these challenges in her section on biomarkers for breast cancers. Another obstacle is the rapid pace of discovery and technology in this area, which risks limiting clinicians' ability to stay current and underscores the need for ongoing education and collaborations between researchers and physicians. Ethical challenges also arise, such as how patients might react to learning about their biomarker profiles or the discovery of incidental findings unrelated to their diagnosis. Additionally, the cost of biomarker development and implementation risks deepening disparities in care, as not all patients or health care systems may have access to these advances. It is imperative to work to make these advancements available to all appropriate patients, regardless of socioeconomic status or geographic location.

Even with these challenges, biomarkers have the potential to reshape cancer treatment for the better. Success will require addressing these obstacles while ensuring that care remains focused on the patient as a whole. Biomarkers should enhance, and not replace, the physician's role in tailoring treatment to individual needs. By integrating this technology with individual patient needs, radiation oncology can move closer to a future of more effective, equitable and personalized care.

Carmen Bergom, MD, PhD, is an Associate Professor in the Department of Radiation Oncology at Washington University in St. Louis. Her research program is focused on improving the therapeutic ratio of radiation therapy by increasing tumor responses and decreasing side effects, with a focus on decreasing cardiac toxicity.

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3. Amatu A, Zampino MG, Bergamo F, et al. Total neoadjuvant treatment with non-operative management for proficient mismatch repair locally advanced rectal cancer: First results of NO-CUT trial. ESMO Congress 2024. Abstract 509O. Presented September 16, 2024.

Dr. Kavanagh welcomes letters to the editor at ASTROnews@astro.org.

SPECIAL*report*

BY VIVEK KAVADI, MD, MBA, FASTRO
ASTRO CHIEF EXECUTIVE OFFICER

2024 **Year in Review**

I AM WELL INTO MY FIRST FEW MONTHS AS CEO of ASTRO and have enjoyed meeting some of you personally and look forward to meeting more of you in the year ahead. As we embark on a new era, I am pleased to present a review of the Society's accomplishments from 2024. I would be remiss to not recognize the leadership of my predecessor, Laura Thevenot, who is enjoying retirement after 22 years leading the Society, and oversaw the completion of many of these accomplishments.

Leading off with one of ASTRO's most significant legislative initiatives to date, the Radiation Oncology Case Rate (ROCR) Value-Based Payment Program Act was introduced by a bipartisan group of health policy lawmakers in May, just days before nearly 100 ASTRO advocates came to Washington, DC, for our annual Advocacy Day. Garnering the support of more than 75 organizations, including one of the top 10 largest U.S. hospital systems and nine oncology societies, ASTRO is preparing for the ROCR Act to be reintroduced in 2025.

> "I am grateful to have the opportunity to lead this wonderful Society and am excited for the future of the field."

In late February and leading into spring, ASTRO hosted the 2024 Multidisciplinary Head and Neck Cancers Symposium and the Annual Refresher Course, and ASTRO welcomed Rachel Jimenez, MD, as the new *Advances in Radiation Oncology* Editor-in-Chief. In that same month, ASTRO hosted the inaugural Radiopharmaceutical Therapy (RPT) Roundtable meeting, bringing clinicians and industry together to discuss opportunities to advance the growth of RPT in radiation oncology. A second RPT Roundtable was held in November.

2024 brought exciting updates to ASTRO's APEx – Accreditation Program for Excellence® program. APEx unveiled updated standards, a new portal, and improved processes. Using the previous nine years of program data, APEx strengthened the Self-Assessment and Facility Visit processes and transitioned to a more robust portal to better serve as the centralized hub for all accreditation-related activities. Additionally, APEx now offers a new RPT accreditation.

June 2024 marked the 10-year anniversary of the creation of the Radiation Oncology Incident Learning System (RO-ILS®). Launched a decade ago in collaboration with AAPM, RO-ILS has grown to include more than 850 facilities and promotes a workplace with a strong safety culture. To date, RO-ILS has published more than 60 educational documents publicly (astro.org/roilsreports), allowing non-RO-ILS participants access to case studies and reports themed on specific topics garnered from data reported in RO-ILS to further educate and promote a culture of safety across the specialty.

A collaboration with Epic was forged to begin including ASTRO's RTAnswers patient education materials on their MyChart Care Companion. The first module launched in May to assist patients diagnosed with intact prostate cancer. The work is spearheaded by the Communications Committee and continues into 2025 when they hope to soon launch a breast cancer module and continue with many other disease sites over time.

ASTRO's ongoing outreach to medical students continued over the course of 2024 with six bimonthly Q&A sessions hosted by a radiation oncologist and radiation oncology resident, as well as attendance at various medical student association gatherings. ASTRO awarded 10 remarkable students with the Medical Student Fellowship Award and invited students in the metropolitan Washington, DC, region to attend the Aspiring Scientists and Physicians program at the 2024 Annual Meeting. This year marked record attendance of medical students at the Annual Meeting, and we are excited to welcome many of these students into the specialty as they continue their medical education.

ASTRO published four clinical practice guidelines in 2024: Partial Breast Irradiation; Bone Metastases; HPV+ oropharyngeal; and a rectal cancer focused update. Eight guidelines are in production: Postmastectomy Radiation Therapy; Grade 4 Diffuse Gliomas; Anal; Gastric; Bladder; Hypofractionated Radiation Therapy for localized prostate cancer; Hodgkin lymphoma; and Pancreas. ASTRO is also working on 12 collaborations with other organizations and completed four in 2024.

Our Grants and Fellowships programs continue to grow as we strive to further support fostering research. In partnership with five other oncology organizations, ASTRO awarded almost $1.4 million across six grants and fellowships, investing in the research careers of nine promising investigators.

In November, ASTRO launched the public awareness campaign, Radiation Therapy in Focus. This online campaign is targeted to cancer patients as they seek information about cancer treatment online. The campaign includes an FAQs handout and a short quiz to test patients' knowledge of radiation therapy and promote the facts about the treatment.

The end of 2024 saw the inaugural meeting of the newly formed Community Practice Task Force, which aims to better integrate community practice physicians into ASTRO committees and increase engagement and satisfaction among this cohort of members.

As 2025 will be my first full year in the role, I wanted to share the seven areas and initiatives where I will be focusing my attention:

1. Member outreach with roadshows
2. Public policy – ROCR
3. Value of radiation oncology
4. Budget and continued financial viability
5. Support of science and innovation
6. International growth
7. Expanding scope of the specialty

I am grateful to have the opportunity to lead this wonderful Society and am excited for the future of the field. This list of accomplishments from 2024 would not be possible without you, our dedicated ASTRO members. Here's to 2025!

CHAIR'S*update*

BY HOWARD SANDLER, MD, MS, FASTRO

Reflections and Outlooks

OUR *ASTROnews* THIS QUARTER HIGHLIGHTS the promise and progress in the field of biomarkers. Just to level set, perhaps a definition of biomarker is in order. According to NCI, a biomarker is "a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition." Of course, a dictionary gets the "defining" job done but only superficially. Please dig deeply into this issue to learn more about prognostic biomarkers and biological indicators that might indicate particular patient-specific sensitivity to the impact of radiotherapy.

As a GU-focused radiation oncologist, I can recall the incredible transformative influence of PSA on the management of prostate cancer, as a molecule that helps define risk grouping and thus treatment management and importantly is a marker of treatment success (or failure). Thus, PSA measurement becomes an integral part of post-treatment monitoring. Biomarkers continue to emerge and provide utility in the prostate cancer space, where truncated androgen receptor, DNA-repair defects, tumor-derived genomic classifiers and even AI-developed tools provide risk stratification. And that's just for prostate cancer.

Looking back to 2024 and when reflecting on the 66th ASTRO Annual Meeting in Washington, DC, I'm struck by the overall positive and energized mood of the meeting. We held our Annual Meeting for the first time in the Washington Convention Center, which provided ASTRO with a warm reception and a facility that was perfectly sized to our meeting exhibits and attendees. Additionally, the location in the heart of the District provided a nice environment for activities outside the meeting hall such as dining, shopping and sightseeing. I think that many were struck with the thought that the meeting seemed to have reverted to our pre-pandemic meetings and so was a pleasant return to normality. I hope future meetings have similar positive vibes.

Looking forward to 2025, ASTRO's important advocacy work continues as we search for a sustainable reimbursement approach that fairly supports our specialty and provides mechanisms for investing in future capital-intensive devices that will help us replace our existing treatment infrastructure with the novel and improved devices of the future. Our advocacy work depends on our engaged members — please consider attending the 2025 ASTRO Advocacy Day on Capitol Hill on May 19-20. We have the opportunity to speak with our congressional representatives and articulate on the issues of the day, including the legislative initiative known as ROCR (Radiation Oncology Case Rate), a value-based reimbursement strategy.

For those of you who have joined ASTRO on Capitol Hill, please consider attending again in 2025. For those who have not spent a day on Capitol Hill, please consider attending for the first time if only to observe and learn how our Congress "works." Entering the Senate and House Office Buildings on any given day are constituents seeking congressional action on behalf of one organization or another. Our role is to provide a radiation oncology perspective directly to those who make important decisions that affect our practices. I look forward to serving as your Chair and representing the Society as we continue to move this legislation forward. Hope to see you there!

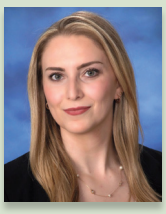
ASTRO and BCRF partner to expand opportunities for students and residents in radiation oncology careers

BY KIRSTA SUGGS, DIRECTOR, DIVERSITY, EQUITY AND INCLUSION

LAST YEAR, ASTRO launched the Radiation Oncology Visiting Away Rotations for Medical Students in partnership with the Breast Cancer Research Foundation (BCRF), recognizing the important role of short-term training and learning opportunities that expand the interest and inclusiveness of medical students in radiation oncology careers. In-person away rotations represent an important aspect of the medical school experience where students have the opportunity to learn in clinical and research settings, allowing them to interact with patients and practice medicine with the supervision and guidance of established, practicing physicians. Through the ASTRO-BCRF Radiation Oncology Visiting Away Rotations, senior medical students are provided financial support to participate in programs where they will engage with radiation oncologists in person and observe firsthand patient interactions, demonstrate and enhance their skills and abilities, and experience the social dynamics and local culture surrounding prospective residency programs.

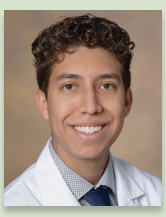
2024 ASTRO-BCRF Radiation Oncology Visiting Away Rotations Award Recipients

Jessica Aduwo



Lauren Bendesky

Oluwatomiwa Awobayiku



Jacob Mapp

The ASTRO-BCRF Radiation Oncology Visiting Away Rotations provides financial support for up to 10 students to participate in four-week visiting away rotations. Students must currently be enrolled in an accredited U.S. DO or MD program. The program seeks to improve the interest and inclusion of talented medical students in the field of radiation oncology and encourages students from populations historically underrepresented in medicine (UIM) to apply. Medical students in all years are accepted to the program; however, preference is given to third- and fourth-year students. The visiting away rotation must take place in an academic setting, with a focus on either direct patient care or research that is clinically oriented. Applications to the ASTRO-BCRF Radiation Oncology Visiting Away Rotations are now open year-round to better meet the needs of students.

In addition to making available support for visiting away rotations, ASTRO launched the inaugural ASTRO-BCRF Annual Meeting Trainee Travel Awards to extend science education and professional development to students and residents from historically underrepresented backgrounds as they continue to advance along the career continuum. The 10 award recipients attended the ASTRO 2024 Annual Meeting in Washington, DC, and participated in scientific sessions, educational programing and events specifically tailored to meet the needs of trainees, including the ARRO Annual Resident Seminar and ARRO Medical Student Workshop. Award recipients were also invited to attend networking events such as the ARRO Reception, ARRO Mentoring and Networking Reception and the Diversity, Equity and Inclusion Reception hosted by HEDI Council. Attendance at the ASTRO 2024 Annual Meeting provided an unparalleled opportunity for ASTRO members in the earliest stages of their career the ability to learn and interact with peers and professionals in the field and network with the Society's leadership.

Continued on the following page

The application period for the 2025 ASTRO-BCRF Annual Meeting Trainee Travel Awards will open in March.

Congratulations to the 2024 ASTRO-BCRF Radiation Oncology Visiting Away Rotations and ASTRO-BCRF Annual Meeting Trainee Travel Awards recipients.

[Pictured L-R] The 2024 ASTRO-BCRF Annual Meeting Trainee Travel Award recipients attended the ASTRO Annual Meeting in Washington, DC: Ulysses Gardner; Patrick Carriere; Kamryn Davis; Ester Sanchez-Valdez; Marco Santos-Teles; Kunika Chahal; Luiza Giuliani-Schmitt; Maya Stephens. Not pictured: Kekoa Taparra and Julianie De La Cruz Minyety

New public awareness campaign focuses on radiation therapy facts

IN NOVEMBER, ASTRO LAUNCHED A NEW ONLINE PUBLIC AWARENESS CAMPAIGN, that gives cancer patients the facts about radiation therapy. The campaign includes video interviews with radiation oncologists and patients about what radiation therapy is and how it can cure or treat cancer. The campaign includes a short quiz to test visitors' knowledge of radiation therapy and an FAQs handout. The campaign is part of the RTAnswers patient website and is being promoted online and through social media as people seek cancer treatment information. View the videos and access the handout and quiz at www.rtanswers.org/RTinFocus.

In Memoriam

ASTRO has learned that the following members have passed away. Our thoughts go out to their family and friends.

Adrian Bourque, MD, *Wausau, Wisconsin*

Felix Feng, MD, FASTRO, *San Francisco, California*

Alexander Jakubowycz, MD, *Richfield, Ohio*

Richard Matthews, MD, PhD, *Jackson, Missouri*

Robert Robbins, MD, FASTRO, *Winston-Salem, North Carolina*

Joseph Rogers Simpson, MD, PhD, *St. Louis, Missouri*

J. Clyde Spencer, MD, *East Lansing, Michigan*

The Radiation Oncology Institute (ROI) graciously accepts gifts in memory of or in tribute to individuals. For more information, visit **www.roinstitute.org**.

Newly elected companies to serve on ASTRO's Corporate Advisory Council

The ASTRO Corporate Advisory Council, representing the Corporate Membership at large, met in October at ASTRO's Annual Meeting in Washington, DC.
Back row [L-R] Andy Nelson, MIM Software; Todd Powell, RefleXion; Seth Blacksburg, Accuray; Ivan Astralaga, C-RAD AB; Michael Bauer, Leo Cancer Care; Marc Mlyn, RaySearch Laboratories; Amir Golan, Novartis Pharmaceuticals Corporation; Michael Pittman, Orfit Industries; Cookab Hashemi, Elekta; Frank Leonard, Novocure, Inc.
[Front L-R] Anu Perera, MD, AstraZeneca; Jeff Michalski, MD, MBA, FASTRO, ASTRO Immediate Past Chair; Howard Sandler, MD, FASTRO, ASTRO Chair; Tim Williams, MD, FASTRO, ASTRO CAC Chair; Amar Rewari, MD, MBA, FASTRO, ASTRO CAC Vice Chair; Vivek Kavadi, MD, MBA, FASTRO, ASTRO CEO
Not pictured: John Steffen, CQ Medical; Rob Morrison, PTW Corporation; and Arthur Kaindl, Varian Medical Systems, A Siemens Healthineers Company

ASTRO'S CORPORATE MEMBERSHIP elected the following companies to serve on the 2025 Corporate Advisory Council: IBA, MedLever, Standard Imaging, all newly elected, and C-RAD AB, which was reelected for another term.

The Council is a representative group of the Corporate Membership-at-large, with a proportional mix of large and small companies from the Corporate Membership base. Seats on the Council are held by high-level decision makers within the corporations and represent a broad cross section of the industry.

The Council allows for collaboration between ASTRO and its Corporate Members by focusing on issues and initiatives of mutual interest. Priorities include increasing awareness of radiation therapy and advancing the science and practice of cancer treatment and patient care.

The Council convenes several times a year via conference call and holds an in-person meeting at ASTRO's Annual Meeting.

All corporate members can nominate their company to serve on the Council. Nominations are accepted every fall with elections conducted during the winter. For more information about the Council and/or Corporate Membership, please contact Joanne DiCesare at joanne.dicesare@astro.org.

2025 Corporate Advisory Council

- AstraZeneca
- CQ Medical
- C-RAD AB
- IBA
- Leo Cancer Care
- MedLever
- Novartis Pharmaceuticals Corporation
- Novocure
- Orfit Industries
- PTW North America
- RaySearch Laboratories
- RefleXion
- Standard Imaging
- Varian, A Siemens Healthineers Company

During ASTRO 2024, ASTRO leadership met with exhibiting companies to thank them for their support of the Annual Meeting. View the photospread at www.astro.org/Winter25News.

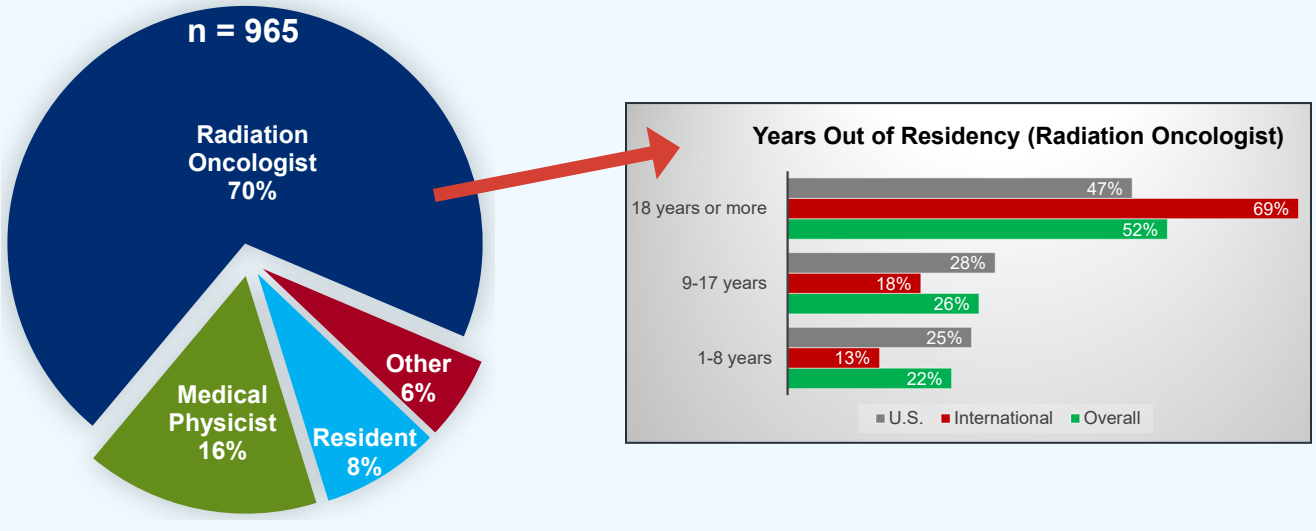
2024 ASTRO Member Survey Results

Members provide feedback on satisfaction, the future of the field, supervision, radiopharmaceutical therapy, peer review

THE ASTRO ANNUAL MEMBER SURVEY provides a snapshot of our membership in addition to valuable feedback about member satisfaction, areas of concern and opportunities for improvement. The 2024 Member Survey was fielded for eight weeks from May 28, 2024, through July 26, 2024, and was emailed to 7,789 members. The survey had a 13% response rate with 70% of respondents identifying as radiation oncologists (ROs). As a special incentive for participating in the survey, 10 lucky individuals were randomly selected to receive a $50 gift card. The results of the survey follow:

SURVEY RESPONDENTS - PROFESSION

RO participation increased by 5 percentage points compared to last year, while medical physicist, resident and other participation each decreased by approximately 2 percentage points. U.S. early career participation (1 to 8 years out of residency) decreased by 6 percentage points. Forty-three percent of the 534 U.S. ROs reported that they are the medical director at their primary work setting.



MEMBERSHIP AND SATISFACTION

In response to the question, "What are your top three reasons for being a member of ASTRO," both U.S. and international respondents ranked Access to ASTRO Journals as the top reason, followed by ASTRO is the Premier Society for Radiation Oncology. Access to Timely Information, e.g., reimbursement, education opportunities, and legislation ranked third by U.S. respondents, whereas international respondents ranked Quality and Safety Recommendations, e.g., guidelines, white papers, etc., third.

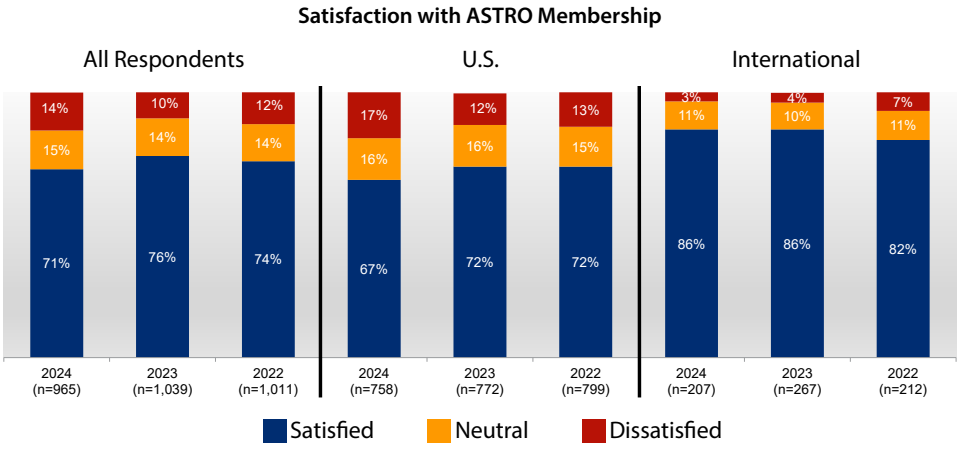
Sixty-four percent of U.S. respondents cited Advocating on Behalf of Members for Appropriate Reimbursement and Coverage as the top function ASTRO performs. Ninety-one percent of international respondents cited Publishing Scientific and Practice Journals (Red Journal, *PRO*, *Advances*) as the top function.

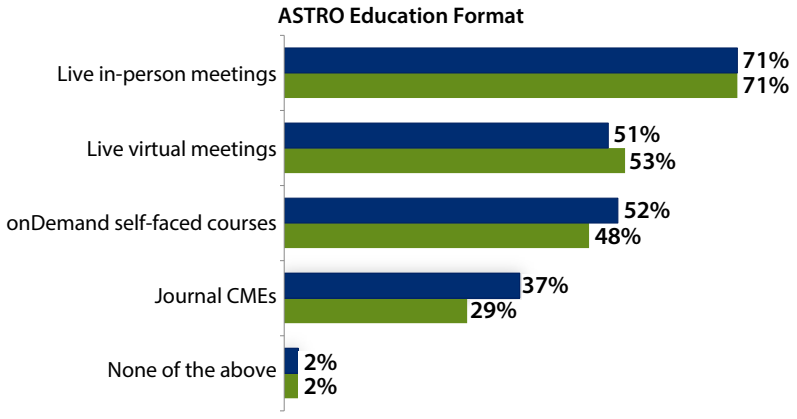
Overall satisfaction among respondents decreased modestly in 2024. This was especially noted by U.S. respondents; however, U.S. resident satisfaction has risen consistently over the past three years (63% in

2022, 72% in 2023, 79% in 2024). This year, ASTRO added an ARRO ex-officio board member to ensure that the needs and concerns of residents were taken into consideration during Board of Director Meetings.

Satisfaction among international respondents was unchanged and ranked very high.

The majority of respondents (84%) indicated satisfaction with ASTRO's educational and professional development offerings. Live meetings remain the preferred education format in which to participate. onDemand self-paced courses and Journal CME courses both saw an increase in the likelihood of participation.





Challenges	U.S. Radiation Oncologist		
	2024	2023	2022
Payor Issues	4.27	3.90	3.94
Government Issues	4.06	3.89	3.87
Practice Issues	4.00	3.93	3.74
Employer Issues	3.83	3.67	3.71
Competitive Issues	3.80	3.70	3.70
Professional Issues	3.69	3.83	3.49
Personal Issues	3.68	3.70	3.64
Patient/Family Issues	3.46	3.51	3.46
Research Issues	3.28	3.21	3.31

Challenges	U.S. Resident		
	2024	2023	2022
Government Issues	4.08	3.95	3.94
Personal Issues	3.99	4.21	4.08
Practice Issues	3.96	4.07	4.05
Payor Issues	3.94	4.01	4.05
Competitive Issues	3.92	4.05	3.96
Professional Issues	3.91	4.00	3.52
Employer Issues	3.75	3.88	3.91
Patient/Family Issues	3.73	3.69	3.56
Research Issues	3.68	3.75	3.59

FUTURE CHALLENGES: U.S. RESPONDENTS

Radiation oncologists and residents see future challenges slightly differently, but they are equally concerned with government issues (reimbursement, business regulation, restrictive regulations) and practice issues, including practice financial viability and workforce (i.e., nurse, therapist, dosimetrist shortage).

Read more results of the 2024 Member Survey online at www.astro.org/Winter25News, including members' thoughts on supervision, radiopharmaceutical therapy, peer review and the future of the field. The Annual Member Survey provides valuable information for ASTRO's continued service and future initiatives. Thank you to everyone who participated. The survey is sent out every spring, so please help us continue to serve the needs of the radiation oncology community by completing the 2025 survey.

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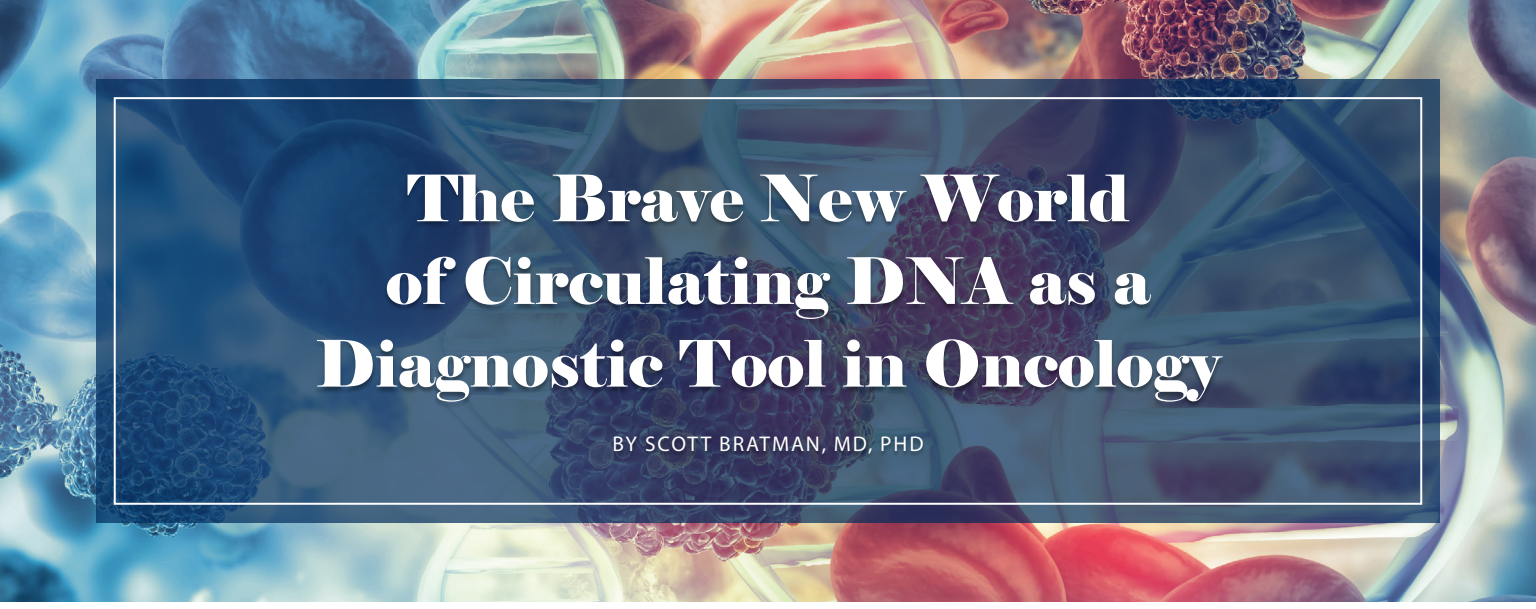

The Brave New World of Circulating DNA as a Diagnostic Tool in Oncology

BY SCOTT BRATMAN, MD, PHD

IN THE 1997 DYSTOPIAN SCI-FI THRILLER "GATTACA," Ethan Hawke plays a character named Vincent whose future is rendered bleak by eugenics-driven genetic predeterminism. DNA testing shortly after birth predicts him to be of unhealthy stock, with limited lifespan, not likely fit for high-level employment, and thus not worthy of the societal advantages offered to those of more favorable genotype. Without revealing any spoilers, suffice it to say that Vincent does everything he can to buck the system.

I think we all know that a buccal swab can't give us nearly so much information as that, and the ill-fated Theranos saga would suggest that simple blood tests to diagnose a wide range of disease remain more in the domain of fiction than science. However, in the last 15 years, there have been substantial advances in genetics technology that do reveal information available in the bloodstream before detectable by a scan or noticed by the patient. And so, in the world of oncology, analyses of circulating tumor DNA (ctDNA) are being studied as tools to screen for cancer, monitor cancer patients' status and guide treatment recommendations.

Predating the capacity to analyze ctDNA are a host of tests that measure proteins in the serum that are produced or shed by various tumors. Many remain informative and are discussed elsewhere in this issue. Early studies transitioned away from serum protein markers (or counts of actual circulating whole tumor cells) toward using ctDNA for monitoring of patients with advanced cancers.[1,2] Monitoring with ctDNA held the promise of tracking disease burden while simultaneously identifying emerging mechanisms of resistance, such as certain mutations in lung cancer patients treated with first generation EGFR inhibitors.[3]

Since 2016, the U.S. FDA has approved several ctDNA tests for use in advanced cancers. These tests impact oncologists' decisions around use of targeted therapies by detecting driver and resistance mutations in the circulation. As a result, tumor tissue testing can often be avoided, which is particularly useful when it is not readily available or would necessitate risky invasive procedures.

Tracking treatment response with ctDNA in advanced cancers can also identify patients benefiting from systemic therapies. For instance, although predicting which patients respond to immunotherapy has remained a challenge, recent studies suggest that ctDNA clearance could be an early response indicator that is more accurate than routine scans.[4]

Moving ctDNA testing into earlier disease settings requires cutting-edge, ultrasensitive technologies that have been evolving on a rapid time scale. Cheaper, faster and more accurate DNA analysis approaches open up new opportunities for test development, such as for the detection of miniscule amounts of residual disease after curative intent treatment that is not yet apparent on scans.[5,6] Termed "molecular residual disease" (MRD), such tests could someday be routinely used to guide treatment decisions by identifying patients destined to recur. Many ongoing studies are evaluating whether MRD tests lead to better outcomes either by improving cure rates among MRD-positive patients or reducing unnecessary side effects among MRD-negative patients. MRD can also be used in the surveillance setting, especially when the optimal surveillance strategy is not defined, such as in head and neck cancer as discussed on page 25 in this issue.

Intuitively, it might be thought that leakage of aberrant DNA fragments into the bloodstream would occur at the earliest hint of a cancer's development. Indeed, ambitious efforts are now underway to use ctDNA as a scalable and (hopefully) cost-effective

Continued on the following page

"How will radiation oncologists be called upon to order, interpret and act on ctDNA results in the future?"

means of cancer screening. There are only four cancer types with screening tests recommended for routine use by the U.S. Preventative Services Task Force,[7] and approximately 70% of cancer deaths in the U.S. are from cancer types lacking a recommended screening test.[8] As a common source of biomarkers across cancer types, ctDNA tests have the potential to address this glaring gap. Such tests could also improve equitable access to screening for cancer types with existing recommended tests (e.g., colonoscopy[9]) where significant disparities in access continue to persist. For now, the cost of the advanced methods required to profile ctDNA could be prohibitive, but these costs are expected to keep falling over time. Sensitivity for early-stage solid cancers also must improve for certain cancer types to give the best possible chance of identifying curable cancers and reducing overall mortality.

How will radiation oncologists be called upon to order, interpret and act on ctDNA results in the future? With rising availability of these tests, our profession has a duty to study how they should be integrated into existing workflows and to advise patients on their optimal usage. It is important to recognize that results can vary widely between cancer types and can be affected by a variety of tumor, host and treatment factors. In general, metastatic cancers produce higher ctDNA levels than localized ones. Kinetics of ctDNA during a course of radiotherapy can be particularly complex and unpredictable, and clearance may be slower than after surgery. These examples underscore the importance of rigorous evaluation of the utility of ctDNA in different clinical scenarios.

"Gattaca's" Vincent embraced self-determination to achieve his goals and was not held back by any perceived genotypic deficiency. In a similar vein, the latest profiling approaches mean that future ctDNA testing can break away from the shackles of simple genetic sequence. Chromatin "epigenomic" features that determine tumor biology and behavior can now be systematically assessed within ctDNA, opening up new exciting applications in cancer diagnostics. Epigenomic profiling methods already underlie the latest advancements in multi-cancer screening and MRD detection, and many more enabling methods are now being tested. So unlike the dystopian future faced by Vincent, ctDNA gives radiation oncologists much to look forward to.

Scott Bratman, MD, PhD, is the Dr. Mariano A. Elia Chair in Head & Neck Cancer Research, Clinician-Scientist at Princess Margaret Cancer Centre and Associate Professor at University of Toronto. Dr. Bratman specializes in the management of head and neck cancer and leads research studies on circulating tumor DNA.

Disclosure statement:
Scott Bratman is inventor on patents related to ctDNA mutation and methylation analysis technologies that have been licensed to Roche and Adela, respectively. SVB is a co-founder of and has ownership in Adela.

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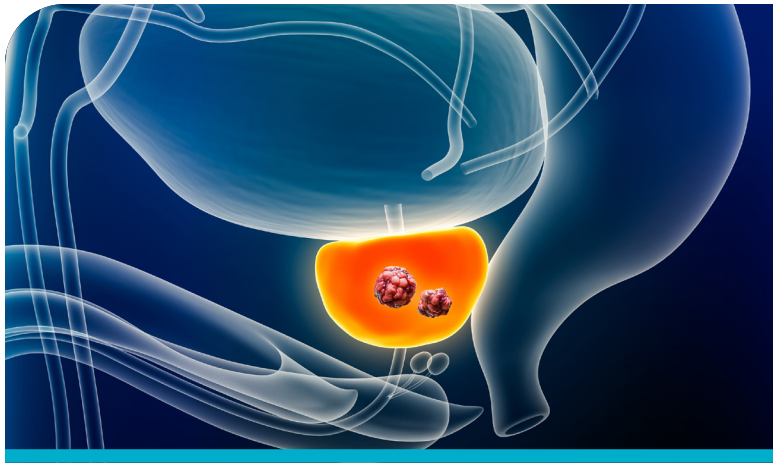

Predicting Prostate Futures: Sci-Fi Meets Real-World in a Positive Way

BY JONATHAN TWARD, MD, PHD, FASTRO

IT SEEMS THAT MOST SCIENCE FICTION MOVIES involving the imagined future uses of genetics or artificial intelligence lean heavily toward the dystopian. In the noir "Gattaca" mentioned earlier in this issue by Scott Bratman, MD, PhD, genetic predeterminism casts a dreary pall over society. Likewise, films like "The Terminator" and "The Matrix" offer terrifyingly dark visions of artificial intelligence gone wrong in the worst ways.

The original "Blade Runner," with its evil androids running amok, was set in 2019. And yet here we are, in the year 2025, where at least in the world of prostate cancer, I am personally optimistic that the AI and genomic tools available to guide treatment decisions and predict the future for patients are a good thing, with a lot more of a utopian than dystopian vibe.

We commonly use National Comprehensive Cancer Network (NCCN) risk groups for localized prostate cancer to aid in treatment decisions. However, these groups depend on subjective assessments, such as a pathologist's interpretation of the Gleason score, a radiologist's MRI analysis, or the rectal examiner's feel. Consequently, treatment decisions regarding active surveillance (AS), radiation with or without hormone therapy, or duration of hormone therapy may vary based on the contributing specialists' expertise, level of alertness at the time, or digital technique. Additionally, contemporary considerations include complex data not accounted for in NCCN risk groups. PSMA scans, germline and somatic genomic profiles, histologic findings such as cribriform patterns, PSA density, and PSA velocity are just some of the extra inputs available.

The past decade has given us several new commercially available biomarkers that improve upon NCCN risk groups in predicting important oncologic outcomes like metastasis after therapy. These tests aid clinicians in deciding between treatment intensification and deintensification. While randomized trials provide population-level guidance, there can still be over- or under-treatment within certain cohorts of patients. The new advanced risk classifiers address this issue by enabling more personalized treatment considerations.[1]

Some of the major new tools currently available are listed in the following table:

Name	Type of Test	Comment
Decipher Prostate (Veracyte, Inc.)	22 genes analyzed from prostatectomy or biopsy specimen	Predicts risk of metastasis
ArteraAI (Artera)	Digital analysis of biopsy images combined with clinical information	Predicts metastasis risk and also whether androgen deprivation therapy (ADT) will benefit men with NCCN intermediate risk
Prolaris (Myriad Genetics)	31 genes analyzed from biopsy specimen	Predicts risk of death with AS; predicts metastasis risk after surgery or radiotherapy
Oncotype Dx Genomic Prostate Score (GPS)	17 genes analyzed from biopsy specimen	Predicts risk of Gleason 7 or higher at prostatectomy; predicts metastasis risk after surgery or radiotherapy

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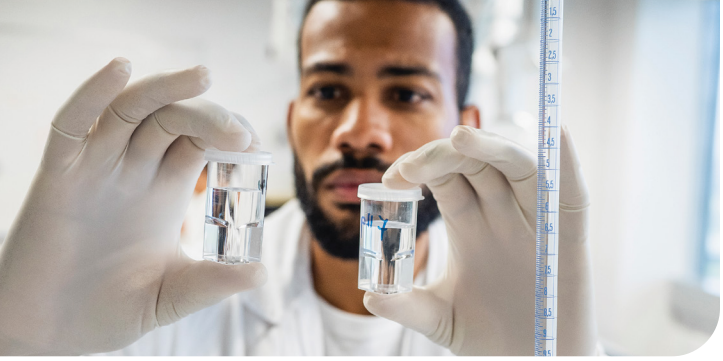


The NCCN guidelines list these biomarkers as advanced tools demonstrating superior prognostic performance to standard risk stratification methods. GPS and Prolaris have been established as pre-treatment guideline considerations since 2015-16, with Decipher and Artera appearing for pre-treatment consideration in 2018 and 2023. Although the current NCCN guideline does not suggest a preferred test, it may seem confusing that they only highlight those (Decipher and Artera) tested in tissues banked by the RTOG. Although testing biomarkers in trial patients is ideal, the limited access of these tissues to biomarker researchers remains a challenge. High-quality observational studies, real-world data, and robust statistical methodologies have generated strong, reproducible evidence in Prolaris and GPS as well.

As a radiation oncologist in Utah, known for its exceptional snow, I understand the importance of not using wide powder skis on icy groomers or thin groomer skis in deep powder. You need the right tool for the right job. Similarly, selecting the appropriate risk classifier depends on the clinical scenario one would like to address. When weighing which biomarker to use, choose the one whose score report tells you explicitly how outcomes would change between the interventions you are considering.

Before we dive into examples, I first want to acknowledge the passing of a giant in this biomarker space. The original intent of this article was to include additional comments from the renowned Felix Feng, MD, FASTRO. Sadly, Dr. Feng passed away in December. Among his many scientific achievements were foundational studies that led to the development of the ArteraAI Prostate Test, and he was a co-founder of the company that commercialized the assay. His significant contributions led to many advancements in this space, and his legacy will certainly live on in the many trainees who benefited from his tutelage over the years, for which he was honored with the ASTRO Mentorship Award during the 2024 Annual Meeting.

Let's consider a few representative case examples, and I will offer my own thoughts on how best to select the right test in these settings.

Case 1: *A 66-year-old overall healthy male has a PSA of 4.2. A biopsy revealed Gleason pattern 3+4 in one of 12 core biopsies. He is considering active surveillance (AS) or active intervention.*

Prolaris is a great option here, as it was developed and tested in surveillance patients for meaningful oncologic endpoints like death from prostate cancer. Among Favorable Intermediate risk patients, about 70% could safely consider AS based on Prolaris testing results. The other tests have thresholds that would suggest that about half could consider AS, but those estimates are not derived from conservatively managed patients and are therefore less certain.

Case 2: *The same patient elected active surveillance, and he is now 70 years old and still very healthy. He has a repeat biopsy, and that reveals Gleason 4+3 in one core and 3+4 in three other cores. He desires to be treated now with radiotherapy.*

The NCCN guidelines recommend using androgen deprivation therapy (ADT) in men with Unfavorable Intermediate risk disease. However, both Artera and Prolaris have something unique to offer from the other tests in their reporting of how ADT may work. Artera has a predictive model that tells you if using ADT is futile, regardless of the risk of metastasis. In contrast, Prolaris will report the absolute risk reduction of using or omitting ADT, so that a patient can consider the therapeutic ratio specific to their case.

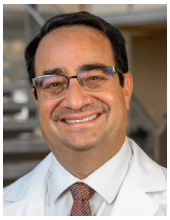
Case 3: *A 71-year-old patient with bad BPH and Gleason 3+3 prostate cancer is considering a TURP versus a Radical Prostatectomy.*

The GPS test will inform the patient about the probability of discovering Grade group 3 or worse prostate cancer and the presence of extracapsular extension at prostatectomy. If these risks are high, he may want to pursue a radical prostatectomy instead of surveillance and a more conservative BPH procedure.

Case 4: *The patient in case 3 had a radical prostatectomy showing Gleason 4+3 and a positive margin. His PSA was undetectable after surgery but is now 0.3 13 months later. He is referred to you for salvage radiation therapy.*

Although RTOG 9601 and 0534 demonstrated a benefit of adding ADT to salvage radiation, post hoc subgroup analyses of RTOG 9601 suggested using ADT may not be effective at PSA values <0.7. The Decipher test can be used to determine if ADT is likely to be helpful versus futile in this patient population.

Hollywood knows many people enjoy a good scare with their popcorn, and so it's no surprise that for every whimsical "The Hitchhiker's Guide to the Galaxy" we have a chilling "Resident Evil" series. Fortunately, though, the present and future outlook for prostate cancer patients is more "Buckaroo Banzai" than "Inception." The previous case examples do not by any means cover the full spectrum of indications for the new wave biomarkers, and each must be used judiciously while accounting for the total clinical context. However, taken together, they represent legitimate progress toward refining and personalizing care for prostate cancer patients.



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Disclosure statement:
Jonathan Tward has received consulting fees from Myriad for the Prolaris test within the past three years and previously received consulting fees from Decipher more than three years ago. In addition, he has been involved in studies with Artera and Decipher (uncompensated).

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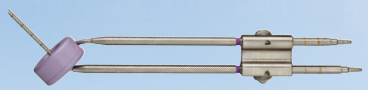

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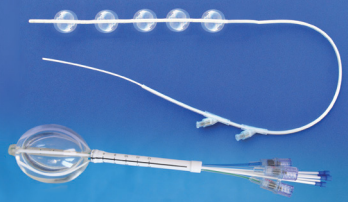

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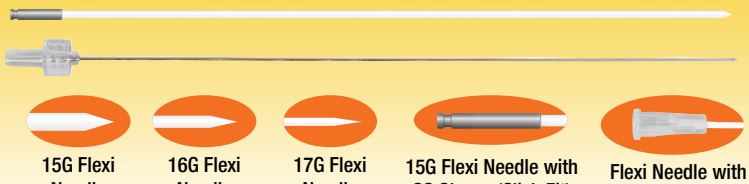

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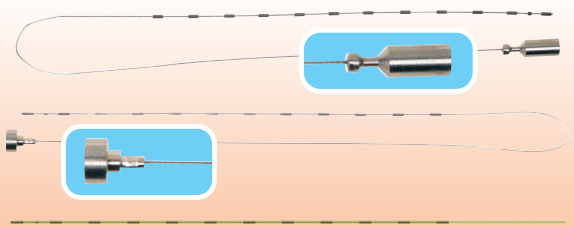

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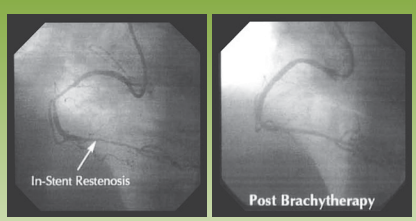

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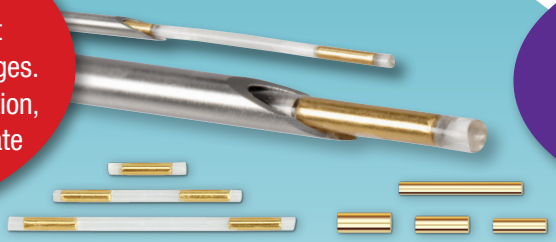

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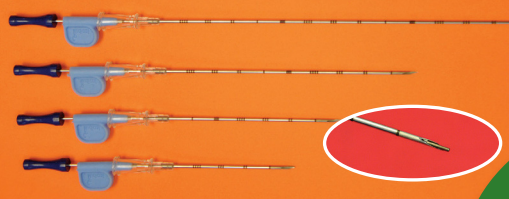

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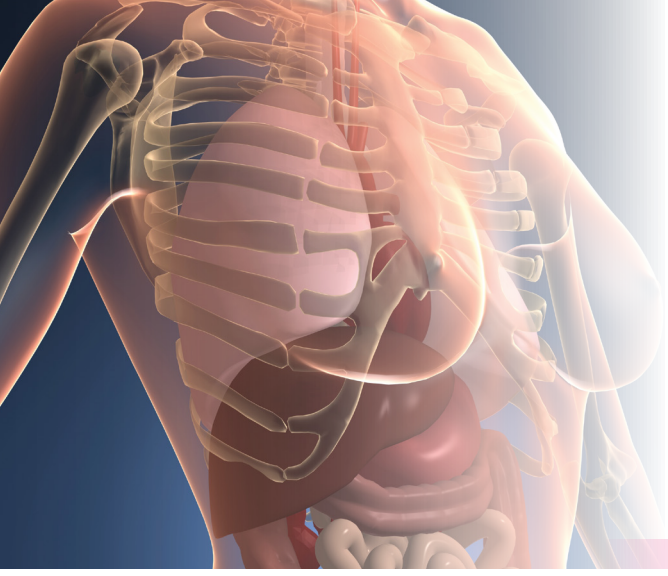


Beyond the Tangents: Biomarkers and the Art of Breast Radiotherapy

BY CHELAIN R. GOODMAN, MD, PHD

IT WASN'T TOO LONG AGO that many residents considered their rotation on the breast service to be the "easy" rotation. *Write a prescription for 15 or 25 fractions, contour the tumor bed, throw on some tangents, and call it a day!* If you're particularly detail-oriented, you could consider contouring a couple of the lymph node basins – but anatomical landmarks, clips and wires were still considered the mainstay for beam placement.

I was therefore surprised when one of my residents admitted he was the *most* nervous about his upcoming breast rotation. With expanded options for treatment decisions (omission, partial breast, whole breast, "high tangents," comprehensive regional nodal irradiation), dose fractionations (26Gy/5Fx QD, 30Gy/5Fx QD/QOD, 40Gy/15Fx, 50Gy/25Fx, 51Gy/34Fx BID), boosts (tumor bed, scar, flaps, nodal basins), and treatment technique (Partially Wide Tangents, Photon/Electron Match, VMAT, Sequential versus SIB Boost) – *phew, I'm tired even writing all of these!* – it's no wonder my resident feels like it's hard to read my mind.

Alongside this diverse menu of treatment opportunities has emerged a bevy of biomarkers with the potential to guide every aspect of breast radiotherapy: patient selection, dose prescription, target volume delineation, and even prevention and management of treatment-related toxicity. And we're not just talking about the standard panel of immunohistochemical receptors (the original "Three Musketeers": ER, PR, Her2) from the old days. Remember when Ki-67 was the hot new thing? There is now a bewildering array of assays that promises to transform breast radiotherapy from a "one-size-fits-most" approach to customized treatment that is as individual as the patient themself. The following is a select sample of my favorite biomarkers with the potential to move the needle in patient care:

Genomic Classifiers for Risk Stratification: "Oncotype, ARTIC and POLAR, Oh My!"

Genomic assays such as OncotypeDx, Mammaprint and Prosigna have been increasingly utilized to guide chemotherapy decisions for patients with early-stage breast cancer. But these tests aren't just limited to systemic therapy decisions; clinical trials currently underway propose a role in guiding radiotherapy decisions as well. While the Oncotype Dx and Prosigna assays are under evaluation as risk stratification biomarkers for radiotherapy de-escalation (e.g., TAILOR RT and PRECISION trials), conceptual frameworks such as POLAR (Postoperative Radiation for Low-Risk Patients) and ARTIC (Adjuvant Radiotherapy for Intermediate-Risk Cases) represent the next wave of risk stratification. Unlike the one-size-fits-all approach of yesteryear, these frameworks incorporate clinical, pathologic and genomic data to optimize radiotherapy treatment decisions for individual patients.

"EnGARD!" Utilizing Genomics to Personalize Radiation Dose

Meanwhile, GARD (Genomic Adjusted Radiation Dose) is competing to bring radiotherapy into the genomic age beyond the limitations of risk stratification alone. Transcending reliance on clinicopathologic data alone to guide dose prescriptions, GARD builds on the Radiosensitivity Index (RSI) to calculate the biological effectiveness of a prescribed radiation dose based on a tumor's genomic profile. Lacking at the moment from the breast radiotherapy armamentarium is the equivalent of *p16 status* for head and neck cancer, which may inform a more nuanced approach to dose prescription. This developing story will be exciting to follow in the coming years.

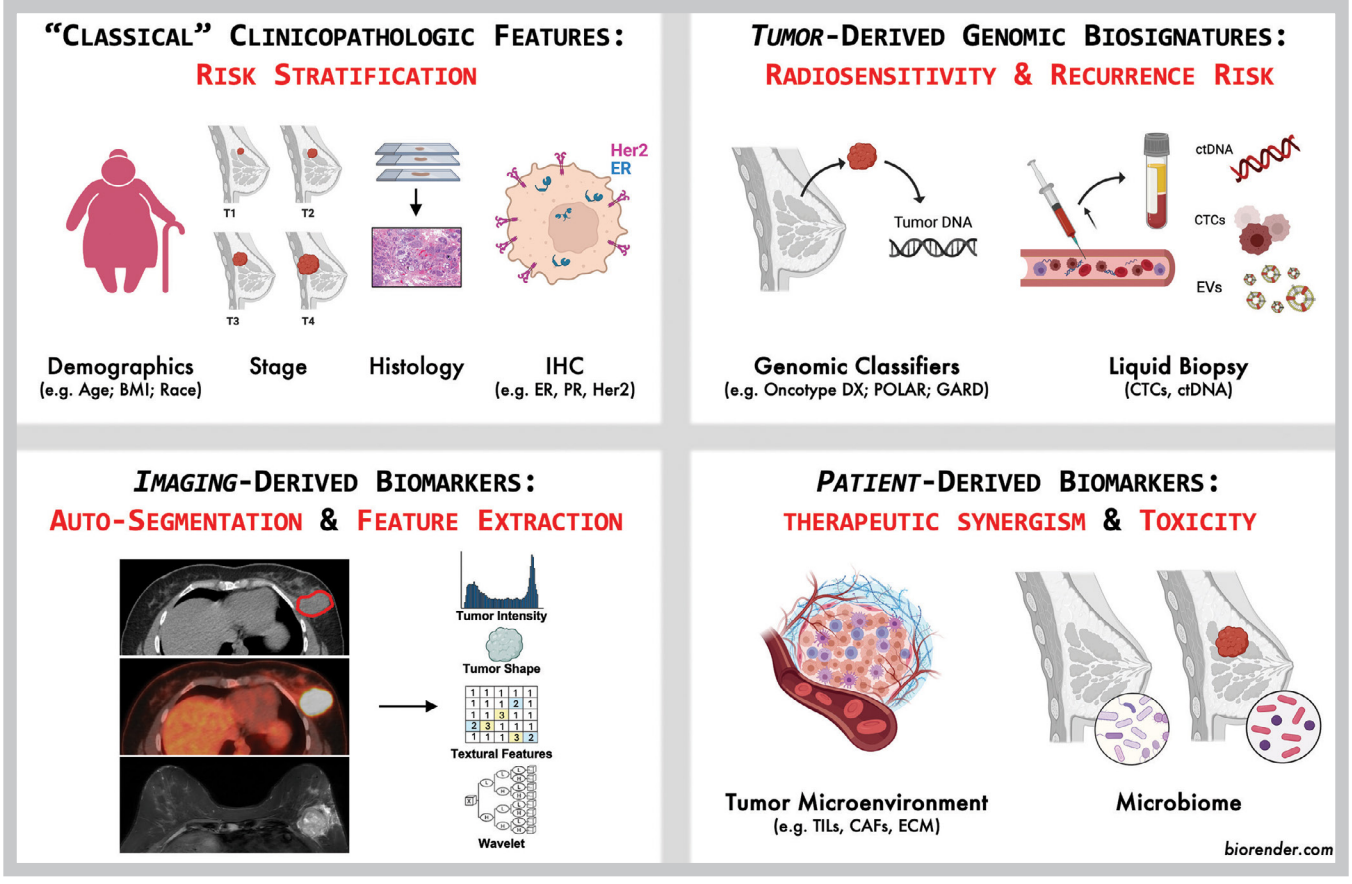
Circulating Biomarkers: Liquid Gold?

Circulating tumor material, including circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA), has been likened to a microscopic "crystal ball" for oncologists, providing a real-time glimpse into tumor dynamics and mutational changes with treatment. In his commentary in this issue of *ASTROnews*, Scott Bratman, MD, PhD, introduced the notion of minimal residual disease (MRD), defined as the presence of circulating tumor material after definitive treatment. Dozens of studies (and counting) have explored the use of MRD in breast cancer to yield prognostic information or even potentially guide management decisions, and it seems we are approaching a time when this type of assay will add value.[1] We are not yet, however, at a point where a ctDNA assay is an established instrument to direct therapy for breast cancer — but stay tuned.

"Always Look for the Helpers": The Tumor Microenvironment

Far more than just a bystander, the tumor microenvironment (TME) may be the true "shadow player" behind treatment outcomes. Consisting of cancer-associated fibroblasts, extracellular matrix components, lymphovascular networks and immune cells, the TME is a complex ecosystem that can modulate tumor radiosensitivity, promote anti-tumor immunity and facilitate (or inhibit) the epithelial-mesenchymal transition associated with distant metastatic spread. An "easy" example of the relevance of the TME is the fact that immune checkpoint inhibitors now play an important role in the management of triple negative breast cancer, but there is reason to believe that additional therapies might eventually exploit other features of the TME.[2] Radiation certainly has myriad effects on the TME, which has been labeled "game changer" for radiotherapy.[3] But at the moment, it seems we are still figuring out the rules.

Figure 1: Breast biomarkers derived from genomic classifiers, circulating tumor material, quantitative imaging, tumor microenvironment and microbiome continue to evolve. Figure courtesy of the author.



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Say "Cheese": The Wonderful World of Quantitative Imaging Biomarkers

The extraction and analysis of quantitative imaging biomarkers can provide insights into tumor biology and radiosensitivity that transcends what may be visible to the human eye. Multiparametric quantitative imaging analysis of tumor heterogeneity can identify microstructural patterns associated with radioresistance, while extraction of features correlating with tumor subtype, proliferation index or genomic changes have the potential to serve as a longitudinal supplement or surrogate for invasive biopsies. Investigators are just now scratching the surface in this domain.[4]

Don't Forget the Patient! Host Biomarkers and Toxicity Prediction

While much of the focus on biomarkers remains on tumor biology and oncologic outcomes, we would be remiss to ignore host-related biomarkers in determining the risk of radiotherapy treatment-related toxicity. Germline mutations in genes like *TP53, ATM* and *TGFB1* may increase sensitivity to radiation and the risk of late toxicities, while inflammatory biomarkers and cytokine profiles are gaining traction for predicting acute and long-term toxicities such as dermatitis, radiation fibrosis and lymphedema. Validation of biomarkers and probabilistic models for treatment-related toxicity would serve as a critical rationale for the development of prophylactic or proactive interventions to improve quality of life without compromising treatment efficacy.

Not All Fun and Games: Challenges Ahead

Alas, biomarker development comes with its own meaningful set of challenges. The validation of biomarkers for clinical or regulatory use requires large prospective clinical trials, while integration into clinical practice demands robust infrastructure. Importantly, we must consider whether biomarker-driven advances will prove to exacerbate disparities in access to care and subsequently address identified barriers to equitable access.

Lastly, while biomarkers offer the potential for unprecedented precision, their effectiveness is only as good as the physician integrating these assays into their clinical practice. As we embrace new treatment tools, maintaining a holistic view of the patient and continuously engaging in patient-centered decisions will remain critical.

The Bottom Line for Breast Biomarkers

As we stand on the brink of this biomarker revolution, one thing is clear: the future of breast radiation oncology is not just delivering *Gray* to kill. With the advent of biomarkers derived from genomic classifiers, circulating tumor material, quantitative imaging parameters, the tumor microenvironment and microbiome, radiation treatment continues to evolve into an ever more personalized art form. For radiation oncologists, the challenge will be not only staying *abreast* of these advances but also weaving them effectively into the fabric of day-to-day clinical practice.

So, whether you're a senior FASTRO, a seasoned community radiation oncologist, a stressed-out junior faculty, or an idealistic resident, one thing seems to be clear: breast radiotherapy is no longer the "easy" rotation — but it might just be the most personalized!

Chelain Goodman, MD, PhD, is an Assistant Professor in the Department of Breast Radiation Oncology at UT MD Anderson Cancer Center. Her research program is focused on the development and validation of novel patient- and tumor-derived biomarkers for the personalization of breast radiotherapy treatment decisions.

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Man's Best Friend and Other Lung Cancer Biomarkers

BY ARYA AMINI, MD

LOW DOSE CT SCANS provide an imaging-based biomarker useful for screening patients at high risk for developing lung cancer. Well established algorithms guide the workup and subsequent interventions for patients with suspicious nodules, but only a small percentage of those who qualify undergo screening. Furthermore, the test sometimes yields indeterminate findings that lead to more questions than answers.

One of the more innovative ideas for an inexpensive, scalable lung cancer screening test is to analyze volatile organic compounds in exhaled breath.[1] Trained sniffer dogs might play a future role in this domain.[2] The technology is not quite ready for widespread implementation, though, since the data are still a bit, um, ruff.

At the moment, the most thoroughly vetted biomarkers involve immunohistochemical or molecular profiling that primarily drive decisions about systemic therapy selection for patients with advanced or metastatic disease. Testing for PDL-1 expression is routinely accessible in nearly every pathology lab, as are analyses for common oncogenes such as EGFR or Ros1 mutations, ALK gene rearrangements, BRAF mutations, and a few others.

Clinical outcomes for patients with targetable mutations identified by these biomarkers are often remarkable. Responses like the one shown in Figure 1 are now commonplace, but it should be appreciated that such outcomes were simply unheard of even just 20 years ago, before the advent of new classes of systemic agents.

Perhaps most challenging to traditional dogma[3] for patients like the one shown in the figure has been a recalculation of how to manage asymptomatic brain metastases in patients with tumors expected to be sensitive to agents that easily cross the blood-brain barrier. Recent publications demonstrate that durable responses, or at least clinically meaningful downstaging, can be achieved with these agents, allowing for a more selective approach to treatment with radiosurgery,[4,5] a rubric endorsed in NCCN guidelines. Patients in this category also very often eventually have oligoprogression in extracranial locations for which locally ablative or palliative-intent therapy in the form of radiation treatment might play an important role.[6] The patient in Figure 1, for example, has had three courses of radiotherapy to various extracranial sites in her over four years (and counting) of survivorship since diagnosis.

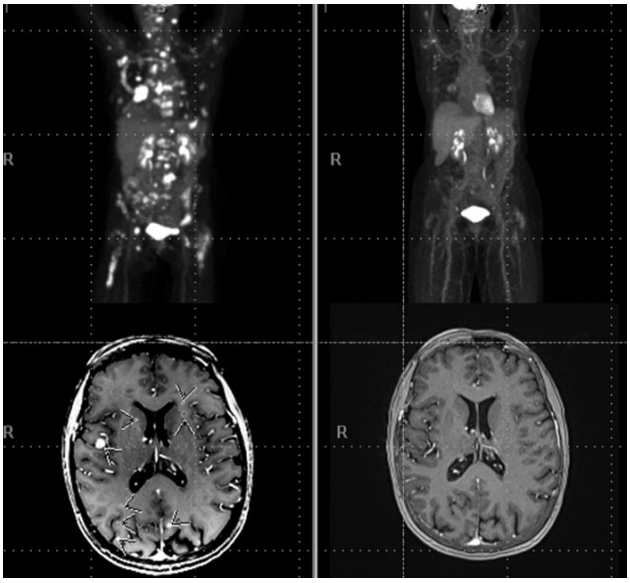

Figure 1. A 64-year-old female never smoker was found to have widespread EGFR mutation+ non-small cell lung cancer. Images at left show the initial PET scan and brain MRI, which had several dozen small lesions, some marked by arrows in this slice. The images at right show a sustained cranial and extracranial complete response after 18 months of osimertinib.

Continued on the following page

There have been efforts to identify a molecular signature that would identify patients whose oligometastatic state might be confirmed as a predictor of future clinical outcome, but working against these efforts is the bedeviling Catch-22 of many cancers whereby different foci of local or metastatic deposits can have different combinations of genetic mutations. Annoying, to say the least. Efforts to identify a genetic profile that predicts lung cancer radiosensitivity are also ongoing, and one of the most intriguing is a single nucleotide polymorphisms signature in DNA repair pathway genes ERCC1/ERCC2, shown to have possible implications for identifying patients who might benefit from dose escalation.[7] Other such markers are in various stages of refinement.[8]

Last but not least, the requisite query about the role of artificial intelligence in this space: where are we with AI and lung cancer at this time? The overarching field of AI offers a number of promising opportunities to analyze data and aid in the diagnosis, treatment and follow-up of lung cancer patients.[9] Of course, an important caveat for AI is that its value is predicted on the accuracy and completeness of the data available for crunching. A collective aspirational goal might be to work with the electronic record systems commonly used in radiation oncology departments (i.e., Aria, Mosaiq and others) and electronic medical records (e.g., Epic) to autopopulate mega databases that can then be analyzed through AI to create treatment algorithms, decision trees, and predictive models. Opportunities are endless but it will require a large, community-wide commitment to move the needle meaningfully.

Putting it all together, I personally think we have only just begun to see how the burgeoning field of biomarkers of all types will ultimately help lung cancer patients, and I look forward to days ahead when the powers will be truly unleashed.[10]

Arya Amini, MD, is an Associate Professor in the Department of Radiation Oncology and Chief of Thoracic Radiotherapy at City of Hope. He is a member of the ASTRO Education Committee and Congressional Relations Committee. Ironically, he is also more of a cat person.
: @DrAryaAmini

Commentary

WE HAVE COME SUCH A LONG WAY in the treatment of lung cancer over the past decade. It is truly amazing to me that we are able to have many long-term survivors with metastatic lung cancer — whether it is PD-L1 high patients receiving pembrolizumab or EGFR mutated lung cancer receiving targeted therapies. As radiation oncologists, our role in the management of metastatic disease has become critical. We are called upon to make important decisions when it comes to interventions for brain metastases, oligoprogression and durable palliation. It is not just a short palliative treatment of 4 Gy x 5 anymore — we are making meaningful contributions in the lives of patients with metastatic lung cancer and helping our patients live longer with better quality of life. I do think there is a huge opportunity for AI-based approaches to further refine our approaches to lung cancer. Together with the biomarkers already in routine use, continued evolution of MRD assays, and AI-based radiopathomic predictors that are being developed, we will continue to see more refined treatment options for our patients in the years to come.

Kristin Higgins, MD, is chief clinical officer for City of Hope Cancer Center Atlanta, where she oversees clinical care and hospital operations. Dr. Higgins is a member of multiple boards and committees in the lung cancer advocacy community, including the National Lung Cancer Roundtable Survivorship Task Group and the NRG Oncology Lung Cancer Core Committee.

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WINTER IS COMING: THE CHANGING LANDSCAPE OF HEAD AND NECK CANCER BIOMARKERS

BY NADEEM RIAZ, MD, AND BHISHAM CHERA, MD, FASTRO

TREATING HEAD AND NECK CANCER can be like a battle for the Iron Throne, and it's not just because of the anatomical complexity or the sheer variety of histologies. No, the real chaos happens at the molecular level, where biomarkers are supposed to be guiding us but instead leave us feeling like we're deciphering the words of a court jester, desperately searching for that magic marker that will bring order to heterogeneity. Let's be honest, the promise of biomarkers has been sitting on the horizon for years now, but it's time to take a critical look at what's real and what're just whispers in the shadows.

In the Beginning: p53, EGFR, EBV, HPV

The "first" biomarkers we had for head and neck cancer were p53 and EGFR – early rulers of a chaotic molecular realm. Disruptive p53 mutations and EGFR amplification/mutations served as grim heralds, prognostic for worse survival. The arrival of cetuximab, a monoclonal antibody targeting EGFR, was akin to the introduction of a promising new claimant to the throne — an aspirant that, despite early victories, ultimately after 20 years of iterative clinical trials could not unseat the enduring power of cisplatin. We subsequently discovered that uniquely many nasopharyngeal and oropharyngeal cancers are caused by viruses: Epstein Barr Virus (EBV) and Human Papilloma Virus (HPV), respectively.

The discovery of HPV-related oropharyngeal cancers emerged as our "Prince that Was Promised" — a beacon of hope for personalizing our most toxic treatments. HPV is spread through intimate alliances and identified through p16 staining, an indirect marker linked to the viral oncoprotein E7. This discovery allowed us to recognize and predict excellent outcomes for these patients under standard treatment. However, over a decade of de-escalation trials — attempting to reduce RT dose or substitute cisplatin with cetuximab — has shown that a one-size-fits-all approach to de-escalated treatment remains out of reach in the standard of care setting.

Intra-Treatment Monitoring and ctDNA

While we discovered a new disease in HPV-related oropharyngeal cancer, we still need to apply greater precision to understand the biology of these tumors and better tailor our treatments. Intra-treatment response monitoring, using tools like circulating tumor DNA (ctDNA) or PET imaging, to identify early responding tumors for de-escalation, has shown promise in early studies. For instance, intra-treatment monitoring of tumor hypoxia with FMISO PET allowed a subset of patients to receive doses as low as 30 Gy, significantly less than conventional therapy.[1] Patients with resolution of hypoxia two weeks into therapy received 30 Gy, while those who did not respond continued with standard treatment. Likewise, intra-treatment FDG PET response monitoring has enabled dose reductions to 54 Gy in responsive patients. Despite these promising results, we must be cautious not to repeat past mistakes; rigorous Phase 3 trials are needed before integrating these approaches into standard care.

Similar to imaging, ctDNA can identify rapidly responding tumors and may be able to de-escalate curative treatment in HPV related cancer. HPV related ctDNA (ctHPVDNA) is easy to detect and widely commercially available today. The intuitive assumption is that ctHPVDNA might be a valuable treatment-personalizing tool by revealing which patients have microscopic disease after surgery and thus need adjuvant therapy. However, early studies suggest these tests may not be sensitive enough today for that purpose.[2] Another emerging use for ctHPVDNA is in the post-radiation treatment surveillance setting. Here, a positive ctHPVDNA test often indicates a high risk of recurrence, necessitating closer surveillance.[3,4] Although not yet included in consensus guidelines, some routinely incorporate ctHPVDNA in this setting. Data suggest that recurrence can be detected in an early state with this approach. Figure 1 illustrates the possible value of ctHPVDNA across the continuum of care for a patient with HPV related oropharyngeal cancer.

Continued on the following page

EBV viral load is a standardly used biomarker for nasopharyngeal cancer. It is not as sensitive or specific as ctHPVDNA because the viral load assay does not provide absolute quantification and cannot distinguish between cancer and acute infection (i.e., mononucleosis) because it is detecting the intact viral genome. Nonetheless, pretreatment, mid-treatment and post-treatment EBV viral load is prognostic, and consensus guidelines suggest EBV monitoring.

Biomarkers at Recurrence

If a cancer returns, we possess several biomarkers to guide our counterattack. The most important of these is PD-L1, an immune checkpoint that can guide decisions on first line therapy in the recurrent/metastatic setting. The Combined Positive Score (CPS) for PD-L1 is complex, counting tumor cells, immune cells and other elements, but it helps identify patients who may respond to pembrolizumab alone, sparing them from combination chemotherapy. Next-generation sequencing can identify actionable alterations in HNSCC, including PI3KCA and H-ras mutations. Unfortunately, unlike our colleagues in lung, prostate and breast cancer, we do not yet have FDA-approved targeted therapies for these alterations, leaving us to recommend clinical trials instead. Similarly, more detailed HPV typing, distinguishing HPV16 from other subtypes, can provide unique trial opportunities for patients.

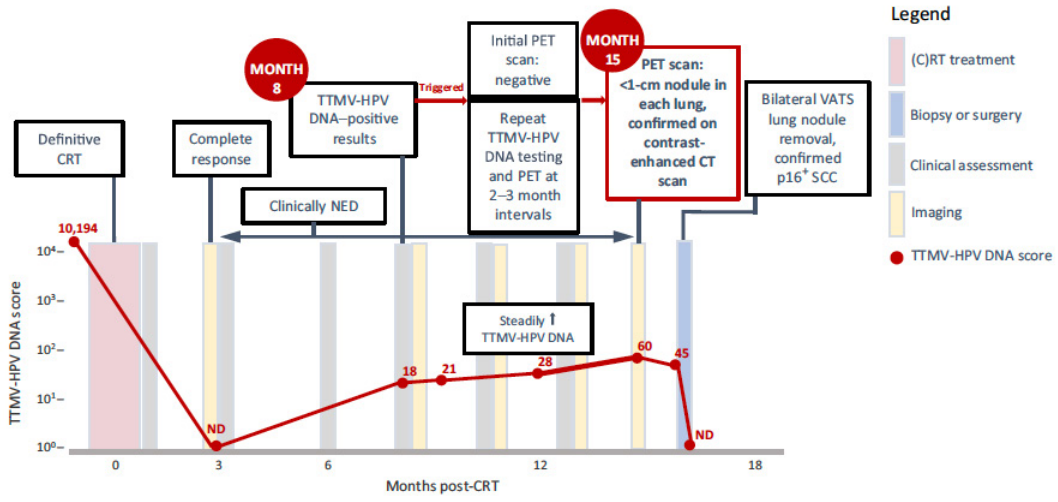

Figure 1: Adapted from Berger et al.[4] Patient with p16 positive oropharyngeal squamous cell carcinoma received definitive chemoradiotherapy resulting in complete response and complete resolution of ctHPVDNA (TTMV-HPV DNA). Eight months post treatment ctHPVDNA became detectable which triggered a repeat PET/CT which showed no evidence of disease. Serial ctHPVDNA steadily increased and repeat PET/CT 15 months post-treatment revealed oligometastatic disease in the lung which was treated with surgery. ctHPVDNA subsequently became undetectable. TTMV-HPV DNA = Tumor Tissue Modified Viral HPV DNA.

In the Heat of the Bite

While it is true that the human papilloma virus (HPV) is sexually transmitted and leads to head and neck and other cancers, at least we aren't plagued by the same malady suffered by *Sarcophilus harrisii*. Best known to children growing up in the U.S. by its Looney Tunes cartoon incarnation, the hapless Tasmanian Devil is susceptible to a facial sarcoma whose transmission is thought to be unique in the animal kingdom. Allografts are directly deposited by bites during a violent mating ritual.[1]

Devil Facial Tumor Disease is no laughing matter, though, and was considered a legitimate threat to species extinction. Fortunately, in recent years there has been the apparent development of resistance to transmission of the tumor, alongside Australian and Tasmanian government programs to maintain a captive insurance population. Also, vaccine tests are underway.[2]

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Closing Out

The next time you're tempted to put your hopes on the latest biomarker buzz, remember that the head and neck cancer landscape is as treacherous as the battle for the Seven Kingdoms. We need more than just intriguing signals. We need reliability, reproducibility and relevance to real-world outcomes. Until we reach that goal, let's keep our eyes open, our minds skeptical, and our focus on what truly matters: delivering the best, evidence-based care for our patients, regardless of how trendy the biomarker may be. Because in the end, it's not just about winning the "Game of Thrones" — it's about who survives to see another day.

Nadeem Riaz, MD, is a head and neck radiation oncologist and physician scientist at Memorial Sloan Kettering Cancer Center in New York. His clinical research is focused on personalizing therapy for HPV-related head and neck cancers and his lab studies the influence of the DNA damage response on anti-tumor immunity.

Bhisham Chera, MD, FASTRO, is Professor of Radiation Oncology and Otolaryngology and Vice Chairman for Safety and Quality Assurance in the Department of Radiation Oncology, and the Wendy & Keith Wellin Endowed Chair in Radiation Oncology at Medical University of South Carolina.

Disclosure statement:
Bhisham Chera: Co-inventor of intellectual property held by the University of North Carolina regarding the ctHPVDNA detection methodology (US Patent 11,168,373); Scientific advisor with ownership interest in Naveris, Inc., a company that has licensed ctHPVDNA technology from University of North Carolina for commercialization.

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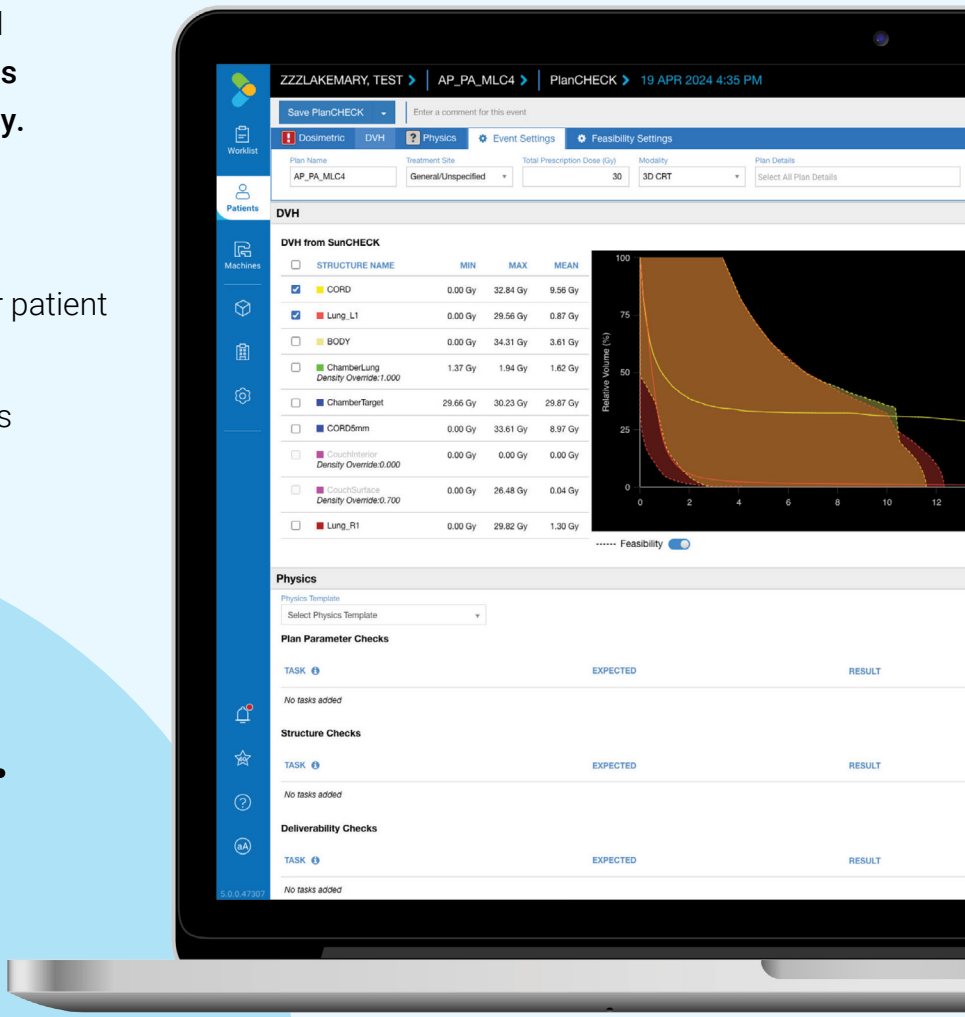

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Improving Quality of Life for Patients with Bladder Cancer

A novel biomarker to guide the use of bladder preservation therapy

BY EMILY T. CONNELLY, MA, CRA

David Miyamoto, MD, PhD (center) and team from Massachusetts General Hospital.

DAVID MIYAMOTO, MD, PHD, and his colleagues at Massachusetts General Hospital are developing a liquid biopsy to personalize treatment for patients with muscle-invasive bladder cancer (MIBC). The innovative blood test will help identify which patients are good candidates for trimodality therapy (TMT), a combination of chemoradiotherapy and surgery to remove the tumor that preserves the bladder. The biomarker would also allow for non-invasive monitoring of treatment response during and after TMT.

Many patients with bladder cancer are treated with radical cystectomy, an invasive surgery to remove the entire bladder, but there are high rates of complications and significant impacts on quality of life. Recent research has shown that TMT and radical cystectomy have similar metastasis-free survival, cancer-specific survival and disease-free survival for select patients. However, 20% to 30% of patients initially treated with TMT experience disease recurrence and require surgery to remove the entire bladder.

"We need a better way to select patients who are most likely to benefit from TMT," says Dr. Miyamoto. "Our team has developed a highly sensitive microfluidic chip technology that efficiently isolates circulating tumor cells (CTCs) that are shed from the cancer into the blood stream. Our innovative method enables sophisticated molecular profiling of tumors based on RNA expression in the CTCs." In 2021, Dr. Miyamoto received a Biomarkers for Radiation Oncology Award from the Radiation Oncology Institute (ROI) – the ASTRO Foundation – to pursue this promising research. With the grant, Dr. Miyamoto's team has made progress toward identifying unique pretreatment bladder CTC and tumor molecular signatures that predict clinical outcomes after chemoradiation therapy and developing a non-invasive test to detect the presence of bladder cancer cells in the blood to monitor minimal residual disease or early recurrence following TMT. They have published some of their findings to date in several journals, including Science Advances and Clinical Cancer Research.

Dr. Miyamoto used the results of the ROI-funded research to successfully compete for an R01 grant from the National Cancer Institute (R01CA259007) to continue the development of this new method of blood-based monitoring for patients with bladder cancer who are treated with TMT. "The grant from ROI provided critical support for our research at a time when we did not have funding to conduct the proposed project. Without this ROI award, it would not have been possible to generate the preliminary data necessary for the NIH R01 grant that we subsequently received to evaluate the liquid biopsy and molecular tissue biomarkers in larger cohorts of patients," says Dr. Miyamoto. The team is currently conducting a clinical study to validate the ability of their CTC-based molecular assay to predict and monitor response to bladder-sparing TMT. They are also testing other liquid biopsies as alternative biomarkers and engaging in deep molecular profiling of CTCs from bladder cancer patients to elucidate mechanisms of resistance to chemoradiation and identify new potential therapeutic vulnerabilities.

Reliable and accurate molecular biomarkers to identify patients who are the best candidates for TMT could increase utilization of TMT and allow more patients to preserve their bladder, providing them with a better quality of life. The liquid biopsy that Dr. Miyamoto and his team are developing would be a practice-changing breakthrough that shows great promise to improve outcomes for patients with muscle-invasive bladder cancer.

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BY MICHAEL YUNES, MD, ABR ASSOCIATE EXECUTIVE DIRECTOR FOR RADIATION ONCOLOGY

Continuing Certification and Online Longitudinal Assessment

THE CONTINUING CERTIFICATION PROCESS with the ABR has four parts:[1]

Part 1: Professionalism and Professional Standing
Fulfilled by maintaining a license to practice medicine.

Part 2: Lifelong Learning
Fulfilled by completing at least 75 Category 1 CME within the last three calendar years. The self-assessment CME (SA-CME) requirement was removed in 2024.

Part 3: Assessment of Knowledge, Judgment and Skills
Meet or exceed the standard in a current cumulative (i.e., weekly) OLA score at some point in year five (5) or pass a Continuing Certification Exam (CCE) in year four (4) or five (5) of the Part 3 cycle.

Part 4: Improvement in Medical Practice
Complete at least one Practice Quality Improvement (PQI) Project or Participatory Quality Improvement Activity within the last three years. This includes chart rounds and multidisciplinary tumor boards.

The ABR has made many changes over the past 18 years to ensure that the Continuing Certification process is effective and represents a minimal burden on diplomates. All radiation oncology diplomates who passed their initial board exams prior to 1995 received a lifetime certificate from the ABR. Eligibility requirements changed several times between 1996 and 2005. Anyone receiving their initial certification during this time frame was required to take a Maintenance of Certification (MOC) Exam every 10 years. Diplomates who did not pass this required exam could re-enter maintenance by taking and passing the initial certifying *oral exam.*

In 2015, in response to concerns from diplomates, the ABR announced significant changes to the MOC process. Along with changes to Part 4, the ABR eliminated the 10-year MOC Exam and replaced the exam with a modern approach to continuous assessment using Online Longitudinal Assessment (OLA) with two questions per week. This process was a significant improvement in many ways. OLA removed the need to study rigorously, take time off from work or travel for an exam (which was required prior to the ABR developing a secure, computer-based system for delivering remote exams). Diplomates can learn from incorrect answers by reading the accompanying rationale and reference and are presented with a similar question soon after. There is an opportunity to skip or decline 10 questions per year out of the total 104 provided, and there is a time limit for each question based on the depth and detail of the question. After completing each question, diplomates are surveyed to help inform the future development of questions, to establish relevance and to help determine the minimum standard for that question. Every question will have a different passing standard based on responses to the optional question rating process; therefore, the minimum passing standard may vary from diplomate to diplomate depending on which questions each diplomate answers.[2]

Diplomates must answer a minimum of 52 OLA questions per year over the five-year period, but the assessment includes only the most recent 200 scorable questions. Up to four weeks of questions can be pooled together before falling off the list of available questions. Diplomates not answering the required minimum of 52 questions will "forfeit" the unanswered questions. For example, if you are required to answer 52 questions and only answer 50, the two unanswered questions will be considered "forfeited" and counted as incorrect. The vast majority (98.8%) of radiation oncologists are enrolled in OLA, and most answer far more than the minimum number of questions required per year. Diplomates who are not performing well in OLA or choose not to participate may also fulfill the Continuing Certification Part 3 requirement by passing a CCE in year four or five of their five-year Part 3 cycle. The CCE is offered twice a year.

The first-time diplomates could potentially lose their certification for not participating in OLA or not passing a CCE before December 31, 2024. The ABR has published, emailed, posted or blogged over 120 independent communications since 2019 to ensure that all diplomates are aware of how to fulfill the Part 3 requirement. In addition, each year when paying their Continuing Certification fee, diplomates acknowledge their responsibility. Essentially, we all

accepted that we are responsible for notifying the ABR of email address changes and for maintaining awareness of potential changes in the requirements. A global Continuing Certification attestation in 2021 required all diplomates from all four ABR disciplines to accept or decline this optional process. Those who signed agreed to participate in OLA or take the CCE to retain certification. Lifetime certification holders were not required to participate, but if they opted out, they were informed that they would not be listed as participating in the Continuing Certification program.

It is important to note that the ABR certifies in general radiation oncology. There is no subspecialty certification, so both OLA and the CCE include all disease sites. OLA questions are designed to be "walking around knowledge" or general radiation oncology questions that should not require study for most diplomates. The CCE, on the other hand, is inherently more difficult (but, as a point-in-time exam, allows for diplomates to prepare through targeted study). Diplomates who elect to take the exam in lieu of OLA should not expect it to be "walking around knowledge." OLA and CCE are not primarily intended to improve your individual ability to provide care or to "make you a better doctor." The target audience is in large part our patients, communities, colleagues and employers who express the importance of physicians being engaged in a continual education process.[3]

Although there are a very small number of our colleagues who are at risk of losing their certification in 2025, there has been near universal satisfaction with the OLA process and associated time requirement. Nonetheless, the ABR continues to refine and improve the Continuing Certification process and OLA content, including advances such as no longer requiring onerous annual attestations.

As one of the final diplomates who was required to take the MOC exam in 2014, I am very pleased with OLA as an alternative solution and appreciate the simple and quick approach to continuous learning.

The ABR continues to work toward providing one of the least burdensome assessment tools that follows the requirements[4] as set by the American Board of Medical Specialties (ABMS).

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ROBIN
RADIATION ONCOLOGY-BIOLOGY INTEGRATION NETWORK

Radiation Central to the Path to Cure: Foundational Research in Radiation Oncology will Form the Basis of the Next Generations of Clinical Trials and Technology

WITH AN INVESTMENT OF $40 MILLION over five years, the NCI has funded five U54 grants and created the Radiation Oncology-Biology Integration Network (ROBIN). This is a collaborative interdisciplinary effort to create and apply new biological knowledge to optimize radiation therapy in combination with systemic drugs, immunotherapy and other agents. Each ROBIN center is described below and has materials and lectures regarding their respective topics, which are free to the community. ASTRO created a webpage for quick access to the various education materials: www.astro.org/professionaldevelopment.

Center for Genomics of Biologics Enhanced Radiotherapy (GenRad)

Principal Investigator:
Timothy Chan, MD, PhD

Radiation therapy (RT) is now commonly used in combination with systemic therapies including biologics. The long-term goal of the GenRad Center is to understand the genomic and microenvironmental determinants, temporal dynamics and efficacy of radiation-based combination therapies. We have launched several trials to evaluate the effectiveness of combining radiation with various targeted biologics. First, we aim to understand the utility and molecular mechanisms that underlie the efficacy of combination with radiation treatment plus antibody drug conjugates (ADC). We hypothesize that specific genetic and immunologic events underlie treatment efficacy with radiation plus ADC treatment. Specifically, we are investigating the use of sacituzumab govetican + RT for bladder preservation therapy in muscle invasive bladder cancer and will determine the differential molecular effects between standard-of-care cisplatin + RT versus ADC + RT. In addition, we are identifying the differential mechanisms underlying anti-tumor activities of cisplatin + RT versus immune checkpoint blockade + RT in head and neck squamous cell carcinoma (HNSCC). We are working to uncover the unique genetic and immunologic factors that govern response to RT when combined with these two classes of agents. We will elucidate the differential molecular effects of the two approaches, characterize immune reprogramming and reveal mechanisms of acquired resistance. Finally, we are aiming to improve identification of patients who are sensitive or resistant to RT-based therapies based on new insights into transcriptional dynamics and temporal reprogramming during radiation-based therapies.

Our team is comprised of investigators from the Cleveland Clinic and Emory University. Our goal is to propel innovative radiation-based therapeutic approaches and to inform future trial design to improve patient outcomes.

Immune system and Radiotherapy (ImmunoRad) Center

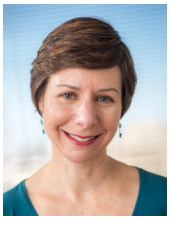
Principal Investigator:
Silvia Formenti, MD, FASTRO

The role of the immune system in cancer response to radiation therapy (RT) is critical, as early studies by Stone et al. demonstrated. They showed how immune mechanisms influence RT outcomes, particularly in tumor control. ImmunoRad, an international initiative, builds on these findings to investigate how RT impacts cancer outcomes through immune interactions, aiming to bridge preclinical evidence to clinical applications. A molecular characterization trial (MCT) involving 50 rectal cancer patients across the U.S. and Europe will assess RT's influence on tumors, surrounding tissues, the immune system and microbiome. Rectal cancer, treated with short-course RT (SCRT) in a preoperative setting, provides an ideal model to examine these immune interactions. Seven academic centers are collaborating to conduct comprehensive tissue and immune profiling, employing advanced molecular

analyses to explore RT's effects on both tumor and healthy tissue, as well as on the host's immune system and microbiome. Additionally, artificial intelligence and machine learning models will predict interactions between patient characteristics, tumor traits and RT parameters. The ImmunoRad initiative integrates with the ROBIN network, encouraging interdisciplinary collaboration among clinicians, scientists and radiation experts. It also includes a cross-training core to prepare the next generation of leaders in radiation science. Findings will be shared across ROBIN and with the wider scientific community, creating a valuable resource on RT's biological effects.

Coordinated by the Immunity and Radiation Oncology Network (IRON), this project exemplifies global efforts to use cutting-edge technology to deepen our understanding of RT's interaction with the immune system.

KIDSROBIN Center



Principal Investigator: Daphne Haas-Kogan, MD, MBA, FASTRO

Although many cancers respond well to radiation therapy, some respond poorly or not at all. Even within cancer subtypes that collectively respond well, the response of individual patients with the same tumor types is variable. Prognostic biomarkers and markers of early responses to new radiation/adjuvant combinations are needed. Toward these unmet needs, we apply contemporary tools of computational biology, data science and natural language processing. The clinical vehicle for our KIDSROBIN team is pediatric cancers — specifically two cancers of neuroectodermal origin (diffuse midline gliomas and aggressive neuroblastomas). Cancers of neuroectodermal origin are the number one solid tumor of children and the number one cause of cancer related death in children. Minimization of confounding passenger mutations is needed to unmask actionable biomarkers, and the mutational burden of pediatric cancers is low. Moreover, insights into pediatric cancers have proven to be generalizable to more common adult cancers. Pediatric solid tumors are less frequent than their adult counterparts. To address the challenge of low "n," KIDSROBIN draws upon tissue available through large pediatric cancer consortia: Children's Oncology Group and Pacific Pediatric Neuro Oncology Consortium and features a strategic alliance between the Dana-Farber/Harvard Cancer Center and the University of California, San Francisco.

MicroEnvironment Tumor Effects Of Radiotherapy (METEOR) Center

Principal Investigator: Julie Schwarz, MD, PhD, FASTRO

The balance between immune *stimulatory* and *suppressive* effects of radiation therapy (RT) predicts whether local treatment with RT generates a systemic anti-tumor immune response. We hypothesize that RT, and in particular standard of care chemoradiation (SOC CRT), can limit the development of anti-tumor immunity by *increasing* the number and tumor permissive phenotypes of myeloid derived cells in the tumor microenvironment (TME). The Washington University MicroEnvironment Tumor Effects Of Radiotherapy (METEOR) Center will comprehensively define the TME in patients receiving CRT for cervical and pancreatic cancer using biologic and radiologic specimens obtained before, during and after RT. We will leverage our institutional expertise in genomics, proteomics, tumor metabolism and immunology to take a "deep dive" into CRT-induced TME co-evolution using both single cell and spatially resolved approaches. Our overall vision is that immunosuppressive SOC CRT associated changes in the TME can be further targeted to *improve* systemic anti-tumor immune responses. Although our preliminary data implicates macrophages and dendritic cells, our research design will allow for detailed study of multiple immune and stromal cell types in the TME. Furthermore, our approach using only small biopsies will facilitate collaboration with others to determine what are the common and tumor site-specific mechanisms of CRT resistance.

Oligometastasis (OligoMET) Center

Principal Investigator: Nicole Simone, MD

Metastasis is the final common lethal pathway for most cancer patient's demise and once cancer has metastasized, it was generally considered incurable. Through paradigm-shifting translational and clinical studies, some of which were pioneered by the U54 ROBIN Oligometastasis (ROBIN OligoMET) team, we now know the metastatic capacity of cancers behaves along a spectrum of disease that contains an oligometastatic state where metastases are limited in number and location. This concept has been

Continued on page 35

BY SHEELA HANASOGE, MBBS, PHD

Giants of Radiation Oncology: Biographical sketches from the ASTRO History Committee

AMONG THE MANY GIANTS who have been crucial in shaping the history of radiation oncology in the United States, Isadore Lampe, MD, PhD, has played a pivotal role. His portrait graces the walls of the Department of Radiation Oncology at the University of Michigan, which he led from 1939 to 1974. His legacy lives on more than 40 years after his passing.

Isadore Lampe, MD, PhD (1906-1982)

Isadore Lampe's story begins, as many great stories do, with his birth on November 16, 1906, in London, England. His parents were Anna Tamarkin and Joseph Lampkovitz, Jewish immigrants originally from Russia and Poland respectively. He was only four months old when he immigrated to the U.S. with his mother to join his father who had come over previously.

He grew up in Cleveland, Ohio, and in high school was a member of the track team and played tuba in the school band. He graduated with honors in 1923. His undergraduate studies were completed at Adelbert College in Cleveland, one of three predecessors to today's College of Arts and Sciences at Case Western Reserve University, where he received his Bachelor of Arts degree in 1927 and was inducted into Phi Beta Kappa. He was subsequently accepted into the School of Medicine of Western Reserve University. Childhood friends had nicknamed him "Lampy" and during this period, he legally changed his name to Lampe. Because of health issues he was forced to repeat his second year of medical school and ultimately graduated in 1931, with honors, and membership in Alpha Omega Alpha Honor Society.

Dr. Lampe's entry into therapeutic radiology was fortuitous. Few institutions in the U.S. at the time offered exclusive or comprehensive training in the field. During his internship in Toledo, he met John Thomas Murphy, MD, director of the Department of Radiology, who would become his mentor. Dr. Murphy influenced him to focus his training on radiation therapy. Thanks to Dr. Murphy's personal effort, Dr. Lampe was given a position of "assistant resident" in the Department of Radiology at the University of Michigan, under the chairmanship of Fred Jenner Hodges, MD. The residency program at Michigan was in general radiology, but Dr. Hodges was anxious to build on therapeutic radiology advances and encouraged Dr. Lampe to concentrate in that area. Dr. Lampe quickly moved up the department ranks to instructor and research instructor within three years. By virtue of his fastidiousness and interest in statistics, he was appointed as a part-time statistician in the Medical Records Division and went on to establish the Medical Statistics Division at Michigan. His coding system became a national model among tumor registries.

In 1938, Dr. Lampe completed his residency and PhD in Roentgenology at the university, where his doctoral dissertation included observations about the relative biological effectiveness of neutrons compared with photons, an area of interest for which he spent six months at the new cyclotron facility at Berkely. He later used the cyclotron developed by the Michigan physics group for additional research.

Despite residency training primarily in general radiology, Dr. Lampe became an autodidact in radiation therapy. In 1939, he was appointed full professor and assumed leadership of the Division of Radiotherapy within the Department of Radiology, a position he would hold for 35 years. He was devoted to the best interest of every patient being treated in the department and liked to check each patient's setup himself every day. In addition to his clinical work, he taught courses in radiobiology, authored chapters in textbooks, kept current with world literature, organized joint Pathology-Radiation Therapy Symposia, and conducted studies and published on a wide range of clinically relevant topics including medulloblastoma, head and neck cancers, radioactive isotope treatment,

endometrial cancers, and ^{137}Cs teletherapy, among others. He continued to make many significant contributions to radiation oncology literature which helped establish him as a leader in the field. Perhaps a small measure of Dr. Lampe's impact can be gleaned by the homage paid to him by his chief Dr. Hodges in 1968 who stated that, "He has become a clinical radiation therapist of outstanding capabilities, based upon rigorous, unrelenting hard work, and complete devotion to this branch of the medical profession." His distinguished friend and peer Juan del Regato, MD, said of him "…the disciplines of which he has become a recognized master, to gain international respect as a true philosopher of therapeutic radiology."

Foremost among American-trained radiotherapists, Dr. Lampe helped train a generation of University of Michigan radiology residents in therapeutic radiology during their six to nine month rotation with him. He worked to impart his superb clinical skills to his trainees, becoming known as a strict but gentle disciplinarian, and training them to be excellent physicians of upstanding scientific and personal integrity. Many of his trainees acquired a great respect for the field. Several went on to specialize in radiotherapy and achieved remarkable personal accomplishments. Among his illustrious trainees were Robert Parker, MD, Philip Rubin, MD, FASTRO, Malcolm Bagshaw, MD, FASTRO, and Seymour Levitt, MD, DSc, FASTRO.

In 1958, Dr. Lampe became one of the founding members of the American Club of Therapeutic Radiologists, the predecessor of ASTRO, of which he was elected president from 1962-1963. He was awarded the ASTRO Gold Medal in 1979, and that same year, received Michigan's Distinguished Teaching Service and Research Award.

In 1943, Dr. Lampe met and married his wife Rae Ethel White with whom he had two sons, William, born in 1945 who became a lawyer, and Matthew, born in 1951 who became a psychologist. He was generally frugal, except when it came to his love of photography and imported sports cars.

Late in life Dr. Lampe developed chronic lymphocytic leukemia. While traveling to receive a transfusion he was in an automobile accident on icy roads. He died on January 26, 1982, of injuries sustained in that accident. His legacy has been continued at The University of Michigan Department of Radiation Oncology with the establishment of an endowed chair in his name which is held by the chair of the department.

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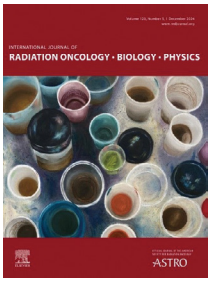
Continued from **ROBIN RESEARCH HIGHLIGHTS**

transformational in the way the clinical field views metastasis; however, a greater biologic understanding is needed to improve cure rates. This OligoMET Center seeks to build from these initial findings to understand mechanistically how radiation may modulate metastatic biologic processes, specifically, unanswered questions related to radiation effects on tumor plasticity, metabolic reprogramming and the tumor immune microenvironment. This in turn will lead to the development of new approaches for using radiation therapy to combat metastases. The OligoMET Center uses oligometastatic prostate cancer as their model, but results will inform future treatment planning and trial design in other oligometastatic cancers. Overall, the ROBIN OligoMET Center was created as a platform for greater adoption of radiation oncology concepts, biomarkers and technologies in the oligometastatic space through academic and/or industrial partnerships.

Additional information regarding these grants and other grant opportunities can be found at rrp.cancer.gov.



Key Findings from Recent Red Journal Research: Biomarkers

The articles below represent a sample of the latest research published in the *International Journal of Radiation Oncology • Biology • Physics* related to biomarkers. For additional articles, please visit redjournal.org.

Biomarker Expression and Clinical Outcomes in International Study of Chemoradiation and Magnetic Resonance Imaging-Based Image-Guided Brachytherapy for Locally Advanced Cervical Cancer: BIOEMBRACE

Chopra et al.

BIOEMBRACE was designed to study the impact of biomarkers in addition to clinicopathological factors on disease outcomes in patients treated with chemoradiation and MRI-guided brachytherapy for locally advanced cervical cancer in the EMBRACE study. P16 negative status and tumor necrosis on MRI are independently associated with poor response to chemoradiation, whereas PD-L1 > 1% and L1CAM ≥ 50% have an independent impact on local and pelvic control, suggesting an impact of biomarker expression on outcomes. For further information on this article, please see the associated video and podcast.

RED JOURNAL PODCAST

In the January 1 podcast, Editor-in-Chief Sue Yom, MD, PhD, FASTRO, and Associate Editor Neil Taunk, MD, co-host a discussion on "Biomarker expression and impact on clinical outcomes in an international study of chemoradiation and MRI-based image-guided brachytherapy for locally advanced cervical cancer: BIOEMBRACE," with guests Supriya Chopra, MD, Professor at Tata Memorial Centre in Mumbai, India, and Remi Nout, MD, PhD, Professor and Head of the Department of Radiotherapy of the Erasmus Medical Center, University Medical Center, in Rotterdam, Netherlands, who were the first and last authors and both principal investigators of the BIOEMBRACE study.

You can listen to this podcast and read the article at www.redjournal.org.

ClonoScreen3D – A Novel 3-Dimensional Clonogenic Screening Platform for Identification of Radiosensitizers for Glioblastoma

Jackson et al.

Patient-derived GBM cell lines were optimized for inclusion in a 96-well plate 3-D clonogenic screening platform, ClonoScreen3D. Radiation responses of GBM cells in this system were highly reproducible and comparable to those observed in low-throughout 3-D assays. The screen methodology provided quantification of candidate drug single agent activity (half maximal effective concentration or EC50) and the interaction between drug and radiation (radiation interaction ratio). The ClonoScreen3D platform was demonstrated to be a robust method to screen for single agent and radiation-drug combination activity.

Prostate-Specific Antigen and Prostate Cancer in Gender-Affirming Hormone Therapy for Transgender or Nonbinary (TGNB) Individuals

Morgan et al.

Gender-affirming hormone therapies are associated with significant decreases in PSA, and TGNB individuals assigned male at birth remain at risk of prostate cancer. Future work should establish if a lower threshold for biopsy should be used in these contexts and if the decreased incidence is a result of ascertainment bias or hormone therapy resulting in a true decrease in the incidence of prostate cancer.

Myoferlin: A Potential Marker of Response to Radiation Therapy and Survival in Locally Advanced Rectal Cancer

Fowler et al.

Patients with locally advanced rectal cancer often require neoadjuvant chemoradiation therapy to downstage the disease, but the response is variable with no predictive biomarkers. High expression of myoferlin in rectal cancer is associated with poor response to neoadjuvant therapy and worse long-term survival. The manipulation of myoferlin led to increased radiosensitivity in vitro. This suggests that myoferlin could be targeted to enhance the sensitivity of patients with rectal cancer to radiation therapy, and further work is required.

Information in this section has been adapted from abstracts of the cited articles.

RADIATION THERAPY IN FOCUS

ASTRO LAUNCHES RADIATION THERAPY PUBLIC RELATIONS CAMPAIGN

Visit RTAnswers.org\RTinFocus
to view a new campaign designed to give patients the facts about radiation therapy.

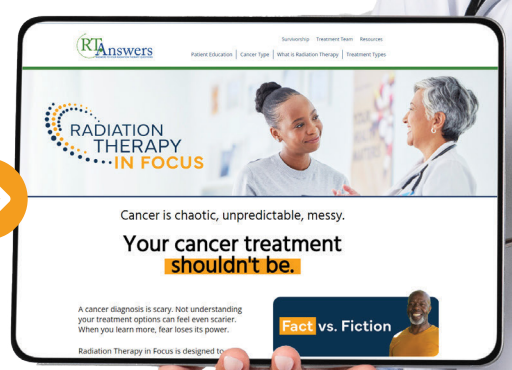
The campaign includes:

- Video interviews with radiation oncologists and patients
- Frequently Asked Questions download
- Fact vs. Fiction quiz to test patient knowledge of radiation therapy
- Social media ads on X, Meta and Reddit

This is phase 1 of a multi-phase campaign to inform patients who receive a diagnosis of cancer about the benefits of radiation therapy and help them make an informed treatment decision.

The campaign is part of the RTAnswers patient education website.

Resources for providers to review with patients are available on the Provider Resources section of astro.org.



Read more about the campaign:

www.astro.org/RTinFocusBlog

ASTRO | AMERICAN SOCIETY FOR RADIATION ONCOLOGY

ASTRO ANNUAL refresher COURSE 2025

BEST PRACTICES AND EMERGING TRENDS

APRIL 9–11 *Virtual* CONFERENCE

Join your colleagues for this informative and interactive virtual conference that provides a comprehensive review of the latest radiation oncology treatment methods and core competencies for the major disease sites. We'll also review the emerging trends and technologies that impact daily practice. Sessions provide updates on potential practice-changing trends to keep you informed. Meeting content connects radiobiological and physics principles to relevant, clinical cases.

IN 2025, WE'RE PROVIDING:

- A virtual format that combines live sessions with Q&A to encourage collaboration with faculty and colleagues.
- Three *e*Contouring sessions — Upper GI, Breast and Lymphomas.
- An excellent opportunity to earn CME — up to 22.25 *AMA PRA Category 1 Credits™*.
- The Refresher onDemand — Access to course content through April 2027.
- New for 2025, there will be a physics lecture on protons and heavy ions, a lecture on radiobiology of benign disease and two bonus onDemand presentations on pediatrics and vulvar and vaginal cancers!

You won't want to miss this! There's an exciting program planned with expert faculty for this essential live virtual course. We can't wait to have you join us!

REGISTER NOW!

www.astro.org/refresher25

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