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Challenges in Pathology Specimen Processing in the New Era of Precision Medicine

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**Context.**—Precision therapies for patients with driver mutations can offer deep and durable responses that correlate with diagnosis, metastasis prognosis, and improvement in survival. Such targeted therapies will continue to increase, pushing us to change our traditional approaches. We needed to search for new tools to effectively integrate technological advancements into our practices because of their capability to improve the efficiency and accuracy of our diagnostic and treatment approaches. Perhaps nothing is as relevant as identifying and implementing new workflows for processing pathologic specimens and for improving communication of critical laboratory information to and from clinicians for appropriate care of patients in an efficient and timely manner.

**Objectives.**—To define the gold standard in delivering the best care for patients, to identify gaps in the process, and to identify potential solutions that would improve our process, including gaps related to knowledge, skills, attitudes, and practices.

**Design.**—We assembled a team across disciplines to systematically perform a gap analysis study to clarify the discrepancy between the current reality in pathology specimen processing and the desired optimal situation to deliver the results intended for patient care.

**Results.**—A practical collaborative workflow for specimen management seeking the cooperation of the stakeholders in each medical discipline to provide guidelines in specimen collection, delivery, processing, and reporting of results with the ultimate goal of improving patients’ outcomes is provided.

**Conclusions.**—New tools are required to effectively integrate data-driven approaches in specimen processing to meet the new demands.

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As changes in the new standard of care are upon us, health care providers are faced with numerous complex challenges to establish systematic and data-driven approaches to meet the new demands for cancer patients. We need to search for new ways to effectively integrate technological advancements into our practices because of their capability to improve the efficiency and accuracy of our diagnostics, precision medicine, treatment approaches, and patient monitoring. Nothing is as relevant as identifying and implementing new workflows for processing pathologic specimens and for improving communication of critical laboratory information to and from clinicians for appropriate care of patients in an efficient and timely manner. With the advent of extraordinary progress in precision medicine, there are new demands on specimen quantity and quality. The time has come for adjusting our accustomed methods of requesting, procuring, and evaluating pathologic specimens.1–4

**THE NEED FOR INTEGRATED MULTIDISCIPLINARY APPROACHES AND REASONS FOR COLLABORATION**

To improve cancer patient care delivery, experts across the different disciplines need to develop efficient, integrated processes that enhance care, reduce cost, and minimize harm. A team approach with institutional oversight is considered the best approach to standardize specimen procurement, triaging, and reporting to achieve our new goals. Improvement of specimen adequacy depends not only on getting the best sample for accurate diagnosis but also on relaying accurate information along with specific instructions on how to handle and process the specimen.5–10

In this study we assembled a team, across disciplines, to systematically perform a gap analysis study to clarify the discrepancy between the current reality in pathology specimen processing and the desired optimal situation to deliver the results intended for cancer patient care. The team included oncologists; pulmonologists; interventional radiologists and gastroenterologists proficient in specimen procurement; and pathologists, laboratory professionals from the molecular testing industry. The goals of the study are: (1) to describe the current workflow of specimen handling from test ordering to procurement, specimen
delivery, processing, triaging, reporting, and final uploading of results into patients’ medical records; (2) to define the gold standard, or best practices in delivering the best care for cancer patients; (3) to identify potential gaps in the process, at each phase of specimen processing, between the current practice and the intended gold standard; and (4) to identify potential solutions that would improve our process, including gaps related to knowledge, skills, attitudes, and practices.

LIMITATIONS OF THE CURRENT WORKFLOWS IN SPECIMEN PROCESSING WITH THE EMERGING NEW REQUIREMENTS

Precision Medicine Depends on Specimen Quality and Adequacy

Appropriate tissue diagnosis can be achieved via surgical resections, wide excisions, open biopsies, and core needle biopsy (CNB) and fine-needle aspiration (FNA) techniques. Despite the promise of precision medicine in enabling physicians and patients to select the best effective therapy and in preventing patients from exposure to ineffective drugs, there is a disconnect between reality and expectations in practice. This discrepancy is partly explained by the lack of precision in biopsy quality and quantity.1–13 There has been a trend toward less-invasive biopsy techniques such as CNBs and FNAs, which has led to further strain on specimen quantity.

Roles and Responsibilities of Different Specialists

In order to fully explain the issues that we are trying to resolve, we must first explain the current roles, responsibilities, and interactions of the different specialists involved in the care of cancer patients. Figure 1 highlights the siloed current approach for specimen handling. Discovery of disease usually starts when patients are examined by their primary care physicians, surgeons, oncologists, gastroenterologists, or pulmonologists, either because of a particular complaint or during a routine examination. Following the appropriate testing, a suspicion of a mass lesion is typically confirmed with an appropriate diagnostic imaging study or studies and ends up with a request for a procedure to obtain diagnostic tissue, which is often chosen with no input from the diagnostic pathologists. Patients are referred to an interventional radiologist, surgeon, endoscopist, and/or bronchoscopist with a request to conduct further specialized studies, including imaging studies and specimen procurement, to evaluate the patient. These specialists are tasked with many activities, including examining the patient, running tests, reviewing imaging studies, and performing procedures to procure the desired specimens. Once the procedure is successfully done, procuring physicians are responsible for releasing reports of their findings that become part of the patient’s medical records, and for issuing pathology requisitions to guide pathologists in their analysis of the specimens. Pathologists play a pivotal role in the diagnostic process. Once specimens with the attached requisitions are delivered and received in the pathology laboratory, they are triaged to different sections of the laboratory. In the anatomic pathology laboratory, including surgical pathology and cytology, specimens are accessioned into the anatomic pathology information system, examined grossly, and processed, and slides are prepared for routine microscopic evaluation and diagnosis. Occasionally, based on the requested information, specimens are triaged to different sections in the laboratory for microbiologic, cytogentic, flow cytometric, molecular biology, and other miscellaneous testing, if needed.

IDENTIFICATION OF POTENTIAL GAPS AT EACH PHASE OF SPECIMEN PROCESSING BETWEEN THE CURRENT PRACTICE AND THE INTENDED GOLD STANDARD

To meet the demands of the new era of personalized medicine, a work group was tasked with looking into the challenges in our current practice of procuring adequate specimens that meet the new demands for management of cancer patients. The assembled team included 3 board-certified pathologists and cytopathologists; 2 board-certified molecular pathologists; 2 board-certified oncologists, 1 with expertise in pulmonary oncology and the other in gastrointestinal and pancreatobiliary oncology; 2 board-certified specialty-trained intervention pulmonologists; 1 specialty-trained board-certified gastroenterologist; and 1 board-certified intervention radiologist. In numerous meetings, the limitations of the current workflow process and possible
ways to improve it were discussed. Our research identified many potential gaps in our siloed practice that could lead to a fragmented and frustrating delivery of cancer patients’ care, including: (1) gaps in protocols, (2) gaps in policies and test order sets, (3) gaps in health care professional education, and (4) gaps in standardization and integration of services, including gaps in information technology as elaborated below.

The first identifiable gap happens at the time when a neoplastic process or a certain medical condition requires a tissue diagnosis (Figure 2). Test order forms were found to be unstandardized: some were online, others were hand-written. In many situations the ordering physicians had inadequate experience or knowledge regarding the required tests or the type of specimen to be collected. The importance of choosing the most appropriate diagnostic procedure to obtain the desired quality and quantity of tumor tissue is often overlooked. The incorporation of protocols to facilitate selection of the most common diagnostic procedures based on clinical indications, pathology needs, and resources of the institution can be very helpful to optimize this step and is strongly suggested. Although the reason or expectation for biopsy may be passed on to the procuring physician, this information may not make it to the laboratory or be communicated to the pathologist. This in turn leads to failure in communicating appropriate instructions about test requirements to the procuring physicians. The end result may be failure of the pathologist to accommodate the wishes of the requesting physician. In fact, in many situations, the ordering physician and physicians performing the procedure were not the treating physician who would ultimately be making treatment decisions for the patient.

Similar to the requesting physicians, procuring physicians, including the interventional radiologist, interventional pulmonologist, and/or endoscopist, are faced with challenges related to deficiencies in protocols, policies, and order sets; gaps in education and standardization; and lack of integration with other services. Furthermore, problems could arise during specimen procurement related to the patient’s clinical condition, complications while performing the procedure, or the experience and skills of the procuring physician (Figure 3). Lack of communication or guidance from the ordering physician was not uncommon. Occasionally, requests were received from an unknown outside physician or an oncologist not known to the proceduralist. Lack of understanding of the pathology workflow and the different pathology services and divisions can lead to downstream problems. Situations might occur in which the collected specimen is accompanied by the wrong pathology requisition (eg, cytology versus surgical pathology versus microbiology versus cytogenetics versus other sections from the clinical laboratory), leading to inadequate or misleading instructions to the pathology laboratory for prioritization of clinically applicable molecular tests that meet guidelines for treatment. Gaps were identified in communicating specific instructions to the laboratory or to treating physicians about the requested test(s) and about the delivery of test results. A major concern was the rudimentary information technology support and the near-total absence of integration between pathology and radiology services for combined reporting of radiology and pathology findings. Pathology and radiology are essential for accurate diagnosis of disease, yet their workflows remain ad hoc and occur in separate silos. Recent studies in breast and lung cancer and interstitial lung diseases diagnosis have highlighted the tremendous value of integrated services.14–18

Pathology is one of the most critical components in the management of patients with cancer. Traditionally, pathology has provided valuable information related to tissue diagnosis, tumor stage, and grade. However, in the modern era of precision medicine, these morphologic characteristics are no longer sufficient, as reliance on molecular and other biomarkers is becoming the new standard of care. Access to timely, accurate molecular and other ancillary tests has become essential but remains challenging.

Unlike in clinical laboratory diagnosis, challenges remain in anatomic pathology in standardizing testing procedures because of individualized professional interpretation-driven decision-making processes. However, many of these procedures have been standardized and algorithms have emerged during the last decade. Yet tissue specimens are often procured without knowing what molecular tests are needed. These specimens are sent to the laboratory, nevertheless, without knowing their acceptance criteria,
putting the laboratory under pressure to accommodate and report results with a disclaimer. Prior knowledge before tissue procurement could avert many of these challenges.

Our analysis has also identified many opportunities for improvement of specimen processing in the laboratory (Figure 4). After procurement, specimens are delivered to a “black box” called the laboratory, where they are accessioned into the laboratory information system and triaged to the respective section depending on specimen type and accompanying instructions. In addition, specimens can be designated for special delivery to outside laboratories for miscellaneous testing. Communication to and from the other clinicians and within the different sections of the laboratory remains an issue begging for a standardized solution. Frequently pathologists were faced with a lack of clinical history at the time of specimen sign-out. Pathology requisition forms were often left blank or contained minimal or meaningless information. Occasionally, electronic medical records (EMRs) were uninformative as to the patient’s past history of neoplasms, which is important for evaluation of the specimens. The fragmented knowledge or lack of knowledge of the procuring physician was a potential factor that impacted the pathologist’s ability in analyzing the specimens appropriately.

An additional gap in communication between pathology and oncology is understanding the struggle between using tissue for accurate diagnosis and conserving tissue for precision medicine testing to drive oncologic decision-making. Order forms/requisitions for pathology need to be updated and standardized. Specimen triaging to the different laboratory sections was found to be confusing to ordering physicians because of lack of appropriate instructions, lack of experience or education of the ordering physicians, or lack of standardized policies and procedures. Lack of procedure standardization and communication causes rejection of 5% to 10% of molecular tests (our laboratory experience is 4%–6%) because of insufficient specimen and another 2% to 3% (our laboratory experience) because of poor specimen quality. Although some biopsies from certain organ sites, such as colon, ovaries, and uterus,
provide ample tissue specimens, biopsies from such sites as lung, brain, liver, kidney, and pancreas have higher numbers of insufficient specimens for molecular testing. Of interest, a few of these tissue specimens could be enough to begin with if the requirements for molecular testing are known prior to tissue procurement. Similarly, some specimens were overfixed without knowing if those specimens would later be used for molecular testing. Cross-linking due to formalin overfixation impacts the amplification process of DNA and RNA. Type of fixative reagents used might lead to polymerase chain reaction inhibition as well. Decalcification of tissue is another preanalytical step that could have detrimental effects on downstream amplification for molecular testing. Laboratories, however, proceed with testing those suboptimal specimens because they are the only available source for molecular testing—eventually leading to rejection of such samples as they do not meet the acceptance criteria for molecular testing, which delays patient care and adds to the frustration of patients and their treating physicians. Nonreportable results cause additional financial stress to the laboratory and the entire system.

One of the issues that should be addressed is the lack of standardization on normal tissue while molecularly analyzing tumors. It may appear simple, but finding normal tissue can often be challenging. Blood is widely used as normal control, but it is processed and tested in a separate clinical laboratory and is often discarded before it is known whether the blood will be needed in future for comparison. In some cases, laboratories cannot get access to normal tissue because sections did not have enough normal marginal tissue, necessitating clinical interpretation by solely relying on the tumor results.

Information technology support to and from the laboratory remains a concern. There was no electronic linkage between the different laboratory results, creating confusion, redundancy, and potential harm to patients. With the implementation of EMRs throughout the country, the current interface between the laboratory information system and the hospital information system has become insufficient in disseminating information between the laboratory information system and the EMR. The currently used siloed anatomic pathology system is incompatible with EMRs, leading to inefficiency, frustration, and potential errors. There is a need for efficient connectivity between EMRs and laboratories. Workflows in laboratories remain ad hoc and involve accessing multiple systems with no direct linkage between patients’ EMRs, prior or pending pathology, and molecular records for the case being analyzed. A major hindrance in timely reporting of these results is the need to incorporate/interface with multiple electronically isolated, fragmented systems.

THE PATH FORWARD

The path for moving forward is challenging, requiring an integrated cooperation among health care professionals in different specialties, hospital leadership, pharmaceutical companies, and the scientific community. Government and pathology and cancer medical societies have a major role in guiding health care professionals and in setting up national standards. Well-thought-of, innovative ideas and new approaches have to be sought to accomplish our goals. For the past 10 years there has been a significant expansion of clinically relevant molecular targets. Precision medicine is helping to move from a one-size-fits-all approach to a specifically tailored targeted therapy for each individual cancer patient. Addressing these challenges in this opinion paper is near impossible. However, we tried to look at potential short-term and long-term solutions where sustained incremental improvements could be achieved.

We have identified many opportunities for process improvement; some are system wide and others are discipline specific, including updating protocols, policies, and order sets; health care professional education; and adoption of standardization and integration. For more than 30 years, the College of American Pathologists Cancer Protocols have offered standardized structured data sets for cancer pathology reporting that have improved patients’ clinical outcomes.19–23

New challenges have arisen with the changing biomarkers and the treatment landscape of cancer. Many institutions are moving away from recommending surgical excisions or open biopsies to procure specimens for identification of malignancy. Core needle biopsy and FNA are minimally invasive procedures for small biopsy specimens that have a high diagnostic yield in most situations. Small specimens, including CNBs and FNAs, despite their value, present many challenges to meet the requirements of the new era.24–28 Several factors impact their diagnostic yield, including acquisition techniques for an adequate specimen, clinical presentation, experience and skill of the procuring physician, and interpretation skills of the pathologist, to name a few.29–46 Some studies have shown that FNA with rapid on-site evaluation coupled with CNB performs better than either alone. Fine-needle aspiration is the preferred method for the evaluation of thyroid lesions and is adequate for diagnosing cystic lateral neck, salivary gland, gastrointestinal, and pancreaticobiliary lesions.32,33 On the other hand, CNB offers greater diagnostic details for breast lesions, lymphomas, and the accurate classification of many solid tumor lesions.34–36 Depending on available resources for each institution, incorporation of immediate on-site assessment of FNAs and core biopsies represents a real-time quality assurance action aimed to obtain the largest possible amount of viable tumor with appropriate and cost-effective triage. Communication, respect, tolerance, and mutual feedback between proceduralists and pathologists are essential to optimize on-site pathologic evaluation.

Some institutions have adopted the practice of specialized reporting, separating the interpretation of cytology and histology specimens by different pathologists. Other institutions have found that bundling the 2 samples for interpretation by one interpreting pathologist may be a better approach. This minimizes the likelihood of redundant testing and delayed release of reports, avoids discrepancy in reporting, and eliminates incorrect billing. Thrall et al47 recently conducted a survey to elucidate the current practices regarding the handling of small CNBs in the new era of personalized medicine. Their study highlighted the lack of uniformity among pathologists about best practices handling such specimens. Different institutions have different approaches, regardless of whether the specimen is derived from an endoscopic or radiologist-performed procedure. Most survey respondents were interested in signing out such small CNBs with more cooperation between cytologists and surgical pathologists and with the need of support for standardized guidance from the American Society of Cytopathology and other pathology societies in the future.48–51 Synoptic standardized pathology
### Collaborative Approach for Specimen Management for Precision Medicine: Gap Analysis

| Gap Analysis Questions                                                                 | Yes | No | If answered question “NO”, identify the specific action plan(s) including persons responsible and timeline to complete |
|----------------------------------------------------------------------------------------|-----|----|------------------------------------------------------------------------------------------------------------------|
| Preprocedure: prior to requesting specimen collection for molecular testing            |     |    |                                                                                                                 |
| The requesting physician fully understands the type of specimen that needs to be       |     |    |                                                                                                                 |
| collected                                                                             |     |    |                                                                                                                 |
| Appropriate requisition is filled with clear instructions and with contact information for consultation if needed |     |    |                                                                                                                 |
| The facility has a process in place to make procuring physicians, pathology, and/or    |     |    |                                                                                                                 |
| laboratory aware of anticipated specimen                                                |     |    |                                                                                                                 |
| Procedure of procuring specimen                                                        |     |    |                                                                                                                 |
| Prior to the start of the case, the procuring physician identifies any anticipated      |     |    |                                                                                                                 |
| specimens, specimen container, and any special consideration for molecular testing      |     |    |                                                                                                                 |
| or other consideration (eg, research specimen)                                        |     |    |                                                                                                                 |
| The facility has a standardized process and clearly assigned responsibilities in place to track specimens procured during the procedure, including |     |    |                                                                                                                 |
| Verbal communication to the team by proceduralist about specimen designation,          |     |    |                                                                                                                 |
| handling instructions, type of testing needed, and any special needs                   |     |    |                                                                                                                 |
| Verbal confirmation of the specimen handling instructions by circulator                 |     |    |                                                                                                                 |
| Appropriate requisition filled with clear instructions and with contact information for consultation if needed |     |    |                                                                                                                 |
| Specimen is labeled appropriately with at least 2 patient identifiers                  |     |    |                                                                                                                 |
| Debriefing process at end of case includes label is correct, label matches patient     |     |    |                                                                                                                 |
| identification, tissue is in container, correct specimen has been collected, correct    |     |    |                                                                                                                 |
| specimen number are in container, correct order has been placed                        |     |    |                                                                                                                 |
| Specimen handling in the laboratory                                                   |     |    |                                                                                                                 |
| Specimen received in the laboratory with appropriate requisition and clear instructions for testing and triaging information in the laboratory |     |    |                                                                                                                 |
| Specimen accession in the anatomic pathology system for appropriate handling and       |     |    |                                                                                                                 |
| instructions to pathologists and other laboratory scientists in molecular laboratory    |     |    |                                                                                                                 |
| The laboratory has a process for tracking specimens                                     |     |    |                                                                                                                 |
| Accurate communication to members of laboratory by pathologists about specimen         |     |    |                                                                                                                 |
| designation, handling instructions, type of testing needed, and any other special needs |     |    |                                                                                                                 |
| Standardized reporting of findings, including College of American Pathologists synoptic reports and molecular test menus for each type of cancer |     |    |                                                                                                                 |
| Clear and standardized instructions for specimen delivery to specialty laboratories for molecular testing |     |    |                                                                                                                 |
| Policies are in place for specimen handling and reporting                               |     |    |                                                                                                                 |
| Health information technology                                                           |     |    |                                                                                                                 |
| The organization is using automation and health information technology within the       |     |    |                                                                                                                 |
| specimen management process                                                             |     |    |                                                                                                                 |
| The EMR transmits accurate and timely patient and order information to the LIS         |     |    |                                                                                                                 |
| The LIS transmits accurate and timely results to the EMR and the specified provider(s) |     |    |                                                                                                                 |
| The EMR generates or electronically transmits a specimen requisition                    |     |    |                                                                                                                 |
| The EMR presents a well-formatted, readable report                                      |     |    |                                                                                                                 |
| There is a standardized process to integrate molecular tests with pathology records in a timely manner |     |    |                                                                                                                 |
| There is an integrated pathology/radiology approach in specimen handling                |     |    |                                                                                                                 |
| There is a mechanism for interfacing between different reports about the same patient   |     |    |                                                                                                                 |

**Abbreviations:** EMR, electronic medical record; LIS, laboratory information system.

*Questions are answered yes or no; if answered no, respondents are asked to identify specific action plan(s) including persons responsible and timeline to complete.*

Reports in an electronic format provide a superb method of communicating between pathologists and other physicians. However, they never address discrepancy or cross-report ambiguity between pathology and radiology reports. These 2 disciplines live in their own siloes with minimal integration or collaboration. The American College of Radiology and the College of American Pathologists have recently identified the importance of collaboration across disciplines and have started piloting several programs to integrate diagnostic protocols to improve collaboration between the 2 departments. Studies have highlighted improvement of diagnostic accuracy and efficiency with...
such collaboration. The interventional pulmonology and gastroenterology communities are actively investigating the value of using new technological methods in collecting specimens for adequate tissue procurement for ancillary testing, some trials of which have demonstrated excellent rates of procurement.\(^{19}\)

There are multiple testing challenges in precision oncology testing—preanalytical, analytical, and postanalytical. Preanalytical considerations include adequate tissue sampling for genomic testing, pathology workflow for tissue retrieval, molecular assay selection and design, tissue adequacy, cost, and resources. The College of American Pathologists, the Association of Molecular Pathology, and numerous cancer associations have been active in publishing guidelines for tissue adequacy helping standardization of molecular testing.\(^{20-23}\)

Challenges in testing include assay selection, turnaround time, and data analysis and storage, and postanalytical challenges include interpretation of results, resolution of discrepancies between test results, reimbursement, timely delivery, and integration of molecular results into medical and pathology records. There is a need for development of a comprehensive, user-friendly patient summary display to integrate the current fractionated subspecialty specific systems. Patient management in the new era requires the interaction of a team of experts. Many academic institutions have adopted regular molecular tumor boards in their practices with the input of molecular pathologists among other specialists. Future directions should include creating institutional multidisciplinary teams to ensure appropriate communication among treating physicians, procuring physicians, and pathologists and to establish standardized testing protocols for the different specimen types, including standardized order forms with appropriate means of communication to ensure that all necessary testing is done up front and to monitor the process of specimen procurement and dissemination of laboratory results in real time. Such teams would be very critical in setting expectations and in providing educational resources and tools to the entire team in this ever-changing environment. Because tissue analysis is a consultation, pathologists are responsible for appropriate test ordering for diagnosis. Rarely, clinicians from other disciplines have the expertise or the talent to drive this as pathologists. Finally, with the advent of digital pathology the door is now wide open for computational pathology as a companion diagnostic that has started to pay dividends in standardizing the results of some molecular tests, like hormone receptors, human epidermal growth factor receptor 2 (HER2), and programmed death ligand-1 (PD-L1). Summarized in the Table is an attempted practical collaborative workflow gap analysis for specimen management seeking the cooperation of the stakeholders in each medical discipline to provide guidelines in specimen collection, delivery, processing, and reporting of results with the ultimate goal of improving patients’ outcomes.

In conclusion, targeted therapies for cancer patients with driver mutations can offer deep and durable responses that correlate with diagnosis, metastasis prognosis, and improvement in survival. Such targeted therapies will continue to increase, pushing us to change the traditional approaches that we are accustomed to. It is of utmost importance to identify those patients who would benefit the most from such therapies in a timely manner. The College of American Pathologists, the Association of Molecular Pathology, and numerous cancer associations are working tirelessly on providing guidelines to pathologists and molecular pathology laboratories. The goals of the study were to describe the current workflow of specimen processing, to define the gold standard in delivering the best care for patients, to identify gaps in the process, and to identify potential solutions that would improve our process, including gaps related to knowledge, skills, attitude and practices. We should be reminded that a search for excellence using a personalized multidisciplinary approach requires commitment to patient care through a constantly evolving and challenging process rather than to static routine events.

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