Personalizing the Attack on Cancer: Zeroing in on Targets

The “War on Cancer” continues with some recent encouraging victories.

Advances in genomics and other laboratory-based diagnostic technologies have transformed our understanding of the fundamental molecular basis of cancer, and applying this knowledge has led to new generations of targeted therapeutics. Pathologists are at the center of this revolution of personalized medicine as they are faced with the challenges of deploying emerging technologies into routine patient care. In addition, pathologists are grappling with the challenge of combining molecular knowledge with long-established systems of tumor classification based on light microscopy.

Unfortunately, pathology practices are often also battling diminishing reimbursements and increasing regulatory burdens. The latest technologies are often considered “research use only,” forcing clinical laboratories into complex in-house validation processes to qualify their use under the Clinical Laboratory Improvement Amendments as laboratory-developed tests (LDTs). Frequently, third-party payers deny coverage of new diagnostic technologies, putting some laboratories out of business. Further complicating matters is the intention of the US Food and Drug Administration to more closely scrutinize hospital laboratory–developed LDTs.

Despite these challenges, there is no question that molecular analysis will become routine and fundamental to the diagnosis and management of cancer.

The application of the knowledge derived from the completion of the Human Genome Project and the rapid collapse in costs for deep genetic and transcriptomic analysis are fundamentally transforming the way pathologists understand and classify cancer and will certainly impact the way oncologists manage and treat malignancies in their patients.

In this issue of Cancer Control, members of the anatomical and clinical pathology departments of the H. Lee Moffitt Cancer Center & Research Institute review several topics of interest to oncologists and other health care professionals, focusing on the transformative effects of molecular pathology on the contemporary practice of pathology.

Dr Saeed-Vafa and I present an update on developments in digital and analytical microscopy. Light microscopy has been the fundamental tool for pathologists to analyze cancer for more than 100 years and has provided the knowledge underlying the classical classification of malignancy based on the organ and cells of origin along with the assessment of biological appearance, which is used for grading. Microscopic examination of surrounding tissues and lymph nodes create the current staging systems.

Advances in analytics, staining reagents, digital microscopy, and computer-assisted vision have created new opportunities to analyze tissue to extract more detailed information, including more precise measurements of prognostic and predictive biomarkers, such as protein and nucleic acids. Improvements in digital image analysis will help reduce errors in pathology and provide more accurate information for treatment selection. To this point, Dr Zota and I review key advances in the analytical methods of molecular biology that recently transformed pathology. The ability to accurately analyze key mutations in driver mutations such as \( EGFR \) in lung cancer and \( BRAF \) in melanoma from routinely acquired tissue specimens has enabled personalized medicine and targeted therapies to be routinely implemented.

The decreased costs of next-generation sequencing now enable hundreds of genes — up to whole genomes — to be cost-effectively analyzed in the hospital laboratory. In fact, one of the greatest current challenges is the management of “information overload.” The so-called “long tail” of cancer mutations illustrates that cancer is a diverse disease characterized by a multitude of diverse driver mutations and a degree of genomic liquidity that results in varied genomic “landscapes” and evolutionary “trees” within tumors. Some driver mutations occur in small numbers of tumors, making it difficult to conduct conventional, large-scale clinical trials. This fact has led to the creation of basket-type trials in which tumors are analyzed and then matched to selective therapeutic inhibitors.

We now conceptualize cancer as a 4-dimensional disease in a patient that evolves over time with populations of malignant cells that react, migrate, and adapt to the therapies oncologists unleash on them. We have also learned that some mutational drivers and events cross anatomical locations, forcing health care professionals to consider novel molecular classifications that transcend conventional histological ones.

On a positive note, the deployment of novel tools, such as digital polymerase chain reaction, will help...
us measure trace amounts of biomarkers in biosamples, such as blood and urine, potentially allowing more accurate screening, monitoring, and effective treatment selection, including the discontinuation of medically futile and toxic therapies and the switch to more effective ones.

Furthermore, the advances in immunotherapy are challenging pathologists to provide new, accurate, and predictive biomarkers to improve patient selection and understand response. Some of these biomarkers may include analysis of the complex composition of the tumor microenvironment.

The paper by Dr Valderrabano and colleagues illustrates the impact of molecular analysis on conventional optical microscopy for the assessment of thyroid lesions. The accurate presurgical analysis and classification of thyroid lesions are essential to avoid unnecessary morbidity. Conventional cytopathology has difficulty distinguishing certain benign from malignant lesions based on light microscopy, thus leading to frequent overtreatment in some patients and possible undertreatment in others. The identification and routine deployment of molecular markers to improve classification of indeterminate lesions will be of great benefit to patients and surgeons and will reduce costs to the health care system by limiting unnecessary surgical procedures.

Researchers in the field of molecular technologies have made inroads into the diagnosis and management of malignant hematological conditions. Dr Hussaini reviews current trends in hematological malignancy testing. These methods and approaches often foreshadow similar advances in the approach to solid tumors and provide a roadmap for effectively implementing novel technology platforms.

Dr Cáceres and others introduce us to the concept of the “liquid biopsy” and circulating tumor cells (CTCs). CTCs hold promise for the sequential temporal examination of malignancy prior to, during, and after therapy. CTC technologies coupled with other molecular methods to analyze cell-free DNA in blood are expected to provide us with tools to better select therapy for metastatic disease and enable health care professionals to determine earlier if a particular therapy is succeeding or failing, thus allowing for the potential real-time modulation of treatment strategies. Further refinements to the sensitivity rates of liquid-biopsy technologies are also expected to lead to improved screening and the earlier detection of cancer, improved molecular-based staging, and novel and practical methods to monitor minimal residual disease.

Drs Zibadi and Coppola review the complex challenges of diagnosing and managing Barrett esophagus, which represents a problematic lesion that can progress to malignancy. Use of novel molecular testing methods may enable us to better manage this difficult clinical condition and avoid overtreatment and overscreening.

Drs Henderson-Jackson and Bui review new developments in the area of soft-tissue neoplasms and the application of molecular classification approaches to improve the classification of these heterogeneous lesions and, perhaps more importantly, to uncover therapeutically useful targets that could be used for treatment.

Drs Khalil and Altiok review how the treatment course for patients with lung cancer has been altered in recent years with the uncovering of the role of key molecular drivers, including EGFR mutation, in a subset of cases. The uncovering of these common mutations in lung cancer has expanded the demand for the routine molecular testing of solid tumors and provided the impetus for routine solid tumor molecular diagnostic laboratories in many specialized hospitals. In addition, the study of acquired resistance mechanisms has uncovered new insights into how tumors evolve and evade personalized treatment options, opening up new strategies for overcoming these resistance mechanisms.

Dr Macaulay discusses how advances in complex molecular testing have significantly impacted the subspecialty of neuropathology and the classification and understanding of brain tumors. The uncovering of driver mutations in IDH1 and other molecular events, including chromosomal alterations and DNA epigenetic events, have driven the development of routine molecular analysis of brain cancer to improve the classification of tumors and drive treatment selection.

In an article by Dr Rosa and coauthors regarding the overexpression of vascular endothelial growth factor A in invasive micropapillary colorectal carcinoma, we are reminded that immunohistochemistry is a molecular technology — essentially “in situ proteomics” — that enables us to evaluate the molecular characteristics of histological structures. Dr Rosa and colleagues show that spaces originally thought to be “preparation artifacts” are actually neovascular structures. This aspect of the biology of micropapillary carcinoma may explain its clinical aggressiveness and potentially offer new therapeutic targets.

Breast cancer is one of the strongest examples of how molecular methods have transformed our understanding of the pathology and classification of this disease. Historically, classification was exclusively based on microscopic examination. However, this classification has now been transformed with extensive basic, translational, and clinical research, resulting in a new molecular understanding of breast cancer. The molecular analysis of breast cancer has uncovered “molecular portraits” that help define distinct subtypes of the disease with different clinical behav-
iors that each require different treatment strategies. In 2 papers, Drs Rosa and Khazai review current methods and trends in the molecular classification of breast cancer and the implications for the improved, enhanced quality of treatment and better outcome for patients.

Classical pathology methods typically require “fixing” tumor tissue, which essentially is killing and preserving the cancer as a frozen moment in time. Although this method has yielded spectacular dividends, it is still a “snapshot” of a very dynamic living system composed of a complex mixture of tissue types, including malignant cells, and a variety of host cells. Drs Kreahling and Altiok discuss alternate methods to maintain cancer cells ex vivo that may enable the detailed evaluation of drug-sensitivity profiles, thus arming health care professionals with the ability to select more effective treatments for their patients.

Also included in the April issue of Cancer Control is original research from Dr Mahipal and colleagues presenting data on the effect of age on clinical outcomes among patients enrolled in phase 1 clinical trials at Moffitt Cancer Center. Dr Grigg-Gutierrez and others share a case report on primary enteropathy-associated T-cell lymphoma type 2. In 2 Special Reports, Mr Patel and Dr Kilgore provide a systematic review of the cost effectiveness of colorectal cancer screening strategies, and Dr Lu and colleagues discuss the risk of colorectal cancer by subsite in a nationwide prostate cancer cohort in Sweden.

Pathology has been profoundly affected by these changes and pathologists — frequently unrecognized by patients — serve as critical members of the health care team. Pathologists remain key to deploying new diagnostic molecular technologies in the ongoing battle against cancer, providing the coordinates and advanced surveillance required for correctly aiming the powerful next generation of targeted therapeutic weaponry in the ongoing war.

In summary, we are living in revolutionary times in terms of how we understand, diagnose, and treat cancer. I hope you enjoy and benefit from reading this issue of Cancer Control.

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