The Anatomic Pathologist Meets Molecular Pathology

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DOI: 10.1309/AJCP3H9ZJKIKEUT

With the publication in this issue of “Stuck Between a Scalpel and a Rock, or Molecular Pathology and Legal-Ethical Issues in Use of Tissues for Clinical Care and Research: What Must a Pathologist Know?” by Dry et al,¹ we launch a new series for the American Journal of Clinical Pathology in a forward-looking celebration of the Journal’s commitment to readers’ education. It will include invited articles that are intended to provide helpful, timely, and informative reviews to assist pathologists and laboratorians alike in anatomic pathology to provide appropriate care when molecular testing is needed.

This first article of the series provides an important and insightful overview of the ethical, regulatory, legal, and technical background needed by pathologists for appropriate specimen management. The articles to follow will include detailed information in specific organ systems and disease processes about current testing for which there is evidence to support its use in clinical care, together with an exploration of questions and challenges that remain unanswered regarding test utilization, validation, and interpretation. In addition to this invited series, the Journal encourages submissions of reports of original research that address the extensive knowledge gaps that exist between descriptions of new diagnostic markers and evidence-based guidance on how to implement them in an ethical and economically responsible manner, adding value to patient care and advancing the quality of treatment options.

Rare diseases and conditions will require collaborative investigation to gain sufficient experience for informed decisions. Practicing pathologists must adapt continuously. Some of us trained in an era of classical histomorphology and electron microscopy and only then learned to apply emerging techniques in immunohistochemistry, confronting over time an ever-increasing number of diagnostic and predictive immunohistochemical markers. Today, pathologists may be much better versed in immunohistochemistry and related techniques, but now we must select among an expanding choice of other evolving tissue-based diagnostic modalities, including in situ hybridization, cytogenetics, image cytometry, and flow cytometry, as appropriate, in a given clinical setting. With more clinical emphasis on therapies that are targeted to specific genetic mutations in neoplasia, we must now rapidly integrate gene-based diagnostic tests into surgical pathology, cytopathology, and autopsy practice. Most of us cannot take time off from our busy practices for specialized fellowship training in molecular pathology, yet we are called on to be primary decision makers in many situations and central consultants to clinicians and patients receiving direct marketing information about commercially available molecular diagnostic tests or drugs that require testing for molecular targets. These increasingly complex demands on pathologists are further complicated in many instances by the small amounts of tissue we may receive, requiring triage and judicious use of precious samples, with the complexity of potential testing in mind.

Dry et al¹ provide an invaluable rudder to help us navigate the rocky shoals of decision making. They detail the differences between laboratory requirements for clinical testing, which must be performed in a CLIA-certified facility, and research testing. They also outline the ethical constraints for providing tissue for research, especially when samples are limited in size and may be needed for concurrent (or future) clinical testing. They provide a summary and useful references that outline the steps required for protection of human subjects when providing biosamples for research, in contrast
with management of clinical samples. These authors touch on some of the challenges that relate to the overlap between molecular testing of somatic targets and germline genetic testing, the latter having important implications for patients and their families.

Much discussion has occurred around the language of modern practice. Many pathologists bristle at the term “personalized medicine,” since our diagnostic practice has always been provided to one patient sample at a time, detailing each report specifically to the findings in an individual person’s specimen. Others struggle with the term “molecular pathology,” since histochemistry and immunohistochemistry are directed against chemical molecules that form the building blocks of human tissue. Wordsmithing aside, the ability to do whole genome testing and to dissect and identify smaller and smaller targets of interest (including DNA at the level of base-pair alterations or altered DNA methylation, changes in microRNA, and subsequent protein changes) transforms the breadth of information available from an individual patient, as well as the specificity of tailored therapy. And soon detailed testing of genetic alterations in drug metabolism will likely be integrated into treatment planning, in addition to molecular diagnosis of the disease process itself. A category of disease, such as non–small cell lung carcinoma, can and must now be further categorized; treatment is different for ALK-positive adenocarcinomas compared with ALK-negative cases. Modern practice requires us to be able to provide this information for patient care and to anticipate the need for this testing at the time of tissue procurement. In some cases, such as with breast carcinoma, specific practice recommendations and guidelines now exist regarding type and duration of fixation of tissue before tissue processing and sectioning. As new tests come into practice, recognition of specific preanalytic variables and guidelines must be integrated into pathology practice.

As anatomic pathology meets molecular pathology, we anticipate exciting new chapters in disease subclassification and therapeutic planning. We invite feedback and suggestions from our readers on how best to help them to practice in this era.

Reference