

Pathology's role as guardian of the patient biospecimen and enabler of precision medicine

Editorial

A fundamental premise of “precision medicine” is that the unique characteristics of a disease will be defined by upfront biomolecular analysis and used to guide downstream decision-making tailored to the specific patient. On the level of the individual patient, the vision encompasses diagnosis based on molecular characterization and treatment based on rationale selection of therapy matched to molecular characteristics. On a systems level, the vision includes molecular analysis and clinical data informing both patient care and research in a continuous feedback loop that will drive progress in unprecedented ways to unprecedented heights.

When I trained as a pathologist, this concept did not exist, largely because it would be impossible to generate wholesale molecular analysis data rapidly, efficiently and accurately at that time. Over the past decades, breath-taking advances in technology development have transformed the pathologist's power to interrogate patient specimens and probe the specific pathobiology of disease. The amount of clinically meaningful and biologically significant data that can be generated from biospecimens has increased by orders of magnitude. These data are the sine qua non of precision medicine, informing ever more challenging and multifaceted clinical decision-making. These data also allow appropriate selection of patients for clinical trials, enable trial-associated correlative science, and drive translational research. Furthermore, when these data are shared, aggregated and analyzed across patient populations, they greatly enhance understanding of disease processes themselves.

The fuel for this molecularly-driven vision of medicine is the source of the molecular data itself: i.e., biospecimens from actual patients. No matter how sophisticated and technologically advanced the analysis platforms, patient samples are the starting materials. They are the gold, whereas the platforms are merely the mining methods. This has been true for the entire history of pathology, but the dazzling power of modern molecular analysis technologies has significantly raised the bar for analyte quality in the test materials.

Shockingly, however, little attention has yet been paid to this issue. Pathology has not put a premium on its role as the guardian of the gold and the role it needs to play to assure analyte quality in patient specimens. With the exception of the guidelines developed by the American Society of Clinical Oncology and the College of American Pathologists (CAP) for breast cancer specimens intended for HER2 testing,¹ no practice standards have been put in place to insure molecular quality and consistency of patient biospecimens. Arguably, this situation may have been tolerable in anatomic pathology in a “pre-molecular era” when well-preserved morphology was the most important quality metric for specimens in anatomical pathology. As immunohistochemistry became a standard analysis method in anatomical pathology and the use of other molecular tests expanded rapidly in routine practice, there was increasing recognition that unsuccessful molecular analysis could be linked to pre-analytical factors that compromised specimen quality. Currently, with analytical methods moving beyond uni-analyte testing to multi-analyte testing, “omics” analysis, and pathway evaluation, control of pre-analytical

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factors to preserve molecular quality in patient biospecimens has become an even more pressing issue. Yet, nothing has changed.

Instead, as analysis methods and technologies evolved, quality assurance concerns have been focused primarily on the tests themselves with little to no attention paid to the specimens being tested. Extraordinary efforts have been made in pathology to rigorously assure the quality of the test platforms, standard operating procedures used to execute tests, the environment in which tests are done, and the proficiency of people executing the tests. In contrast, little, if any, rigor is applied to the control of factors that adversely affect biospecimen quality before molecular testing is even performed.

Known collectively as “pre-analytical variables”, such factors include steps in the acquisition, handling, processing, and transport of biospecimens. Some of these steps occur while the biospecimen is still viable and capable of reacting to the extreme biological stresses that these iatrogenic interventions present to the living cells and tissues. Others occur after the biospecimen has been “stabilized” in some fashion, such as fixation in formalin, to stop biological activity. However, the different steps in the “lifecycle” of a biospecimen have a variable ability to either alter a biospecimen's biomolecular composition (through altered gene expression, protein translation or modification, or other intracellular reactions), to compromise molecular integrity (through molecular degradation or alteration), or both, depending on the specimen (tissue) type and lability of the biomolecular species of interest.²

It is unclear exactly why the requisite attention to pre-analytics has been lacking in anatomical pathology for so long. Beyond the obvious challenges of increased effort and cost that control of pre-analytics might pose for a pathology practice, several other factors also may contribute. For example, there is a relative paucity of data on the impact of specific pre-analytical variables on specimens, molecules, or tests of interest, and this, in turn, limits efforts to design workable evidence-based practices to control key pre-analytics. For some specimen types, like cytology specimens, pre-analytical factors are highly varied in routine practice, and no authoritative guidelines for cytology pre-analytics currently exist. For specimen types such as tissue and blood, guidelines for pre-analytics have been developed and published by organizations like the National Cancer Institute, the Clinical and Laboratory Standards Institute (CLSI) and the International Society of Biological and Environmental Resources, but none are mandatory or routinely employed in clinical practice. In fact, pre-analytical issues are typically afforded little attention in

either pathology training or practice. Some pathologists may not even be fully aware of the clinically significant impact of pre-analytics on specimen integrity and molecular test results. Lastly, there is also a widespread albeit mistaken belief that the selfsame technological advances that have made molecular analysis faster, better and cheaper are also able to compensate for analysis limitations posed by poor quality specimens. This is simply incorrect. Dazzling as the new technologies might be, none have yet been invented that can spin straw into gold. No matter what the platform, the quality of the analysis data is dependent on the quality of the target analytes in the starting materials. There is still no such thing as “garbage in, diamonds out”.

Another critical issue that is separate from but related to the lack of control of pre-analytical factors is the lack of documentation of pre-analytical factors. Namely, except in cases involving breast cancer specimens, there are no requirements to document what actually occurred during specimen handling and processing with reference to the type or degree of pre-analytical variation. Thus, the provenance of almost all biospecimens in anatomical pathology remains largely or entirely unknown for posterity, for either downstream patient care or translational research should the patient enter a clinical trial.

Preservation of specimen quality is a time-sensitive and labor-intensive endeavor, requiring immediate attention to and prioritization of specimen handling in every case. However, this is not a reason that it should not be done. It may require new support staff, new reimbursement codes, new laboratory accreditation requirements or all three. A reasonable initial step in addressing the challenge of pre-analytics would be to employ data-driven but practical and achievable set of standard operating procedures for controlling the most critical steps in the collection and handling of specimens that have the greatest adverse impact on DNA, RNA and protein (the most commonly analyzed molecular species). This would establish a benchmark for minimum standards to which additional stringency could be added, as required, for specific platforms or other molecular species. The goal would not be to optimize pre-analytics for any given molecule type or analysis platform, but to establish baseline practice metrics for controlling key pre-analytical variables where none currently exist and to document compliance with those metrics in every case. This would confer a defined and documented level of quality and consistency

on all patient samples. Implementation of such metrics in pathology practice would represent a bold departure from the current norm in which pre-analytical variation is both uncontrolled and unrecorded.

Development of the above described benchmark metrics for control of key pre-analytics is the aim of the Pre-analytics for Precision Medicine Project Team (PPMPT) within the personalized healthcare Committee of the CAP. This group was initiated following a national multi-stakeholder convergence conference sponsored by the National Biomarker Development Alliance (NBDA) and the establishment of a memorandum of understanding between the NBDA and the CAP. With the support of other relevant expert committees and CAP leadership, the PPMPT has reviewed all relevant scientific literature referable to key pre-analytical variables for tissue, blood and cytology specimens in everyday pathology practice. Based on their findings and informed by other authoritative sources of expert guidance for pre-analytics, the PPMPT will develop practice metrics and documentation guidance for pathologists that are evidence-based but practicable enough for broad implementation in CAP-accredited laboratories. The ultimate aim is to assure that all biospecimens are fit for molecular analysis, not just those of breast cancer patients. It's the right thing to do, and the time has come to do it.

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Conflict of interest

The author declares no conflict of interest.

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