# Error Reduction and Prevention in Surgical Pathology

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*Editor*

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*Editor*
Raouf E. Nakhleh
Pathology
Mayo Clinic Florida
Jacksonville
Florida
USA

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# Contributors

**Timothy Craig Allen** Department of Pathology, The University of Texas Medical Branch, Galveston, TX, USA

**Richard W Brown** System Laboratory Services, Memorial Hermann Healthcare System, Houston, TX, USA

**Amelia Huck** Department of Pathology, Massachusetts General Hospital, Boston, MA, USA

**Michael O. Idowu** Department of Pathology, Virginia Commonwealth University Health System, Richmond, VA, USA

**Shannon J. McCall** Department of Pathology, Duke University, Durham, NC, USA

**Frederick A. Meier** Department of Pathology and Laboratory Medicine, Henry Ford Hospital, Detroit, MI, USA

Department of Pathology, School of Medicine, Wayne State University, Detroit, MI, USA

**Carolyn Mies** Division of Anatomic Pathology, Department of Pathology & Laboratory Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA, USA

**Raouf E. Nakhleh** Department of Pathology, Mayo Clinic Florida, Jacksonville, FL, USA

**Vania Nosé** Anatomic and Molecular Pathology, Massachusetts General Hospital, Boston, MA, USA

**Liron Pantanowitz** Department of Pathology, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

**Seung Lyung Park** Department of Pathology, University of Alabama in Birmingham, Birmingham, AL, USA

**Anil Vasdev Parwani** Department of Pathology, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

**Stephen S. Raab** Department of Laboratory Medicine, University of Washington and Memorial University of Newfoundland, Seattle, WA, USA

**Maxwell L. Smith** Department of Laboratory Medicine and Pathology, Mayo Clinic Arizona, Scottsdale, AZ, USA

**Paul E. Swanson** Cumming School of Medicine, University of Calgary, Pathology and Laboratory Medicine Calgary Laboratory Services, Foothills Medical Centre, Calgary, AB, Canada

**Keith E. Volmar** Rex Pathology Associates, Raleigh, NC, USA

# Chapter 1
# Introduction

**Raouf E. Nakhleh**

## Introduction

As surgical pathologists, we are excited by every case that comes before us because of the opportunity to make a diagnosis that matters to patients and clinicians. A correct diagnosis sets the patient and clinician along an appropriate treatment path. At the same time, there is an understanding that surgical pathology processes and laboratories are complex systems that offer ample opportunity to make mistakes. Errors occur for a variety of reasons. Some occur because of poor processes, some occur because of a lack of knowledge, some occur due to carelessness, and some occur because of external stresses. Trying to evaluate every possible source of error can be daunting. By breaking down the system into segments and evaluating each segment, errors can be more easily classified, analyzed, and addressed.

Surgical pathology is a laboratory discipline of testing that has a defined test cycle of preanalytic, analytic, and postanalytic. Preanalytic and postanalytic challenges of specimen identification and processing as well as report generation and delivery are similar to processes that occur in clinical laboratories. The specimens in surgical pathology are unique and many times cannot be obtained a second time as can be done with blood or urine specimens. The procedures to obtain surgical pathology specimens are also far more complex making it unpalatable to lose, mislabel, or mishandle a specimen. In this book, we include two chapters addressing the preanalytic phase of the test cycle including specimen identification, specimen handling, and the use of lean methodology to reduce errors in specimen processing. Three chapters are included to address the postanalytic phase of the test cycle including the complete surgical pathology report, communication of the results, and error reduction in transcription and report delivery.

Also, unique to surgical pathology is that the analytic phase of the test cycle is largely depended on pathologists' cognitive ability to interpret visual evidence

R. E. Nakhleh (✉)
Department of Pathology, Mayo Clinic Florida, 4500 San Pablo Rd.,
Jacksonville, FL 32224, USA
e-mail: nakhleh.raouf@mayo.edu



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and recognize disease. This adds to the complexity of the process but also offers potential solutions. It is the author's belief that the analytic phase of the test cycle is dependent on five factors, each to be addressed in a chapter:

1. The pathologist's knowledge, experience, and training,
2. Clinical correlation,
3. Use of ancillary confirmatory testing,
4. Use of standardized criteria for diagnosis and reporting standardized elements, and
5. Selectively reviewing cases to assure accuracy.

In this book, we have attempted to describe aspects of practice that lead to error as well as define practices that avoid error. The book is organized to address each of the phases of the test cycle (preanalytic, analytic, and postanalytic), as well as how to deal with errors when they occur. In addition, there is a chapter that addresses how often and where in the test cycle errors occur as well as a chapter that discusses general principles of error reduction. This latter chapter examines what has been learned in other industries and the science of process optimization and error reduction. The final two chapters discuss the legal ramification of errors and possible actions to try and minimize deleterious effects of surgical pathology errors.

Medicine has changed a great deal in the past few decades. Public perception of physicians has also changed a great deal. Fifty years ago, physicians were highly regarded professionals who could do no wrong. Today, the lay media has depicted numerous examples of medical errors leading to patient harm, and the public is weary and sensitive to any suggestion of error in their healthcare. At the same time, we must have the realization that errors will occur; after all, we are all human and are fallible and prone to error. In this book, we try to systematically examine sources of error and offer what has been learned to avoid these errors. Our current systems are far from perfect, but there is evidence that we are inching forward with improvement and reduction of error.

# Chapter 2
# The Landscape of Error in Surgical Pathology

**Frederick A. Meier**

## Definitions: Geographic Features of Error

*Error*: In everyday language, error is getting things wrong, usually in relation to aims and purposes [65]. There is a different technical use of the term error in statistics. For statisticians, error means differences in repeated measurements. These measurement differences arise from either random variation or bias. Random variation causes inconsistent differences between measurements; bias produces systematic differences between measuring methods or devices.

*Ordinary language and statistical error*: Ordinary language and statistical uses of error have this in common: we *make* both errors and measurements. Study of the two kinds of error connects in this way: observers detect differences between random variation and events gone wrong by measuring characteristics of the events that fail to achieve their purposes. Observers may then act rationally from their understanding of nonrandom variation to reduce and sometimes prevent practical errors. This way of connecting systematic event measurement with process improvement follows from the insight into production processes first articulated by the statistician Walter Shewhart, then extended and made famous by, Shewhart's student W.E. Deming [13, 77]. The Shewhart–Deming approach investigates *practical errors*, failures of steps in a process to achieve their objectives, and attacks the variations in events that go wrong because of identifiable *root causes*, influences on processes that are motors of nonrandom variation.

*Interpretative error and observer variation*: Interpretative errors are impressions of how things are that turn out to be wrong. Investigations of statistical error make another distinction that carries over into the study of surgical pathology error: this concept is *intermethod* or *interobserver* variability. Observer variability is impor-

F. A. Meier (✉)
Department of Pathology and Laboratory Medicine, Henry Ford Hospital,
2799 West Grand Blvd, Detroit, MI 48202, USA
Email: Frederickmeier4@gmail.com

Department of Pathology, School of Medicine, Wayne State University, Detroit, MI 48202, USA



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tant if one is to understand the strengths and limitations of *review*. Review, looking again at diagnoses that have already been made, is the most frequent way to study everyday *interpretative error* in surgical pathology. The important statistical distinction for interpretative errors is between variability that occurs when the same method or observer makes repeated measurements (*intramethod* or *intraobserver* variability) and variability that occurs when two or more methods or observers measure the same phenomenon (*intermethod* or *interobserver* variability). Most of the time, interpretative error in surgical pathology, comes wrapped in *interobserver* variability, while *intraobserver* variability lingers in the background.

*Practical errors in the surgical pathology production process*: A production process is a series of steps. In the case of surgical pathology, the process turns patient samples into diagnostically, prognostically, and therapeutically relevant information. At each step in the process, marks can be missed. As outlined in Fig. 2.1, the production process begins with identifying patients, goes on to select specimens, then proceeds to label, transport, and accession them. The process continues with steps of describing received specimens, sampling them, fixing, embedding and cutting them, mounting processed sections of samples on slides, then staining the slides, labeling them, and delivering them to surgical pathologists. These interpreters of slides, in the central step in the process, examine the sections on the slides. At

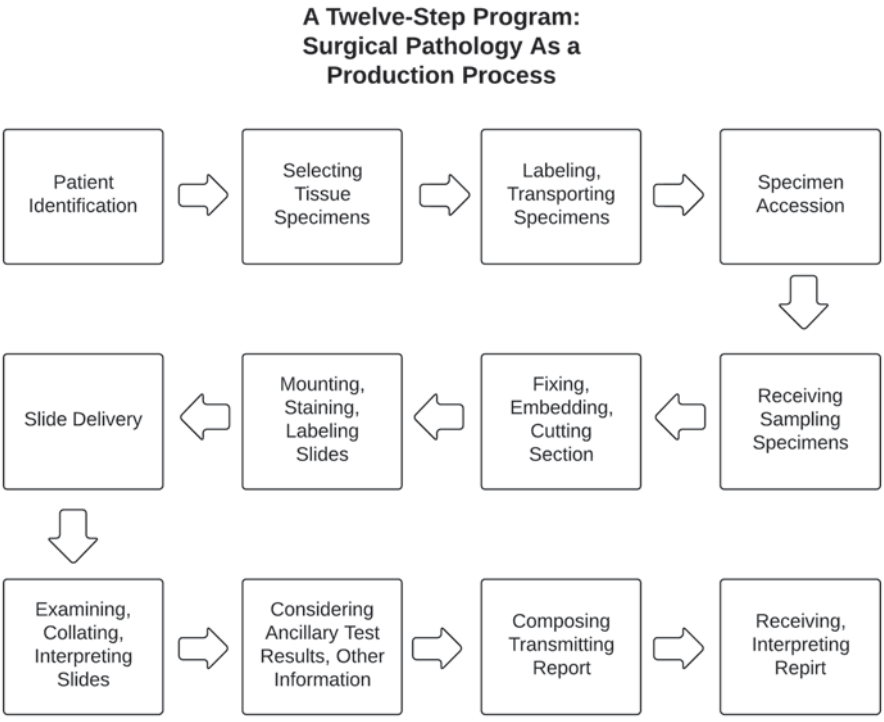


**Fig. 2.1** A twelve-step program: surgical pathology as a production process

this point, surgical pathologists also obtain information from other sources—especially ancillary test results and reports of clinical circumstances—and may request further in these reports they transmit, ultimately, to readers, who may act or not on the information.

*Amended Reports and practical errors*: Amended reports in surgical pathology are like accident reports. As sources for a taxonomy of defects, amended reports particularly help practitioners study practical errors in surgical pathology. They highlight the sorts of defects that lean production policies and procedures help decrease or eliminate in the surgical pathology production processes.

*Information theory and error*: In terms of Claude Shannon's *mathematical theory of communication* [13], observer variability is variation in signal reception. Shannon's theory, on which computer programming is based, predicts that getting from antecedent potential message to subsequent actual message always entails making errors [19, 75]. Information theory, as worked out by Shannon and his colleagues, provides a framework within which to think about the making of diagnostic message, the central task of surgical pathology.

*Interpretative error in the surgical pathology information flow*: Error arises in the information flow (Fig. 2.2) either by commission, not getting the information that is signaled from slides right, or by omission, missing the potential information that the slides have to offer. Practical and interpretative errors are distinct sorts of defects. They are studied differently [37]. In this chapter, we focus on amended surgical pathology reports as the most convenient source of information about practical errors and reviews as the most available source for rates of interpretive errors.

*Root causes*: Root causes are primary defects that occur earliest, farthest upstream, in the practical production processes. There are more steps in the production

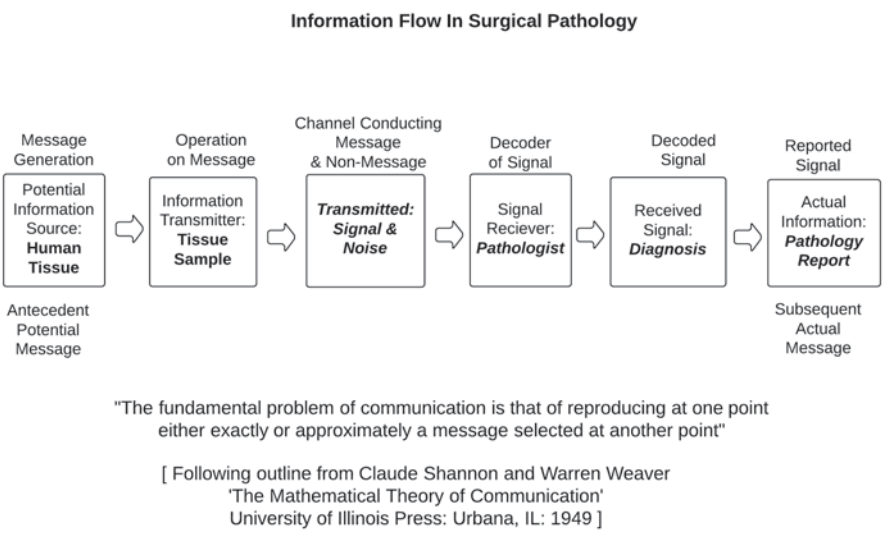


**Fig. 2.2** Information flow in surgical pathology

process (Fig. 2.1) than there are in cognate information flow (Fig. 2.2). Practical errors are, it follows, most often the root causes of errors in surgical pathology; this is particularly true of errors that can be prevented. For this reason, root cause analysis of errors in the surgical production process is the key to developing practical counter measures to improve the process's performance [64].

*Cognitive errors*: Information theory gives the best account of how errors about facts arise in the interrogation of tissues. As presented in reports, surgical pathologists' mistaken beliefs about matters of fact and classified states are *cognitive errors*. Nicholas Rescher observes: "specifically cognitive error roots in our human need to resolve issues of thought and action in conditions of imperfect information" [63] or, in the foundational insight of the information age, articulated by Claude Shannon, any sort of information is always imperfect [19, 75].

*Information theory maps surgical pathology error*: As outlined in Fig. 2.2, surgical pathologists search tissue samples for answers to questions: in the most frequently considered example they question whether or not a malignancy is present, what sort of neoplasm it may be, which features predict its behavior, and whether characteristics are present that indicate a particular therapy. Pathologists' reports convey information about primary matters of fact: a tissue sample does or does not contain lung cancer; primary matters of classification: a lung cancer is or is not adenocarcinoma; they also inform about secondary matters of fact: an adenocarcinoma does or does not appear within vessels or lymph nodes; and secondary matters of classification: a particular sample of adenocarcinoma of the lung has or lacks specific molecular signatures that indicate susceptibility or resistance to specific chemotherapeutic agents.

*The information stream*: Shannon discovered that, in the flow of information, a message is selected at an anterior (upstream) point then reproduced at a posterior (downstream) point. This sequence always runs from information sources to messages. In Fig. 2.2, we match the Shannon sequence to surgical pathology terms. From an information source (human tissue) of antecedent, potential information, a transmitter (the tissue sample) selects antecedent message, but the transmitter emits both a signal (anterior, potential information) and noise (mixed-in nonsignal that yields nonmessage). From this mix of signal and noise, receivers (surgical pathologists) select received signals (diagnoses, in Shannon's terms, subsequent message), which they then pass on as posterior, actual messages (reports).

*Interpretive errors and uncertainty*: This is a reality beneath interpretative error: any communication system that fits Shannon's pattern entails uncertainty. Every second, posterior, actual message (every reported diagnostic claim) has some chance of being wrong (for pathologists, either missed diagnoses, wrong diagnoses, or misclassified diagnosis). Quantification of this chance of being wrong calculates greater or lesser likelihood of interpretive error. This is the underlying variation that review of diagnoses aims to define.

*Surgical pathology is also an interpretative framework*: At this point, it is worth observing that, besides being a production process, and a pattern of information flow, surgical pathology is also a conceptual structure. This framework is a group of classifications or taxonomies. The taxonomies aim to transmit the diagnostic, prog-

nostic, and therapeutically relevant information that the production process creates. An act of interpretation places a received signal in a category within a classification. The characteristics of various classifications set limits to the reproducibility of the information. The variable applications of taxonomies also limit the validity, reproducibility, and detail of surgical pathology reports [37]. Taxonomic variability, like intraobserver variability, always lurks in the background, when we think about surgical pathology error.

*Validity, reproducibility, and detail*: In studies of interpretative diagnostic variability, three properties of measurement—validity, reproducibility, and detail—come into play again and again. *Validity* is the extent to which measurements correspond to real states of how things are. Increasing validity depends on decreasing systematic differences between observed appearances and real states of being. *Reproducibility* depends on how often repeated measurements return the same result, Random variation sets limits to reproducibility. *Detail* depends on the amount of information that measurements provide. The degree of detail determines how much an observer knows about what he has measured after he has measured it. Keeping these three attributes in mind aids orderly study of error in surgical pathology. Importantly, interpretative discrepancies produced by review of surgical pathology diagnoses combine differences in validity, with variability introduced by differences in reproducibility, and variation in matters of detail. In review discrepancies, these three contributing features are usually inseparable.

*Surgical pathology is, in addition, a dynamic scientific discipline*: The scientific discipline is the larger context that surrounds study of both process and interpretative, error. As a discipline, surgical pathology has assimilated increasingly elaborate techniques that assist in acquiring and processing information. These ancillary techniques find information both on the slide (as most prominently from immunoperoxidase stains) and from handling the sample in different milieux (as most prominently in molecular tests). The information gleaned from samples by converging morphological, quasi-morphological, and molecular techniques yields the explanatory criteria on which the informative classifications base themselves. In particular, sources of information besides histopathological morphology, especially immunohistochemical profiles and molecular motifs, increasingly influence classification. In this wider context, complexity leads to error. As we will emphasize below, increasing practical complexity of process compounds increased complexity of interpretation [46, 48].

*Oversimplification*: Surgical pathologists always generalize from particular findings on slides to general diagnoses of disease states. As actual message, emerging from the information stream, pathology reports inevitably oversimplify. Another of Claude Shannon's seminal insights is that informativeness of a message increases in proportion to its vulnerability to disproof. This is the juncture where detail joins validity and reproducibility in the trio of important attributes of surgical pathology information. As they compose reports, pathologists arrange information content. They may reduce complex data presentations to simple ones; they may proliferate qualifications; or they may take away informative detail. In these three ways, they limit, obscure, or decrease the amount of information transferred to clinicians. With

these strategies, pathologists try to prevent error by hedging; they trade off informative message for evidential security. This tactic fails when it drains reports of detail, exactness, and precision [66].

*Errors of commission and omission*: Errors of commission are misleading messages; these diagnostic failures (wrong diagnoses) appear among positive reports. Errors of omission fail to receive anterior diagnostic message. Errors of omission hide among negative reports. To recognize the commission:omission dichotomy, interpretative error detection must combine two different review approaches: (i) review (often redundantly called double review) of positive reports at risk and (ii) review of negative reports in high-risk categories of specimens [67].

*Review in search of error and hindsight bias*: Review checks the information transfer step in which the pathologist moves from receiving the signal or the slide to composing a report. Important conditions of review are when, where, how, and by whom review is done. *Hindsight bias* is made up of the systematic differences between looking forward at a new set of facts and looking back at an old set. Six systematical differences between the initial diagnostic event and the review event define various mixes of hindsight bias. The first of these distinctions is between *internal* and *external review*. Internal review is carried out within the practice in which the diagnoses under scrutiny were originally rendered. Pathologists in other practices perform external review. The second distinction is between *pre-sign-out review* and *post-sign-out review*. Pre-sign-out review takes place before a report is issued. Post-sign-out review happens after reports are released. A third difference is between *conference review* and *non-conference review*. Conference reviews are those that surround multispecialty gatherings at which cross-specialty agreement on diagnosis, prognosis, and therapy are sought. A fourth distinction appears between *expert* and *non-expert review*. Expert review is by a pathologist with increased knowledge and experience with the sort of diagnoses under review. A fifth pertinent difference is between *blinded* and *non-blinded reviews*. Blinded reviews are those reviews by pathologists with no more information than the primary pathologist possessed about a case; indeed a blinded reviewer sometimes is given less case-specific information. The last of these variations in review schemes, but probably not the least important, is that between *focused* and *unfocused reviews*. Focused review trains the reviewer's gaze on specific sorts of specimens or diagnoses. Unfocused reviews either take all comers or check a defined fraction of cases without requiring that they be of specific specimens or types of diagnoses. The variable influences of these half dozen factors together make comparison of review discrepancy rates difficult.

*Information sources about surgical pathology error*: At least two kinds of studies yield useful information about error in surgical pathology: classification of errors turned up by amended reports and sorting of discrepancy rates by review of surgical pathology diagnoses.

## Amended Reports as a Source for a Taxonomy of Surgical Pathology Defects

*Amendments*: Because practical errors are more frequent than interpretive errors, root causes of amended reports map more often to the twelve-step production process (Fig. 2.1) than to the six-step information flow (Fig. 2.2). Mapped to either sequence, amended reports offer opportunities to study systematically both surgical pathology errors and the counter measures aimed to decrease them [1, 33, 34, 84].

*Amendments vs. addenda*: To achieve semantic consistency, the alterations of surgical pathology reports after they have been issued must be separated into dichotomous groups. One group is composed of *amendments*: all changes that were not purely additions of information. The other group is made up of *addenda*: altered reports that include only alterations that purely add information. Adherence to this dichotomy has proven necessary both to detect reports with errors in them and to separate error from other sorts of report variation [32–34].

*Taxonomic consistency*: Across many institutions, classifiers of altered reports have been able to agree on four defect categories and to sort consistently into these categories [32, 84]. The categories are: *misidentifications, specimen defects, misinterpretations,* and residual *report defects*. Report defects are residual because they classify the amendments that are left over after misidentifications, specimen defects, and misinterpretations have been classified.

*Misidentifications* fail to designate accurately *patients, tissues, laterality*, or other *anatomic localization. Specimen defects* include submitted specimens that are *lost*, those of *inadequate sample volume* or *size*, those with *absent* or *discrepant measurements*, and those with *inadequately representative sampling*, as well as, importantly, and less intuitively, those with *absent* or *inappropriate ancillary studies.*

*Misinterpretations* fail to state diagnostic information accurately. They have an internal structure more complex than misidentifications and specimen defects. This complexity has led to misinterpretations being divided into three *subtypes.* The first subtype includes errors of commission; these are false-positive diagnoses, or *overcalls*. This sort of amendment registers the retraction of wrong information. The second subtype is made up of errors of omission; these are false negatives or *undercalls*. This second sort of amendment registers either failures to recognize accurate information or initial loss of information that later was found to reside in the sampled tissues. The third subtype is *confusion* or *conflation* of relevant, similar, but distinct diagnostic categories. The findings in the third subtype are not over- or underdetermined, rather, they are misnamed diagnostic designations. The three misinterpretation subtypes, in turn, relate to two *levels* of diagnostic message: *primary level* amendments register failures to distinguish positive from negative, malignant from benign; and *secondary level* amendments mark failures to characterize subordinate diagnostic features appropriately. The subordinate secondary diagnostic features affect clinical context, prognosis, or susceptibility to specific therapies. Most often these secondary characteristics are grade, stage, state of surgical margins, or lymph node status in specimens resected for malignancy.

*Report defects*: After misidentifications, sample defects, and misinterpretations have been excluded, the residual category in the taxonomy is *report defects*. Report defects also present themselves in three subtypes: (i) missing or erroneous *non-diagnostic information*—absent or wrong information about practitioners, procedures, billing codes, etc., (ii) *dictation or transcription errors*—typographical errors in the strict, proof-reader's sense, and (iii) failures or *aberrations in electronic report formats* or transmissions—the miscues colloquially called computer glitches. These report errors are all defects in product, but they have in common that they do not directly affect diagnostic information. Misidentifications, misinterpretations, and specimen defects, in contrast, all directly interfere with the diagnostic message itself. Report defects, however, are not unimportant. Although they fail to muddle message directly, as they harm the information flow by reducing information redundancy [19]. Redundancy is the informative context in which the text of any message always arrives.

*Root causes of amendment types*: In the twelve-step production process (Fig. 2.1), the root causes of misidentifications and sample defects appear mostly in the early steps of the surgical pathology process, during specimen collection and sample processing, but, in a minority of instances, they pop up later. The root causes of misinterpretation focus in the middle of the process, when the case is on the pathologist's desk. Root causes of residual report defects inject themselves into the process at multiple points, but they also tend to cluster at its beginning, before the case reaches the pathologist, and at its end, after the pathologist has settled on diagnostic interpretations.

*Application of the Amended Reports Taxonomy*: Uniform application of this taxonomy allows consistent monitoring of amended reports among institutions and also within an institution over time. Important to process improvement, when amended rates are followed longitudinally over time, they also evaluate the success or failure of interventions aimed to reduce errors that amendments identify [1, 32–34].

*Three characteristics of defect discovery*: The amendment taxonomy revealed a trio of characteristics surrounding the discovery of defects. First, the more observers monitoring amendments, using the dichotomous definition, the more amendments are identified, usually at the expense of addenda. Second, clinicians discovered most misidentifications; pathologists found most misinterpretations; but discovery of specimen defects were scattered among different observers and discoverers of report defects usually remained anonymous. Third, clinician calls were the most frequent mechanism for detecting misidentifications, and, initially, conference review was the most fruitful mechanism for detecting misinterpretations. Conference review discovered, in various settings, between a little more than 40% to a little more than 80% of all misinterpretations that produced amendments [32].

*Effects of lean interventions*: In a large surgical practice that accessioned 45–50,000 specimens each year, real time editing of altered reports, undertaken together with changes in process aimed at reducing and preventing the underlying defects, had the following consequences over a 5-year period. Initially, active monitoring caused amendment rates to rise, from approximately 5-amendments/1000 reports to 10/1000 as altered reports were consistently defined as amendments or addenda.

Next, as monitoring continued and counter measures were applied, amendment rates fell back to the 5-amendments/1000 reports level. Lean interventions in surgical pathology report production then caused misidentifications to fall from 16 to 9% of all amended reports. Despite similar interventions, however, the fraction of amendments caused by specimen defects remained at about the same low magnitude (<11%) and continued to be highly variable from year to year. In contrast, the fraction of misinterpretations fell dramatically, from 18 to 3% of all amendments. This fall was associated with introduction of pre-sign-out review of all breast and prostate cases, then, in addition, cases of some gastrointestinal tract lesions. Finally, and reciprocally, as misidentifications and misinterpretations fell, the residual category's report defects increased its fractional contribution, from 64 to 83% of all amendments.

*Lessons from root cause analysis*: When case-by-case root cause analysis of amendments assessed success or failure of interventions, three findings emerged: (i) efforts to reduce misidentifications at the specimen collection level (where most of these errors occurred) had a measurable, but modest beneficial effect, (ii) extensive standardization of specimen accession and gross examination reduced specimen defects surrounding ancillary testing, but not specimen defects overall, and (iii) introduction of internal pre-sign-out review of all breast and prostate and some gastrointestinal cases was specifically associated with a reduction in misinterpretations [34, 32].

*Amendments vs. addenda*: The problem with amendment monitoring caused by misclassification of amendments as addenda continued over time. During active monitoring, 10% of so-called addenda have consistently turned out to be amendments. The adoption of misclassification amendments as an index of ongoing professional performance evaluation (OPPE) has now worsened this tendency to misclassify amendments as addenda [, 33, 34].

*Q-PROBES study of amendments using validated taxonomy*: In 2011, as part of a College of American Pathologists Q-PROBES study, 73 participating institutions analyzed almost 1700 amendments over a 12-week period [19]. The Q-PROBE study's salient results are presented here to complete our account of how amendments characterize errors.

*The taxonomy-classified amendments effectively across 73 institutions*: Using the taxonomy, Q-PROBES subscribers classified 1665 of 1688 amendments (98.6%). In contrast to our large institutional experience, however, the fractions of misidentifications (13.3%), specimen defects (13.7%), and misinterpretations (14.6%) were about equal [1].

*Amendment rates*: Median defect rates among Q-PROBES participants hovered around 5-amendments/1000 published reports: the aggregate defect rate was 4.7-amendments/1000 cases and a median participating institution's defects rate was 5.7/1000. This median amendment rate is similar to the 5/1000 experienced in our single institution monitoring. However, among the 73 Q-PROBES study participants, the range around this median was wide; it extended from 0.9/1000 to 13.5/1000 amendments/reports issued [1].

*Misidentifications and sample defects*: In the Q-PROBES study, among 225 misidentifications, 31.5% were of patients, 20.0% of tissue type, 23.0% of laterality, and 25.5% of anatomic localization [1]. Among 231 sample defects, more than three-quarters (77.4%) involved ancillary testing and the rest mostly involved gross and microscopic sampling [1]. The association of sample-related defects with misdirected or failed ancillary testing is a phenomenon also observed in our single institution's longitudinal monitoring.

*Misinterpretations*: Analysis of 247 primary and secondary misinterpretation amendments found only 5.7% false positives and only 11.8% false negatives. These fractions are dramatically different from our single institution longitudinal experiences. The difference stemmed from very different rates of diagnostic relabeling. In the Q-PROBES cohort, 44.1% of misinterpretation amendments were attributed to confusion or conflation of similar but distinct diagnoses (misnaming). The Q-PROBES subscribers also produced a different pattern of interpretative errors from that found in the single institution experience. Misinterpretation amendments among the Q-Probes study participants were revised mainly for secondary features in amended reports of malignancy. These amendments usually changed grade or margin status [1].

*Residual report defects*: Among the Q-PROBES study participants, as in our long-term experience at one institution, the most common causes for amended reports were residual report defects: typographical errors, missing nonidentifying, noninterpretative report attributes, or wrong nondiagnostic report information [1].

*Anatomic sites of origin of specimens that produce amended reports*: In the Q-PROBES study, the most common tissues of origin for defective reports were the most common sites sampled: the skin, breast, and gastrointestinal tract. Submissions from these sites were about equal defect contributors (18.2, 17.7, and 18.1%) [1].

*Benchmark amendment rates from Q-PROBES study of amendments*: The Q-PROBES study of amended reports yielded two benchmarks: First, with a 5/1000-defect rate, the current surgical pathology production process is a 'three sigma' production system for surgical pathology reports. Second, median rates of misidentifications and misinterpretations are fairly consistent. These two rates both run below 1/1000 and are about equal: 0.6 amendments for misidentifications/1000 reports and 0.8 amendments for misinterpretations/1000 reports [1].

*Defects in the surgical pathology production process as normal accidents* [46]: Findings about surgical pathology errors uncovered by root cause analysis of amendments agree with studies of other production processes in different settings [46, 48]. From studies in a variety of complex production processes, Charles Perrow defined untoward events, like those which amendments document as *normal accidents*. He argued that these events occur in conditions of *complexity* created by interconnecting subsystems. In surgical pathology, the interconnecting subsystems are the preanalytic, analytic, and postanalytic phases of the report production process. A second error-inducing characteristic, *tight coupling*, then mediates the connection between subsystem derangement and damage to the final product. A third characteristic is *concentration*. In surgical pathology laboratories, high vol-

umes of specimens are concentrated by converging from multiple collection sites to enter the production process. Once concentrated in the process, these specimens are also subjected to complex ancillary tests. Computer-enabled communication tightly couples pathologists with pathologist assistants, histologists, and clinicians. Perrow argues persuasively that such concentration, complexity, and tight coupling together inevitably amplify practical error [45, 47].

*Eight contributors to normal accidents*: All eight features that make systems prone to normal accidents are present in the surgical pathology production process [45]. In the following list we cite, next to each error-promoting feature, examples of its appearance in the surgical pathology setting:

1. *Proximity of components*: proximity appears among specimen jars awaiting samples in endoscopy suites and in shopping bags full of many different patients' skin biopsies arriving at accessioning stations
2. *Common-mode connections*: large specimen gross examination stations are common mode connections when pathologist's assistants examine in succession multiple partial mastectomy and lymph node dissection specimens or multiple colon resections during the same accessioning shift
3. *Interconnected subsystems*: subsystems interconnect when prostate biopsies obtained in an ambulatory surgery setting arrive simultaneously at the same accession desk with the products of a radical neck dissection from a frozen section room
4. *Feed-back loops*: different feed-back loops cycle simultaneously as telephone calls go back and forth between pathologist's reviewing slides and pathologist's assistants returning to fixed specimens to harvest more tissue samples, while, at the same time, pathologists send computer messages to histologists to request additional levels and special stains
5. *Limited substitutions*: the constraints due to the different tissue processor cycles limit substitutions of cassette batches depending on run times
6. *Multiple interacting controls*: multiple interacting controls appear at accession in identification of specimens, in the histology laboratory, with the sorting of blocks, and on pathologist's desks at the arrival of slides
7. *Indirect information transfer*: indirect information transfer occurs when clinical features about cases are reported only in shouts over the shoulder of an operating room technician hurrying down a hallway, critical choices in specimen sampling are made only in whispers among residents at specimen processing stations, or vital new clinical information arrives only in muttered remarks from a clinical fellow who has come to look at slides
8. *Limited understanding of the requirements of the process*: clinical staff collecting specimens have limited understanding of what requirements for histologic diagnosis are; pathologists as they interpret slides have limited understanding of what information clinicians imagine reports will contain

*Ambivalent effect of electronic information transfer in complex processes*: Computerization brings both positive innovations and dangers to the complex process that fits Perrow's description. The positive changes have reduced unwanted variation,

standardized data input, and reduced dependence on the variable information transfer media. Computerization has also helped by programming formats like synoptic report checklists and has facilitated automation of routine tasks, like bar-coded logging-in specimens, collated with bar-coded requisition documents. However, negative changes brought by programmed processes of electronic information transfer require invariant sequences, stipulate one way to perform a component task, allow only limited buffers, and force only designed substitutions [45]. As computer-facilitated standardization has been achieved, former safeguards, redundancies, buffers, and alarms in previous surgical pathology systems have been eliminated. With newer complex systems come tighter couplings. High volume, complex, tightly coupled systems open themselves to untoward events in which two or more, failures interact in error-causing ways that process designers and operators have not anticipated. Such event sequences, Perrow and another student of system error, James Reason, find, precipitate disproportionately bad outcomes that Perrow has designated *catastrophes* [48, 57].

*Lessons of lean principles and practices*: In these circumstances, sustained practical error reduction, incorporating lean industrial engineering principles and practices, has become a valuable response [3, 7, 11, 80, 92–94]. The lean approach, (systematic practical error detection, then error reduction, prevention, and amelioration through countermeasures), addresses all four defect types recorded by amended reports. For the three practical sorts of defects, the analysis makes connections presented in the next three paragraphs.

1. *Misidentification* is the practical error with the most devastating potential [80, 94]. To attack it, colleagues who labor upstream in the process must accept forcing functions, labeling standards, and new labeling procedures; the beneficial effects of this apparently extra upstream effort often exert themselves only downstream where those making the changes cannot see their laudable effects. Nevertheless, a trio of worthwhile points has emerged from lean interventions that improve patient and specimen identification. Detecting and preventing misidentification entails: (i) training in labeling standards that extends outside surgical pathology premises, to dermatologists' offices, endoscopy suites, and operating rooms, (ii) recognizing that batched printing of labels is a recurrent misidentification threat; flow design must avert it as much as possible, (iii) designing identification checks into multiple steps in the process, especially at two important checkpoints—(a) arrival of requisitions and specimen containers at accession and (b) reconciliation of requisitions with reports just before reports are released [80, 94].
2. *Specimen defects*: Root causes of specimen defects increasingly reveal that ambiguities and delays in potentially decisive ancillary test results, especially those from molecular tests, are a growing cause of specimen defects [80].
3. *Result reporting*: In result reporting, the increasing importance of ancillary testing in surgical pathology often now forces a Hobson's choice. The unattractive decision falls between either issuing an incomplete report liable to later amend-

ment or delaying the report until potentially modifying ancillary information can be combined fully into an integrated report [16].

*Report errors and the benefits of redundancy*: Another lean lesson also involves errors documented in residual report defects. As Shannon deduced about communication in general, redundancy has more substantial benefits than may be intuitively obvious [19, 75]. In the surgical pathology report production process, completeness of report information, other than patient and specimen identifications and diagnoses themselves, turns out to be helpful in averting error. For example, the presence of inconsistent clinical information on a requisition may be the only sign that a specimen jar has been mislabeled. Electronic medical records (EMRs) also supply useful redundancy. As counter measures, structured searches of EMRs confirm or expand the clinical context in which a submitted specimen has arrived. These routine searches can be of great assistance, in reducing practice report defects.

## Case Review to Detect and Reduce Interpretative Error

*Active vs. Passive Monitoring*: Reports of reviews are the main source of studies about surgical pathology interpretative error [37, 71, 79]. Review looks again at cases that have already generated diagnostic message, so review entails *active monitoring*; it searches for discrepancies, where classifying amended reports and pursuing their root causes which we have just discussed, is, in contrast, *passive monitoring*.

*Review and information flow*: In relation to information flow (Fig. 2.2), review exposes the same signal to different receivers each of whom has his or her own noise thresholds and variable sensitivities to signal reception. These different receivers generate discrepancies, the products of review.

*Effect of interobserver variability on review*: In active monitoring, interobserver variability always comes into play because implicit diagnostic thresholds and the application of explicit classification criteria are products of experience. Experience among pathologists inevitably differs. Importantly, primary diagnosticians and secondary reviewers also tend to function at different diagnostic thresholds.

*Internal vs. external review*: There is a relevant contrast, mentioned earlier in this chapter, *internal review* [39, 42, 44, 58, 61, 87, 90] among members of the same practice group and *external review* [29, 81] that involves members of different practices. In the first context, the internal reviewer is checking to see whether a local colleague is right. In the second context, the external reviewer is checking to see whether a distant noncolleague is wrong.

*Expert vs. non-expert review*: Another contrast appears when either internal or external reviewers are or are not subspecialist experts. In internal expert review, subject matter specialists within a department may set different diagnostic thresholds and use different explicit or implicit classification criteria than do general pathologists in the same practice. However, the internal expert's view of things usu-

ally affects his or her nonexpert colleagues' thresholds and criteria by feedback over time and through accumulation of shared cases (see calibration effects paragraph later in the text) [53]. Primary pathologists and external expert reviewers may diagnose against not only different horizons of experience but also different clinical objectives. In a common setting of external review, reviewers at an oncology hospital locate diagnoses on different horizons of experience than do less specialized referring pathologists. The oncology hospital pathologists also prepare their reports for specialist oncologists whose needs (and sometimes prejudices) are opaque to the primary diagnosticians [26].

*Blind vs. informed review*: A different sort of variable that affects the difference between thresholds is whether the secondary examination of the case is *blind review*, whether the secondary case examiner does not or does know the primary pathologist's initial diagnosis, and whether the second examiner does or does not know more or different clinical information than did the primary pathologist [60, 62].

*Effect of calibration*: Active monitoring within a practice group may also produce *calibration* effects. Calibration appears when pathologists compare many cases over time and converge on similar thresholds and criteria. In practices with a dominant expert, calibration often converges on the dominant expert's thresholds and criteria in "the big dog effect" [53].

*Interventions that lessen interobserver variation*: Experience argues that calibration through consensus conferences and calibration slide sets are counter measures, which reduce the interobserver variation. These two strategies provide structured opportunities for practice colleagues to articulate agreement on diagnostic criteria and develop a shared vocabulary in which to discuss problematic cases. Consensus and calibration mechanisms also provide critical occasions for practice colleagues to address together the influence of modulating factors on diagnostic differences.

*Taxonomic variation*: Differences in application of taxonomies present one more obstacle to the equation of review discrepancies with errors. Different diagnoses may or may not reflect the same constellation of signal findings. As observed earlier, diagnostic taxonomies have explicit and implicit features that nonexpert and expert users deploy differently. This is a specific instance of a general phenomenon. Each pathologist throws various taxonomic nets of diagnostic designations over histopathological realities. Different taxonomic nets may fit a reality better or worse, but different nets may also just fit the same reality differently, mesh. It is very hard to compare and contrast the relative fit to the reality of different taxonomic nets; however, these differences seem to lead to discrepancies in how different observers register the same realities [88].

*Disparate information sources*: A final barrier to equating discrepancies with errors arises when disparate pairs of diagnoses are reviewed. Examples of odd couples under review are frozen section:permanent section comparisons and cytological:histological correlations. In both these pairs, the initial diagnosis in the dyad was from a different sample—or a differently processed sample—compared with a subsequent more information-rich specimen presentation. In these settings,

method differences and observer differences get mulched together as diagnostic discrepancies [51, 52, 17].

## *Different Sorts of Review Compared and Contrasted*

*Internal vs. external reviews*: Timeliness give pre-sign-out internal review major advantages: It often prompts prospective resolution of diagnostic discrepancies (for example between cytological and histological diagnoses from the same tissue source) that can trouble both pathologists and clinicians in retrospect. It gives internal experts opportunity to calibrate a practice's diagnostic thresholds and standardize application of taxonomies. Most importantly, it obviates need for report amendments when discrepancies are discovered. For large practices, internal review is usually faster and less expensive than external review, but the time commitment involved in internal review may be impractical for small practices. In small practice settings, the more probative weight of external expert review also carries added value with skeptical clinicians. For medium size and larger practices, external review is more expensive; it also may provide revision of diagnosis only after an embarrassingly long time. Clinical decision making is then either delayed or second-guessed. To avoid delays and potentially contradictory revisions, middle size practices tend to rely on conference-based review. This format combines opportunity for local expert review with additional clinical context.

*Inevitably retrospective reviews*: The benefits of internal, upstream, over external, downstream review, suggests that reviews should be carried out, in most settings, either before cases with identified risks are signed out or before their clinical implications can be acted on. Some correlations, however, remain inevitably retrospective. The correlation of uterine cervical cytology or cervical biopsy diagnoses with diagnoses from excision specimens is an example of this sort of unavoidable retrospection. Another, necessarily retrospective sort of review is the practice, already discussed earlier, of reviewing diagnoses of malignancy after patient referrals to centers for cancer treatment. Both of these review mechanisms remain ingrained in good practice [17, 20, 31, 89, 74].

*Unfocused vs. focused reviews*: As will be cited again, complete and set percentage reviews tend to produce lower frequencies of discrepancies than do focused reviews [55]. They do, however, remove selection bias. Reviews of cases focused on specific organs detect both false-positive and false-negative interpretations as well as misclassifications. In contrast, reviews focused on specific diagnoses catch only false positives and misclassifications. They provide, however, initial confirmation of the most significant diagnostic product of a pathology service: positive diagnoses are usually the most clinically relevant products of the surgical pathology production process, so, if only one sort of case can be subjected to review, new positive diagnoses should be it [36, 40].

*Subjects of focused reviews*: Focused reviews most often train attention on specimens that are both relatively often submitted and relatively challenging to classify.

Preneoplastic or borderline neoplastic breast [24, 43], melanocytic skin lesions [23, 78, 82, 86], and female genital tract lesions [31, 91] are frequent foci of review. Another criterion for focused review is a high likelihood of interobserver variation. In these situations, the wisdom of sorting out local interobserver variation prospectively rather than retrospectively recommends internal, pre-sign-out review. Gleason grading of prostate adenocarcinoma [6, 15, 27, 49, 85], grading and staging of uterus and ovary malignancies [14, 91], and classification of thyroid lesions [4, 12, 25] commonly satisfy this criterion. More recently subclassification of adenocarcinoma of the lung has joined this group of classification challenges [21, 41, 56, 72].

Taxonomies that interact with ancillary studies, like those for adenocarinoma of the breast, lung, and kidney, are instances in which ancillary information's integration can be decisive. Classifications of leukemias and lymphomas and bone and soft tissue sarcomas are further instances in which complexity increases the degree of difficulty encountered on the way to review consensus [28].

*Percentage vs. focused review*: Stephen S. Raab led a study that compared two contrasting review approaches—percentage review and focused review [55]. Raab and his colleagues compared random review of 5% of specified sorts of cases with focused review of suspected troublesome specimen types of primary diagnoses. The study found a much higher discrepancy rate from focused review: 13.2% from focused review vs. 2.7% from percentage review. Raab and colleagues also looked at potential downstream implications of the uncovered diagnostic discrepancies. Instances they classified as major errors were found a power of ten more often in the focused review approach than they were in the random review scheme: 3.2 vs. 0.36% of cases. In Raab's study, higher yield makes focus review appear a wiser use of review time and expertise [50].

*Focus of review and amendment rates*: Andrew A. Renshaw and colleagues have used amendment rates to project the relative utility of different review strategies, by comparing the fractions of different case types with discrepancies and amendment rates in these case types [58–62]. In one study, they demonstrated that breast lesions, cytological:histological correlations of genital tract lesions, and thyroid diagnoses were particularly likely to lead to amendments. The relationship between the two fractions of discrepancies and amendments was: 27% of discrepancy-producing cases produced 88% of amended reports [59]. Renshaw also found a less dramatic but similar disproportion when he examined the case discrepancy: amendment relation for initially nondiagnostic or atypical/suspicious diagnoses. Cases with borderline diagnoses made up 4% of discrepancy-producing cases but 14% of amendments [59]. Two take-home lessons appear here: First, the mix of cases that a practice examines influences discrepancy frequency patterns. Second, borderline lesions (intraductal and lobular breast proliferations, intraglandular prostrate proliferations, equivocal gynecological cytology classifications, and ambivalent thyroid cytology findings) increased the likelihood of discrepancies [59].

*Burdens of review*: Reviews cost time and effort. The essential burden of documenting individual reviews and collating the information aggregated from reviews is a major investment in data analysis. As a rough estimate of the number of cases that fall under the gaze of review, a recent survey by Nakhleh et al. found that,

in typical settings, review protocols cover approximately 8% of a practice's cases [39]. Raab's seminal study (which should be duplicated in multiple, different settings) suggests, that focusing review on sorts of cases with known high rates of missed decisions or revised diagnoses is the preferred approach to case selection [55]. Another pivotal decision, which bears further investigation, is whether review should be blinded or not.

*Review as a quality measure*: We now reach the central paradox of review. Despite all the influences and interferences that make a one-to-one correspondence between review discrepancies and errors impossible, case review remains the main source of information about interpretative errors. Pathologists' knowledge and experience, their ability to correlate clinical failures with histopathological findings, their skill in combining morphological with nonmorphological (or quasi-morphological) ancillary findings, and their mastery of coherent taxonomy are four basic professional aptitudes into which review delves, however inadequately. The results of review offer both providers and users of surgical pathology reports imprecise but implication-rich indicators of diagnostic integrity. This indicator function is currently review's main contribution to the evaluation of quality in surgical pathology. Because so many variables affect review, comparisons among discrepancy rates, from one set of reviews to another, remain, however, unavoidably approximate.

*A hedge around discrepancy studies' comparison*: Studies of interpretative error are hard to compare head-to-head because of the variables that we have been calling to mind as well as differences in study design, variable definitions of discrepancy, differences in mixes of tissues of origin, various canons of case selection, and application of inconsistent classifying taxonomies.

*Discrepancy rates*: In the complicated context of interferences and modulating factors, that we have just considered, the range of published discrepancy rates is wide. They are, however, stratified relevantly by the different subject matters that they survey: different anatomic origins of the reviewed specimens, different breadth of focus on reviewed characteristics, and different numbers of cases in the reviewed series. Within this wide frame of references, published series do produce a "range of ranges" of discrepancies.

*"Range of ranges"*: A series that take in large numbers of various specimen types anchor the low end of the spectrum (or, better, spectra) of discrepancy rates. A recent well-organized internal random review of surgical pathology reports ($N=1523$) found a discrepancy rate of 2.2% [44]. Such relatively low magnitudes of review differences can be expected from wide-angle, all comers, and fractional reviews.

The next segment of the discrepancy rate spectrum takes in malignancies from specific organ systems (e.g., lymphoma or urological malignancies), all specimens from specified anatomic locations (e.g., gastrointestinal and liver lesions), a specific neoplasm (e.g., breast cancer), and a genre of neoplasms (i.e., pediatric cancers). At the low end of this segment, one finds lymphoma with discrepancy rates of 6–7% ($N=1291$) [2, 28]. In the next higher stretch of the spectrum are urological malignancies (10%; $N=213$) [85] and gastrointestinal and liver lesions (12.4%; $N=194$) [22]. Next, up in this part of the range is breast cancer (16–20%; $N=610$) [26, 30]

followed by pediatric neoplasms (25.1%; *N*=705) [73]. At the top of this segment of the "range of ranges" are, from a small but responsibly done study, in a resource-challenged environment, soft tissue tumors (47%; *N*=34) [76].

*Cytological:histological correlations*: Correlations of diagnoses from different modalities produce an extraordinarily wide range of discrepancy rates. At the low end of this segment, with relatively few discrepancies, is a correlation of cytological with histological samples obtained at the same bronchoscopy procedure but interpreted independently. Cytological histological correlations of specimens from this source produce a discrepancy rate of only 2.3% (*N*=231) [72]. Next up the scale is over-all cytological:histological correlation of cervical histology specimens for which a recent, large well-done study locates the discrepancy rate at 6% (*N*=5159) [8]. This discrepancy rate is similar to that in a smaller but well-designed study of correlations for all female genital tract tumors, where the rate was 6.8% (*N*=279) [14]. Next in line is fine-needle aspiration noncervical cytological:histological correlation. From this source discrepancy rates are higher, 9–12% (*N*=898) [4, 41]. More focused comparisons produce discrepancy rates dramatically higher on the scale: bladder cancer cytological:histological correlations have a 41% discrepancy rate in a carefully done large (*N*=508) study [54], and cytological:histological correlations of negative fine-needle aspirations from breast lesions have a discrepancy rate 46% in a moderately sized study (*N*=90) [5].

*Cytological:histological vs. cytological:cytological discrepancies*: An interesting observation about the cytological segment of the discrepancy spectrum is that in the same well-sized study much lower cytological:histological discrepancy rates were achieved in an environment where high cytological:cytological review discrepancies were documented. The observers who documented the relatively low, 6%, cytological:histological discrepancy rated cited earlier in the text for cervical specimens reported a very high overall similar 45% cytology:cytology discrepancy rate (*N*=13,745) [8]. Their high rate of intercytological discrepancies is also seen in a similarly designed, smaller comparison (e.g., 54%; *N*=209) [10].

*Dermatopathological variation*: Another wide variation in the range of ranges appears in the main histological:histological review segment. This variation involved discrepancy rates in comparisons of skin biopsies. Similarly-sized studies (*N*=589 [82] and *N*=478) [23] came up with discrepancy rate as different as 6.5 and 35%. In another disparate pair of studies, skin biopsies for pigmented skin lesions found a 14% discrepancy rate (*N*=392) [78], but a similarly-sized (*N*=354) comparison of primary and review diagnoses of skin biopsies found a four times higher discrepancy rate of 56% [18].

*Discrepancies in difficult diagnostic situations*: Finally, in our selective tour of the "range of ranges" of discrepancy rates, one finds relatively high and wide (20–60%) discrepancy rates in studies focused on diagnostic situations that are known to be difficult. One example of this is a small study (*N*=30) of liver transplant biopsies that showed a 43% discrepancy rate between a primary pathologist's and an expert's diagnoses [9]. Thyroid cytology is another example. Comparisons that focused on this well-known trouble spot found, in two modestly sized studies of thyroid aspirates (*N*=50 [25] and *N*=113) [12], very high but also very different

discrepancy rates of 52 and 34%. A third and fourth example of foci on known difficult diagnoses both come from the female genital tract: a 23% discrepancy in diagnoses of vulvar dysplasia in a small study ($N=60$) [83], and a 26% discrepancy rate in the diagnosis of gestational trophoblast disease in a well-done, large series ($N=1851$) [20].

*Discrepancies due to variable application of taxonomies*: The most impressive instance of multiple discrepancy studies documenting poor reproducibility in a specific diagnostic situation regards Gleason grading. A large study of discrepancies ($N=2015$)in resected prostate specimens found discrepancies in Gleason grading in 45% of cases [27]. In two moderately sized studies of prostate biopsies ($N=278$ [6] and $N=151$ [49]), (the former, larger study comparing diagnoses from microarrays); both found 42% discrepancy rates.

*General patterns in discrepancies or review*: The last few paragraphs are just an aerial tour that points out only selected landmarks on the landscape of interpretative error, as it is imperfectly transmitted by discrepancy rates. Pondering review reveals that specific rates are rarely comparable; a general pattern does, however, emerge from wandering across the range of ranges. The widest-angle (all comers or random) reviews produce the lowest discrepancy rates. Reviews of diagnoses from organs or organ systems or genres of linked diagnoses (like pediatric neoplasms) produce higher rates. Reviews focused on specific, difficult diagnostic categorizations produce the highest discrepancy rates. Among histological:histological review, differences in discrepancy rates among studies are particularly wide in dermatopathology. Otherwise, cytological:histological diagnoses agree rather well, at the level of organ-system comparison; this is remarkable, given the noise documented by attempts at correlation is cytological:cytological reviews. Finally, among the most commonly used classifications, Gleason grading produces the most discrepancies on review [6, 15, 27, 85].

"*Errors are indeed there to be made*" [69]: Just as the practical complexity of the surgical pathology report production system requires vigilance to detect errors and invention of countermeasures to avoid them, so Error will not disappear from making diagnostic interpretations. "Our only route to cognitive progress proceeds along a pathway paved with error—we are creatures to whom truth becomes available only by risking error. Our knowledge grows only by eliminating error" [70]. On this pathway, review is valuable. Review does not, in discrepancies, detect interpretative error as such, instead it finds interpretative error encased in other sorts of variation.

## Conclusion

*Two main sorts of error*: The landscape of error has two main geographical features: practical errors called process defects and interpretative errors uncovered by diagnostic discrepancies. Study of amended reports reveals process defects. Review of diagnoses produces the diagnostic discrepancies. Both of these strategies have been of value in characterizing and reducing surgical pathology error.

*Sources of the two main sorts of error*: The dangers that lurk in this landscape are also of two sorts. The concentration, complexity, and tight couplings of electronic information transfer, as we have stressed, both engenders practical defects and provides countermeasures against them. Variable validity, reproducibility, detail in diagnostic interpretations, extensions from particular findings to general diagnoses, variations in classifications and changing evidence bases, we have also argued, all contribute to diagnostic discrepancies that include but are not entirely due to interpretative errors.

*Analysis of amendments to understand process error*: The reports of accidents, in our initial metaphor, are amendments of surgical pathology reports. Studies of amended reports classify surgical pathology production process errors as misidentifications, specimen defects, misinterpretations, and report defects. These studies document a 5-amendments per 1000 (three sigma) defect rate for current surgical pathology production systems.

*Review to uncover discrepancies*: In this chapter, we emphasize how characteristics of review events whether they are internal vs. external, unfocused vs. focused review as well as, most importantly, the diagnostic domain in question, all influence discrepancy rates. We have presented evidence that internal reviews have, in general, advantages over external reviews and focused reviews have, in general, advantages over unfocused reviews and that, from one diagnostic domain to another, discrepancy rates are dramatically different.

*The bottom line: monitor amendments and discrepancies*: Published evidence suggests that surgical pathologists' most systematic and sensible design for living in the landscape of error is to monitor process errors, to find and eliminate their root causes, and to review interpretative discrepancies in schemes that factor in a discrepancy's relative likelihood in different diagnostic situations.

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# Chapter 3
# General Principles of How Errors Occur and How They May Be Reduced

**Maxwell L. Smith and Stephen S. Raab**

## How Errors Occur

Medical errors have devastating potential for the patient and provider alike. A basic understanding of how errors occur is the first necessary step in a process to identify and reduce errors. This section covers the definition of error, different classification systems for errors, and various models for error causation.

### *Definition of Error*

In its landmark publication, the Institute of Medicine (IOM) estimated that medical error was the cause of between 44,000 and 98,000 patient deaths each year [1]. While these estimates have been challenged [2], there is no doubt that the medical system in the USA generates errors that result in patient harm and death. The IOM also estimated the financial cost of these errors between $ 17 and 29 billion annually [1]. In the present day of health care reform and cost reduction [3], error reduction looms large as a potential target, even in laboratory medicine [4]. Keep in mind that the estimates provided by the IOM are based on *deaths* related to medical error, and fail to include the likely larger numbers related to medical errors resulting in increased patient *morbidity* and cost.

As defined by the IOM, medical error is the failure of a planned action to be completed as intended or the use of a wrong plan to achieve a specific aim [1].

M. L. Smith (✉)
Department of Laboratory Medicine and Pathology, Mayo Clinic Arizona, 13400 East Shea Boulevard, Scottsdale, AZ 85259, USA
e-mail: smith.maxwell@mayo.edu

S. S. Raab
Department of Laboratory Medicine, University of Washington and Memorial University of Newfoundland, Seattle, WA, USA



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In laboratory medicine, this equates to the failure to diagnose/result correctly the disease process/laboratory test occurring in a patient. Critical analysis of the IOM's definition reveals no requirement for patient harm. Because error identification is independent of patient outcome, many will further qualify errors as "harmful," "no harm," and "near miss" [5, 6]. Observational studies show that the majority of medical errors do not result in patient harm and fall into the "near-miss" or "no-harm" category [5]. The distinction between "near miss" and "no harm" is that "near miss" events are errors in a work process that are caught before reaching the patient, while "no harm" events are errors that reach the patient but do not result in harm. A good example is found in the blood transfusion service. A unit of blood is issued for patient A but is incorrectly hung on the intravenous (IV) rack for patient B. If, prior to hooking up the IV line, a nurse recognizes the error and returns the blood to the blood bank, this is a "near miss." However, if the nurse transfuses the blood but fortunately the patient has no adverse reaction, this would be a "no harm" event.

Unfortunately, the term "error" has a negative connotation, especially in the medical field. This has led to difficulty in the transparency of reporting medical errors. This problem is furthered by a near-complete lack of education with regard to error in the US medical training system [7]. Because of these issues, some authors refer to errors as "defects" in an attempt to increase acceptance and discussion of medical error [8]. The laboratory environment is particularly suited to the term "defects" because of the similarities to manufacturing processes [9].

## *Classification of Error*

A variety of different error classification schemas have been developed. During root cause analysis (RCA) of medical errors, it is often found that errors have both active and latent components [5]. An active error is when a person or machine does something outside of the standard workflow process. An example is a pathologist picking up a slide and correctly interpreting a tubular adenoma, but reporting that on the incorrect patient. A latent error is when there are aspects of the workflow process that encourage an error. An example is having colon polyps from two different patients on the same slide tray.

Another way to classify error is by testing phase. Lundberg et al. described the total testing process (TTP), which includes six phases of laboratory testing:

1. clinician decides to perform a test and selects a test: pre-preanalytic;
2. test sample is obtained and transported to the laboratory: preanalytic;
3. laboratory processes and interprets the test: analytic;
4. laboratory reports the test result: postanalytic;
5. clinician makes a treatment decision based on the results: post-postanalytic [10].

Stroobants et al. [4] studied the error frequency of the various phases of testing and found that the majority of errors occurred in the preanalytical phases. Of course, the laboratory often only has control of the analytical phase. Laboratorians will often

dichotomize the analytic phase into technical phases and interpretive phases, as the administration and leadership over these two domains are usually different [11].

The Eindhoven Classification Model classifies errors into three main root cause domains and helps to focus the root cause on the process and latent factors rather than blaming the human perceived to be responsible [12]. The technical domain includes the information technology, tools, machines, and forms. The organizational domain includes the protocols in place, transfer of knowledge, management priorities, and the culture. The human factors are broken down into knowledge-based, rule-based, and skill-based behaviors.

In the amendment RCA work by Zarbo et al. [8], four main categories of error were determined which include reporting, patient identification, specimen, and interpretive errors [13].

## *Models of Error Causation*

There are two popular models of error causation: the Swiss Cheese Model and Heinrich's Safety Pyramid.

The Swiss Cheese Model (Fig. 3.1a, b) illustrates how patient harm is often the result of several errors, either latent or active, that occur in each step of the care process [14]. In this model, each step in a work process is represented by a single slice of Swiss cheese. The "holes" in the cheese represent latent or active defects.

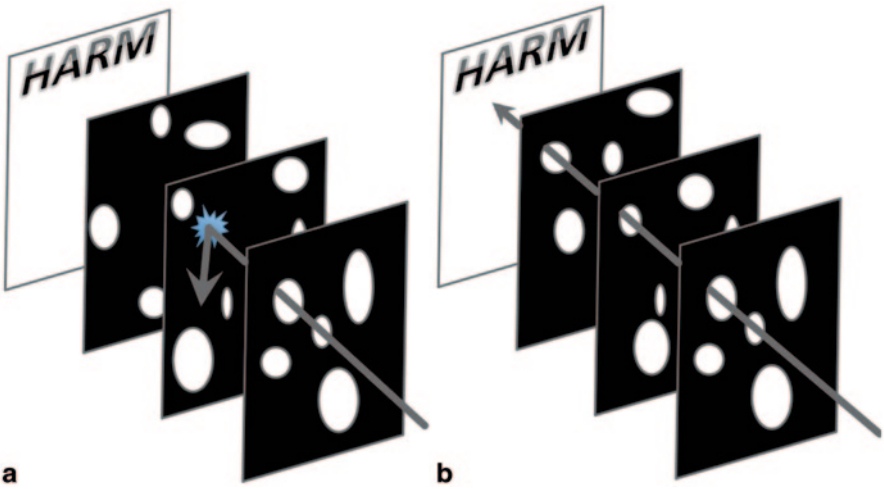


**Fig. 3.1** The Swiss Cheese Model of error causation. Each slice of cheese represents a step in the health care process. The "holes" represent errors in each individual step, either active or latent. Some of latent holes are relatively consistent. The active holes may open and close depending on worker behavior. **a** Most errors result in a near-miss event as the subsequent step recognizes the threat and disarms it. **b** Rarely, defects in all the steps line up and provide access to the patient for harm. (Adapted from Reason [14])

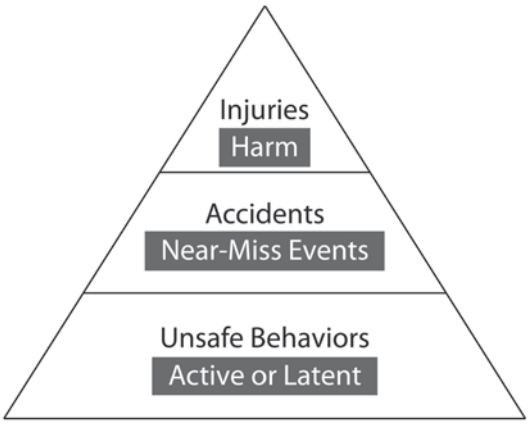


**Fig. 3.2** Heinrich's Safety Pyramid. Heinrich's original concepts are in *black* text. Updated concepts are in *white* text illustrating how active and latent conditions in a system can lead to near-miss events, which ultimately have the potential for patient harm if not caught and corrected. (Adapted from Heinrich [16])

Most often, errors that occur in one step are caught and corrected before reaching the patient with a resulting near-miss event. However, when multiple errors across several steps line up, there is access to the patient for harm. One of the benefits of this model is that it helps focus investigation of defects on the health care system as opposed to the individual. Although the model is well known in the quality literature, there is no agreement among quality and health care professionals as to all the details of the metaphor [15].

Heinrich investigated safety and accident causation in the industrial field and developed the Safety Pyramid, which is often referred to as Heinrich's Safety Pyramid (Fig. 3.2) [16]. His original theory was that the base of the pyramid consisted of unsafe behavior by workers. This widespread unsafe work occasionally led to accidents in the workplace, the middle tier of the pyramid. Finally, these accidents rarely led to severe workplace injuries or death, the top of the pyramid. He postulated that focusing on safe workplace behaviors (the base) would in turn decrease the frequency of accident and risk of severe injuries or death in the workplace. Heinrich's focus was on the worker and unsafe, acts and this has led some to refute the usefulness of the Safety Pyramid, claiming unsafe acts are not the principle cause of accidents and, furthermore, that decreasing accident frequency will not reduce severe injuries [17]. However, updating the pyramid with a more current theory of active and latent errors as the base, near-miss events as the middle tier, and patient harm as the top tier results in a refined and current Safety Pyramid for health care.

## *Human Behavior*

While the preceding models of error causation help to direct the investigation of the system in which workers are functioning, human behavior must also be addressed. The spectrum of human behavior and how it is managed has a direct affect on the ability of an organization to learn from their mistakes. One of the more popular

systems, and one used by other industry such as aviation, is the fair and just culture [18–20]. The goal of the fair and just culture is to create a culture that is focused on education rather than blame when errors arise. In the fair and just culture, the analysis of each error begins first with an analysis of the contributing active and latent components. The active components relate to the individual human choices being made in the work place. Choices may result in human error—defined as lapses, slips, and mistakes; risky behavior—defined as behavior choices where the actual risk is underestimated or the behavior is justified; and reckless behavior—defined as a willful disregard for standard operating policy with knowledge of the risks. Each of these behavioral choices requires a different managerial strategy in order to propagate a fair and just culture. For example, human errors may be best handled with consoling the worker, while reckless behavior may require corrective action, including termination.

## How Errors May Be Reduced

General principles and definitions for medical error have been discussed. This next section focuses on general concepts regarding error reduction. Types of error detection are reviewed, followed by strategies for error reduction, both in technical and cognitive areas of the laboratory.

### *Error Detection Methods*

There are a variety of different error detection methods available, and most laboratories use a combination of several different techniques. Before discussing specific techniques, some general comments are warranted. Passive, retrospective error detection is easily the most common method used by most laboratories [8, 21]. In this setting, the laboratory passively waits for prior results to be questioned or flagged as a potential error. This detection method severely underestimates the true error rate of the laboratory. One reason for this is the difficulty in linking pathology services to patient outcome. Take the example of a tubular adenoma diagnosed in an incorrect patient discussed earlier. This patient may come back earlier than needed for repeat surveillance colonoscopy, which will be negative. There is nothing to prompt re-review of the originally incorrect diagnosis and outside of an unnecessary procedure; the patient suffers no ill effects. Examples of this type of detection method include errors identified at conferences, tracking revised reporting such as addenda and amendments, random review, cytological–histological correlation, and frozen-section diagnosis discrepancy. This technique is in contrast to prospective active surveillance for errors, a technique rarely used in laboratory medicine because of its perceived cost. However, active error detection has the potential to identify a vast number of errors that would otherwise have been missed [5].

Many departments randomly review 10% of their cases for accuracy. Some have argued that a focused review would be more effective, targeting traditionally difficult cases, such as prostate needle core or transbronchial biopsies that are reported negative by the first pathologist. Cytological–histological correlation is another type of retrospective review, but is not passive. These cases are actively sought out to correlate the subsequent histology with initial cytology specimens. Because amendments are typically unexpected changes to the report, many laboratories will review cases with amendments as a way to screen for errors [8].

Clinicians likely drive many of the true medical errors discovered in pathology. This might be done informally with a personal phone call or formally through a standing pathology conference. Either way, it is the clinician recognizing that the diagnosis rendered does fit with the clinical picture. If the pathologist had access to all the clinical information, he/she too would likely have recognized the clinical discrepancy. Unfortunately, pathologists far too often have little to no clinical history when reviewing specimens.

## *Error Reduction*

A fundamental key to error reduction is an RCA on each error identified in the laboratory. There are a variety of different tools available for performing an RCA, including Five Whys, the Eindoven method, and the no-blame box.

The Five Whys method is designed to dig deep into a problem in an attempt to find the true source of the problem. Once the true source of the problem is identified, corrective action should be more effective. For example, if a histologist makes a microtomy error and places a patient specimen on an incorrectly labeled slide, the investigator would perform a Five Whys analysis:

1. Patient identification mix-up at microtomy. Why?
2. Histologist picked up the wrong slide. Why?
3. There were several patient slides in the work area at once. Why?
4. The histology laboratory practice is to preprint all hematoxylin–eosin slides before microtomy. Why?
5. The laboratory manager only purchased one slide printer due to cost constraints. Why?
6. Decision was made prior to a critical interest in patient safety.

Sometimes, the Five Whys analysis will reach an RCA that cannot be solved. In these settings, it is advised to solve the problem at the deepest “why” possible.

Raab et al. [22] developed the no-blame box (Fig. 3.3) for assisting in the RCA during cytological–histological correlation. The no-blame box was developed because pathologists and cytologists could not agree on the “interpretability” of the specimens. The tool helps cytologists recognize and standardize their approach to the “interpretability” of cytological specimens and recognize that the RCA of some cases lies beyond that of the interpreting cytologist.

The Eindoven method, discussed in the first section, is another way to classify errors. In addition to classification, this method helps guide the user to other potential

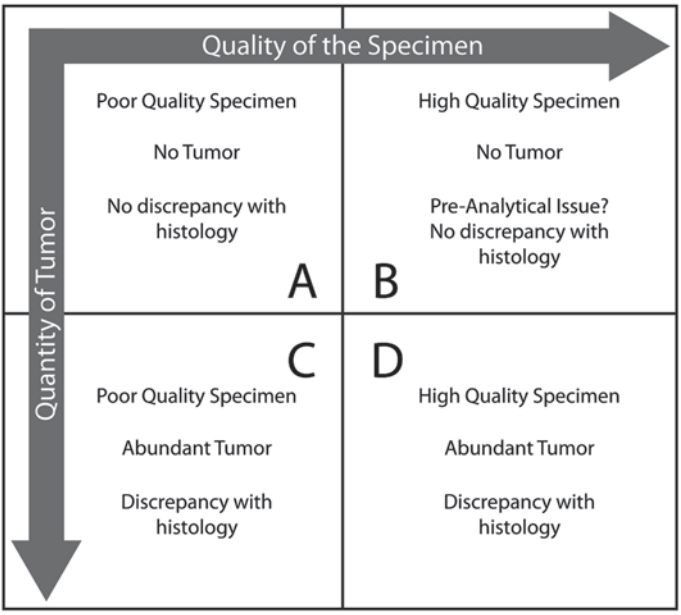


**Fig. 3.3** The no-blame box as a tool for root cause analysis in cytological–histological correlation. (Modified from [30])

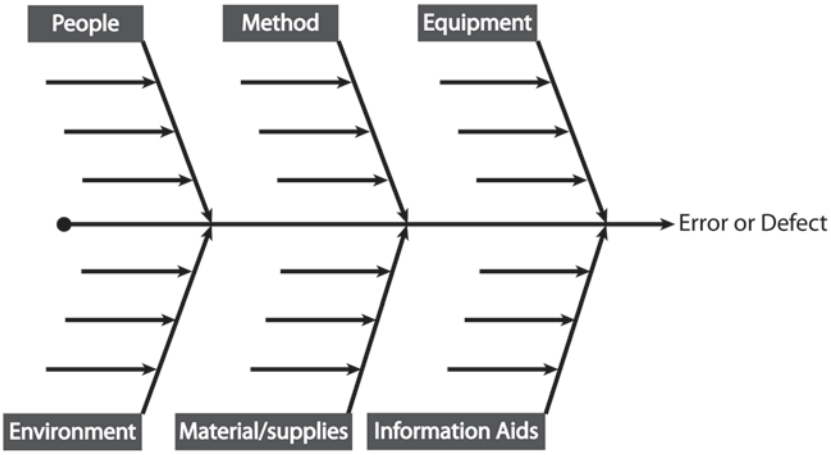


**Fig. 3.4** The fishbone diagram is designed to be a brainstorming tool to uncover domains that may be contributing to the error

contributions to the error in the latent (technical, organizational) and active domains (knowledge-based, skill-based, rule-based) [23].

The fishbone diagram (Fig. 3.4) is a brainstorming tool designed to assist the user to critically analyze six key domains as potential contributors to an error. This

tool is a great starting place after an error has occurred and works well when filled out as a group with frontline staff and pathologists alike. The error is written at the right hand side and then each domain (people, methods, equipment, environment, material/supplies, and information aids) is evaluated for a possible contribution. In the final analysis, the cause of the error is often found to be multifactorial.

## *Quality Improvement Methodologies*

RCA, reviewed previously, is a key component to any quality improvement methodology, of which there are several. Despite the vast number of different methods, there are many similar and overlapping methodologies.

"Lean" is a production practice that considers any work that does not add value to the product or service is wasteful and should be eliminated. Value is defined in terms of the customer, and therefore, value is anything a customer is willing to pay for. Patients, as customers of the healthcare system and pathology services, are willing to pay for a correct diagnosis that is based on their own tissue (not mixed up with a second patient) and is rendered on a timely fashion. Clinicians are also willing to pay for similar quality pathology services. Pathologists are customers of the technical processing components of our laboratories. With regard to value, pathologists are likely willing to pay for adequate grossing and sectioning, timeliness, accuracy, and confidence in the process.

Liker, in his 2004 book, described 14 principles that helped Toyota function as a lean organization [24]. Spear and Bowen distilled the essential philosophies of Toyota management by describing four fundamental rules [25]. Because of the importance of the customer in lean, we have added the customer rule.

1. The Customer Rule: The needs and desires of your immediate and ultimate customer must be at the forefront of why you are performing your work. There are levels of customers in an organization, immediate and ultimate customers.
2. The Activity Rule: All activities should be highly specified as to content, sequence, timing, location, and outcome. The activity rule is synonymous with standardization.
3. The Connection Rule: The handoff between two people or machines must be direct, and there must be an unambiguous yes-or-no way to send requests and receive responses. This allows for clear communication between people and groups. An example of a failure in connections is when there is no clinical information included on a specimen requisition form.
4. The Pathway Rule: The pathway for every product and service must be simple and direct without loops or forks. A clear path also ensures everyone connected is essential and value added.
5. The Improvement Rule: Any improvement to activities, connections between workers or machines, or pathways must be made in accordance with the scientific method, under guidance, and as close to the actual work as possible.

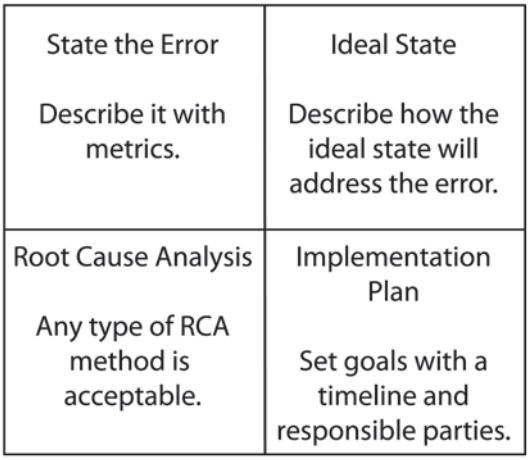


**Fig. 3.5** An A3 is a problem-solving tool that can be used to address medical errors. The problem is described in the *upper left*, a root cause analysis is done in the *lower left*, the ideal state is described in the *upper right*, and the implementation plan is outlined in the *lower right*

These philosophies provide a backdrop to discuss various tools that have been developed to help bring lean philosophy into practice. It should be emphasized that implementation of the tools alone, without a background philosophy as to why the tools are being used, is a worthless activity, as no real meaningful change will take place. The tools must be used in a context of the basic lean philosophies and in an appropriate and accepting organizational culture.

A3s are the problem-solving tool used by Toyota and other lean organizations. They allow for all essential aspect of a problem to be represented on a single sheet of A3-sized paper (Fig. 3.5). The sheet is divided equally into four parts. In the upper left quadrant, the problem is described, including any data metrics. In the lower left quadrant, an RCA is done. In the upper right quadrant, the ideal state is described. Finally, in the lower right quadrant, the implementation plan is outlined, including the metrics to be followed and responsible parties.

Observation is a powerful tool for process improvement. Observation can be done either directly or indirectly and may be performed by staff familiar to the activity or staff completely unfamiliar to the activity. All these situations offer distinct advantages. For example, direct observation by an observer unfamiliar with the process can shed an entirely new perspective on why and how particular steps in a work process are performed. Observation is one of the most powerful lean tools and is actively used by management in lean organizations on a daily basis. It is also a tool that can make workers uncomfortable and represents a significant investment by an organization in terms of staff time. Therefore, unfortunately, it is a tool often overlooked.

Spaghetti diagrams are tools used to focus on the pathway a product or service might take through a work process. They can help highlight loops and forks in a process that create waste and potential for errors. A spaghetti diagram starts with a plan view of the workspace, and then every time a product moves, the movement is tracked on the diagram. Anytime a line crosses or has to fork, an opportunity for waste elimination is observed.

Continuous flow manufacturing (CFM) is a just-in-time manufacturing process that minimizes batch processes and waste as it exposes inefficiencies in an effort to manufacture a single given product at a given time. Benefits of CFM include built-in quality, which means patient safety engineered into the process; rapid discovery and immediate RCA on active errors; improved efficiency; promotion of standardization of activities; creation of transparency; faster turnaround time; decreased floor space requirements; and improved morale. Built-in quality refers to the systems engineering that builds quality into the work process itself, including self-checks and successive checks [26].

DMAIC is a quality improvement methodology and stands for *d*efine, *m*easure, *a*nalyze, *i*mprove, and *c*ontrol. This is an overarching method that gives freedom to incorporate tools from other methodologies, such as lean. This method is used by several large manufacturing companies and is the method of choice for the Mayo Clinic Quality Academy.

Plan-Do-Study-Act (PDSA) is a repetitive practice to achieve the ideal state. It is understood that implementation may have unintended consequences or may not reach the stated goals. In the PDSA cycle, each successive test of change is evaluated and further action is undertaken.

Six Sigma is an ambitious quality tool where the methodology is really focused on a goal of reaching Six Sigma without defects. That results in only 3.4 defects per million opportunities. Although more widely used in industries, some aspects can be applicable to high-throughput testing like routine blood and chemistry testing in the clinical laboratory.

## *Interpretive Error Reduction*

As with technical tasks, cognitive tasks also may be deconstructed into more basic components. For anatomic pathologists, the main cognitive task is diagnosing disease. Novice pathologists learn to diagnose disease by learning to recognize individual diagnostic criterion found in a specific disease. The combinations of criteria are the patterns of disease. Although the patterns of different diseases may overlap, expert pathologists either are able to identify specific diseases based on the unique presence of some criteria or are able to identify specific cases that need ancillary information (such as results of immunohistochemical or laboratory studies) that facilitate classification.

In the early learning process, novice pathologists first look carefully at slides and identify individual criterion and patterns and assimilate other information. This is the process of learning criteria and pattern recognition. Daniel Kahneman characterized this cognitive process as *slow thinking*, which consists of a rational, deliberate, methodical, and logical process of reaching a solution to the problem of accurately classifying the disease [27].

As pathologists become more experienced, they see the criteria and patterns quicker, and the diagnosis becomes more based on pattern recognition than on assessing individual criterion one by one. In the process of pattern recognition, we use a heuristic, or a mental short cut, to move from criteria to pattern to disease. A pathologist will quickly recognize that a specific pattern is present and cognitively jump to the conclusion that the associated specific disease also is present.

Heuristics are simple, efficient rules, which explain how people make decisions, come to judgments, and solve problems, typically when facing complex problems or incomplete information. Kahneman characterized this cognitive process as *fast thinking*, which we use most of the time, each day. A typical example of fast thinking is in driving a car. Experienced drivers watch for patterns and do not consciously and rationally evaluate every step in the driving process. If experienced pathologists encounter a challenging case, they may move away from fast thinking to slow thinking and more rationally analyze the criteria and patterns of a case. In this example, they may recognize that the pattern that they see does not match with a specific disease and that they need to think more carefully about the information before rendering a definitive diagnosis. Causes of pathologist cognitive error include failures in attention, memory, knowledge, and heuristics (also known as bias). A bias in pathologist cognition is when the rules of pattern recognition fail and the correct link between the pattern and the diagnosis is not made. For example, *recall bias* occurs when a pathologist makes a diagnosis that is strongly influenced based on the recent memory of having seen a case with that specific diagnosis. Kahneman recommends that individuals should use a process known as reference range forecasting to limit bias. In this cognitive process, an individual uses slow thinking and moves away from fast thinking (pattern recognition) to more fully evaluate a specific case [27].

## Conclusion

The general principles of how errors occur and how they can potentially be prevented have been reviewed. Because of the negative connotation related to error and litigation risk, there is a serious challenge with regard to reporting of errors and transparency. This is a necessary first step in the quest for laboratory systems to reduce error and improve quality. That is why we need leaders, as Zarbo suggests [28], to help move the field forward. But the leaders have to be empowered to act and make change. For this to occur, laboratory leadership also needs to focus on tort reform and on building the case for change. With recent changes in health care, it is possible that reimbursement will be linked with quality [29]—a step that would immediately make a case for change.

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# Part I
# Pre-analytic Factors Contributing to Errors and Error Prevention

# Chapter 4
# Error Reduction in the Preanalytical Process

**Richard W. Brown**

## Background

Historically, the histology laboratory has not been regarded as a significant source of error in anatomic pathology; the focus has been primarily on errors in diagnosis. However, the production of a microscopic section for pathologist review and diagnosis is a complex, error-prone process with many handoffs and manual processes, including specimen accessioning and grossing, tissue processing and embedding, the cutting and flotation of tissue sections onto microscopic slides, and the process of slide "sign-out," in which the microscopic slides are reviewed for quality, matched with typed gross descriptions, and distributed to the pathologist. As these processes occur before the pathologist reviews the case microscopically and determines a diagnosis, they have been collectively termed the "preanalytical" phase [1].

Troxel was among the first to call attention to preanalytical processes as a source of error. In a review of pathology malpractice claims from 1998 to 2003, he documented a significant increase in what he termed "operational errors" as the cause of the claim, 8 versus 1.2% in a prior study of claims from 1995 to 1997 [2, 3]. Among these, the most common error leading to misdiagnoses was a specimen mix-up between two patients followed by the presence of extraneous malignant tissue from another case, lost tissue, and mislabeled slides; others have affirmed these categories of error as of greatest clinical importance [4, 5]. In contrast to earlier studies that focused on the analytical phase (i.e., diagnostic errors), in a survey of 34-member laboratory directors from the Association of Directors of Anatomic and Surgical Pathology, published in 2006, 53% of the respondents indicated that most of the errors in anatomic pathology occur in the preanalytical phase [6].

R. W. Brown (✉)
1System Laboratory Services, Memorial Hermann Healthcare System,
7600 Beechnut, Pathology, 2nd Floor, Houston, TX 77074, USA
e-mail: Richard.brown50@memorialhermann.org



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The most comprehensive data regarding preanalytical errors has been gathered through the Q-Probes studies of the College of American Pathologists. In a study of 1,004,115 cases from 417 institutions, 6% of the cases were reported to have defects in specimen identification and accessioning [7]. A subsequent study of 427,255 cases from 136 institutions documented a rate for misidentification and/or mislabeling of 0.11%, with a rate of 0.1% for specimens, 0.17% for tissue blocks, and 0.11% for slides [8]. This study noted that errors occurred most frequently at the time of accessioning, when transferring tissue into blocks and when sections were cut and transferred onto glass slides, and also documented that laboratories in which specimens were handled one at a time had a lower frequency of mislabeling errors. Finally, a study of 321,577 retrospectively reviewed and 57,083 prospectively reviewed slides from 275 laboratories documented extraneous tissue in 0.6 and 2.9% of slides examined, respectively [9].

Meier et al. in a review of amended reports developed a "taxonomy" of defects that included: (1) misidentification (patient, tissue, laterality, or anatomic localization); (2) specimen defects (lost, inadequate size/volume, absent or discrepant measurements, inadequate representation); (3) misinterpretation; and (4) report defects. In that study that documented an amended report rate of 4.8/1000, misidentification and specimen defects, the preanalytical variables, accounted for 19 and 9%, respectively, of the amendments; in a later multi-institutional validation study, these defects caused 20–38% and 4–10% of the amendments [10–12]. In an 18-month study encompassing 29,479 cases, Layfield demonstrated a 0.25% rate of mislabeled cases, 0.068% mislabeled blocks, and 0.030% mislabeled slides [13]. The majority of the errors were made in the grossing room by a grossing assistant. Of the 75 labeling errors, 13 (17%) could have substantially harmed the patient, if not identified. Changes in pathology practice, such as the advent of laboratories processing only one specimen type (e.g., gastrointestinal or prostate biopsies) have introduced a greater potential for misdiagnosis of malignancy because the opportunity to identify an error based on mismatched tissue types is eliminated. Indeed, a recent study by Pfeifer et al. of 13,000 prostate needle biopsies from 54 laboratories, studied prospectively with a molecular assay to confirm patient identity, identified a rate of transposition between two patients of 0.26% (0.06–0.37%), and a rate of tissue contaminant from another patient of 0.67% (0.27–0.93%) [14].

In general, the first step in error reduction is in the identification of process issues and their prevalence. Individual occurrences can be mapped effectively through the use of root cause analysis or failure modes and effect analysis [1, 15–17]. Direct observation can also identify key defects; one observational study of specimen accessioning and grossing documented a remarkable 5.5 near-miss events (errors identified during the process) per specimen [18]. Zarbo and colleagues at The Henry Ford Hospital have emphasized the utility of blameless error self-reporting and implementation of the Henry Ford production system, with short-term focused review of practices, as a method for identifying process defects [19, 20]. In their initial study, 27.9% of surgical pathology cases contained defects, leading to an amended report rate of 2.4%; these defects included issues with specimen receipt (8.3%) but much more commonly in accessioning (24.9%), gross examination (20.0%),

and production of histologic slides (30.8%) and recuts (13.4%). This study also documented identification defects in 1.67% of cases with mislabeling of slides and blocks accounting for 78% of these defects.

Nakhleh has focused attention on process issues leading to laboratory error and those issues particularly applicable to histology laboratories, including: (1) variable input, (2) complexity, (3) inconsistency in training and procedures, (4) the need for human intervention, (5) time constraints, (6) frequent handoffs, and (7) an inflexible hierarchical culture that is unable to adapt and change or to acknowledge the source of errors [21, 22]. He proposed a number of global error reduction strategies, including:

- Built-in QC processes that decrease reliance on vigilance
- Use of standardized operating procedures
- Simplification of processes, with a specific effort to reduce the number of handoffs
- Implementation of processes to detect errors
- Attention to human resource issues, including adjustments in work schedules, in order to minimize time constraints, adjustments to the workplace, in order to minimize distractions, adequate training, and assuring that staff with the proper skill set are assigned to each position

Raab and colleagues have demonstrated the efficacy of a lean-based quality improvement program, which allowed that group to decrease near-miss events in the preanalytical workflow from 5.5 per specimen to 1.8 [23]. More recently, there has been significant focus on the use of barcodes, assigned at the time of accessioning that can be applied to, and read from, all tissue cassettes, paraffin blocks, and microscopic slides that are derived from a specimen, providing unambiguous identification throughout the entire histology process [24, 25]. Zarbo and colleagues decreased their misidentification rate from 1.67 to 0.63%, including a 95% reduction in glass slide misidentification, through the use of a bar-coded system accompanied by process redesign [24]. Radiofrequency devices have received similar attention for specimen tracking [26]. While these innovations can significantly reduce the preanalytical error rate, they are in place at a relatively small number of laboratories; therefore, the discussion that follows focuses on manual processes, considering each of the steps in the preanalytical process, the potential sources of error and error reduction strategies.

## Accessioning and Grossing

### *Potential Sources of Error*

The preanalytical process in surgical pathology begins when the specimen is received in the frozen section or histology laboratory, and is accessioned into the laboratory information system. The first opportunity for specimen mishandling, and

therefore the error, is in the operating room, physician office, interventional radiology or endoscopy suite from which the specimen arises. The practice of preparing specimen containers and labels prior to a procedure is common, and therefore, there is significant opportunity to pair a specimen from patient B with the labels from patient A who was previously in that room. One study from a large surgical service documented an error rate of 4.3/1000 specimens with unlabeled specimens, empty containers, incorrect laterality or tissue site, incorrect patient, no patient name, and no tissue site identified representing the most common errors [27]. While it is possible to effect error reduction through strict adherence to a policy that requires a matching of two patient identifiers at every step of the process and accountability in the form of requirements for provider initials on the specimen container to verify proper identification and the presence of tissue in the container, in reality these processes are beyond the control of the laboratory [28]. Therefore, the true opportunity for error reduction begins at the time of accessioning.

When specimens are received in the laboratory, the specimen identification on each container should be rigorously matched with the specimen requisition, with confirmation that there is a match in the patient using two patient identifiers and an exact match in the specimen source. Failure to do so introduces an opportunity to assign one or more specimens to the wrong patient, a serious error if a malignant diagnosis is involved. Similarly, if the accessioning personnel do not carefully match the patient name and a second identifier, typically date of birth or medical record number, it is possible to erroneously accession the case to the wrong patient, one who shares a name with the index patient. When the accessioning is complete, there should be a unique case number associated with specimens from one patient as well as a unique alphanumeric designation for each part of that accession. For example, a uterus with separately submitted adnexa might be accessioned as S-year-unique number (e.g., S-13-4506) with parts A (uterus), B (right fallopian tube and ovary), and C (left fallopian tube and ovary). Another opportunity for error exists when the specimens are not correctly matched with the alphanumeric designation.

The next step in the process of accessioning is the labeling of tissue cassettes. There are three essential elements to a cassette label: the case number, the alphanumeric designation of the specimen, and a sequential label for each cassette within that specimen. The latter should then be specifically identified in a gross description. For example, a cassette labeled S-13-4506 A1 in the example above might contain sections of uterine cervix while S-13-4506 A2 might contain a section of uterine serosa, and S-13-4506 B2 a section of fallopian tube. Incorrect cassette labeling, with a failure to detect the error at the time of tissue submission, can result in an incorrect diagnosis, when, for example, cassette A1 in a cancer resection contains a surgical margin and cassette A11 does not.

Perhaps, the greatest opportunity for error is in the process of submitting tissue for microscopic examination (“grossing”). The prosector could potentially: (1) erroneously submit tissue in a cassette belonging to a different patient (tissue from case 4506 submitted in a cassette labeled 4507), (2) submit tissue in the wrong cassette within a case (in the example above, the margin is submitted in A11 instead of A1), or (3) inadvertently submit extraneous tissue. The latter typically occurs when

the prosector is submitting tissue from more than one case at a time, or when the workspace and instruments have not been adequately cleaned after each accession, providing an opportunity for inadvertent tissue carryover from case to case. Finally, error can occur as the result of inadequate dictation of the macroscopic findings as they relate to the tissue cassettes submitted. Common errors in this category are failure to unambiguously identify each of the surgical margins with ink of a designated color in cancer resection cases, and failure to provide a "section code" that links each tissue cassette submitted to a particular tissue site or lesion.

## *Strategies for Error Reduction*

- At the time of accessioning, each specimen container should be matched to the requisition. Both the tissue source and the patient name and second identifier (medical record number, date of birth) must match exactly. If they do not or if a specimen container is received unlabelled, the submitting nurse or physician should be notified immediately and the inconsistency resolved; any delay in this notification will likely result in the inability to adequately resolve the discrepancy, as the labeling staff may no longer be on duty. Cases with incorrect data should never be accessioned until the inconsistency has been addressed, either by a correction or by a discussion with the submitting physician. This resolution should be documented in an error log maintained either in written form at the bench or in the laboratory information system (LIS). In addition, all specimen containers should be visually inspected for the presence of tissue and, if tissue is not present, a similar approach to remediation and documentation should be applied.
- Accessioning personnel must be trained to check each patient's full name, as it appears in the LIS, and a second unique identifier against the requisition and specimen container as the case is entered to ensure that the case has been accessioned to the correct patient.
- Tissues of the same type (e.g., prostate or breast needle biopsies) should not be accessioned sequentially. This significantly decreases the likelihood for diagnostic error, in that, if there is an error in submitting the tissue between two cases, the different tissue type involved should be readily apparent. It is recognized that there will always be cases in which this is not possible (e.g., GI, skin, or prostate biopsy only laboratories). In these instances, use of colored inks or alternating color cassettes may be of similar utility.
- Best practices in cassette labeling include: (1) using an automated cassette printer linked to, and driven by, the LIS; (2) labeling each case as it is grossed, rather than labeling multiple cases and lining them up with the containers in advance; and (3) including a full or partial patient name on each cassette. It is recognized that these may not be achievable goals in every laboratory.
- Tissue cassettes that have been prelabeled should be checked for accuracy by both the grossing assistant, if applicable, and by the prosector, matching both the

accession number and the alphanumeric designation before the tissue is placed into the cassette.
- Only one case should be grossed at a time. At the conclusion of the case, all paper towels or pads on which the tissue was grossed should be discarded, and all instruments carefully cleaned and wiped dry to avoid contaminants. All unused tissue cassettes from that case should be discarded.
- Small biopsies should not be transferred to the cassette using forceps. A lens paper or mesh bag should be inserted inside a funnel and the specimen contents should be poured directly into the paper or bag; this practice essentially eliminates the possibility of introducing contaminant tissue.
- For cases with multiple cassettes containing different tissue types or sites, the gross description should include a section code designating the origin of the tissue in each cassette. For complex cases, it is prudent to write the section code as sections are submitted and dictate the code at the conclusion of the case. For tumor cases with margins, an ink code should also be included that matches the ink colors with the margin they are meant to designate.
- The laboratory should maintain a written log that specifies the number of blocks taken from each specimen, the type of tissue they contain; and, if these logs are available to embedding and sign-out personnel, the number of tissue pieces submitted. Any special instructions (e.g., decalcification) should be included as well.

## Tissue Processing and Embedding

### *Potential sources of Error*

After the process of specimen grossing and tissue submission, tissue cassettes are processed through dehydrating solutions and paraffin. In most laboratories, this is accomplished by automated tissue processers that are driven by a user-defined processing schedule. The paraffin-impregnated tissues are then re-embedded into the same tissue cassettes in which they were submitted, with additional paraffin as needed, in order to provide a tissue surface that can be subsequently trimmed and sectioned by the histotechnician performing microtomy. With the increasing number of multi-site laboratories, it is increasingly common for tissue cassettes to be transported to a core laboratory for processing. There are three major opportunities for error in these processes: (1) tissue is lost, either a portion of tissue within a single cassette or one or more tissue cassettes in their entirety, (2) tissue cannot be adequately examined microscopically due to inappropriate tissue processing, and (3) extraneous tissue (i.e., tissue from another patient) is introduced inadvertently. In general, tissue cassettes are fenestrated, with parallel slits or small, round holes that allow processing fluids to flow freely through the cassette. Although these fenestrations are of small diameter, it is theoretically possible for minute tissue fragments to

flow into or out of a cassette during processing, leading to a loss of tissue or gain of extraneous tissue fragments. Much more commonly, however, these misadventures occur at the time of embedding, when the embedding personnel do not carefully observe the number of tissue fragments to be embedded, work on more than one case at a time, and/or do not rigorously clean the embedding forceps between cases. Tissue processing is beyond the scope of this discussion; however, for purposes of error reduction the avoidable sources of error leading to loss of tissue integrity, and therefore, the potential for an erroneous interpretation due to poor visualization of microanatomy, include: (1) submission of tissue of inappropriate size, (2) inadequate time in formalin fixative prior to processing, and (3) failure of personnel loading the tissue processers to recognize that a tissue is of inappropriate type for the processer onto which it is loaded (e.g., a small biopsy processed using a schedule intended exclusively for large tissues).

## *Error Reduction Strategies*

- Prosectors should be instructed to never submit portions of tissue greater than 1 cm in diameter or greater than 2–3 mm in thickness. Unless the processing schedules are very long or microwave-assisted fixation is employed, it is unlikely that tissue larger than this will adequately fix and process. Personnel assisting the prosector, if applicable, should be empowered to not accept a tissue that exceeds a size and thickness predetermined to be acceptable by that laboratory.
- Biopsies should be submitted either in a filter paper/bag or in a cassette specifically designed for smaller tissues in which there are small holes rather than slits.
- Tissue cassettes should be matched against the log sheet generated at the time of grossing to ensure that the number of cassettes being loaded (and their accession labels) matches the log sheet exactly. When specimens are transported between two sites, this matching process should occur both at the site of origin and when the cassettes are received at the core laboratory.
- Most laboratories maintain separate processing schedules for small (biopsy) and large tissues. The personnel loading cassettes should visually inspect the cassettes to ensure that the tissue size is appropriate for the processor being loaded. In addition, if the submitted tissue appears inappropriately thick or large, this cassette may be returned to the prosector for remediation prior to processing.
- Tissues likely to shed minute fragments, particularly friable tumors and placentas/products of conception, should be processed apart from other tissues whenever feasible, either on the last processing run or on a dedicated processer. Similarly, these tissues should be embedded last or at a dedicated embedding station in order to minimize the possibility for cross contamination.
- The laboratory should maintain and enforce strict embedding policies that include: (1) only one cassette should be open at any given time during the embedding process, (2) forceps must be carefully cleaned between cases (and within a case if friable or minute tissues are involved), and (3) any tissue fragment that

cannot be unambiguously assigned to a given case (e.g., a fragment found on the exterior of a cassette or within the paraffin pot of the embedding station) should be quarantined to a separate cassette designated "floater" for embedding and microtomy. It is then the responsibility of the medical director or pathologist designee to determine microscopically the origin of this tissue relative to the cases examined.

- When a cassette is found to contain no tissue or a cassette is missing at any step in processing and embedding, a search for the tissue should be immediately initiated. While not feasible in all laboratories, it is a best practice to retain the trash from the grossing, processing, and embedding areas within the laboratory for up to 3 working days in order to facilitate the search for missing tissue, should the need arise. Similarly, all specimen containers that do not contain residual tissue should be retained at least until a case has been finalized.
- In larger laboratories, it may be useful to identify, by means of initials or alternate code, the individuals responsible for loading cassettes on processors and embedding cassettes in order to facilitate investigation of problems encountered subsequently. This may be accomplished by initialing log sheets or, in the case of embedding, by including a small piece of paper with the name or ID of the embedding technician in the paraffin block.

## Tissue Sectioning and Staining

### *Potential Sources of Error*

Two potential errors dominate this portion of the histology process: a mismatch between the paraffin block and slide, a so-called "cutting" or "floating" error, and the introduction of extraneous tissue. In the workflow of most laboratories, a histotechnician brings a tray of paraffin blocks, which may contain multiple cases, to their microtome workstation. At that workstation will also be sets of microscopic slides that typically will have been prelabeled by an automated system that derives the label from a barcode and prints the slides, either at a central unit or ideally at each workstation. In many laboratories, however, slides are hand labeled, either in advance or at the time of cutting. The technician then faces each paraffin block and obtains a "ribbon" of tissue embedded in paraffin that is floated on the surface of a water bath. The tissue ribbon is then "picked up" or "floated" from the water bath onto the correspondingly labeled microscopic slide. If at this point the technician fails to meticulously match the case number and block designation between the block and the slide, it is possible to mix up slides between two patients or within a case. It is not difficult to imagine how a technician with a stack of sequentially numbered biopsy blocks could pick up a slide for case number 2001 and float a section from case 2002 onto it, potentially leading to a diagnosis of cancer on the wrong patient. Similarly, if 2001 block A1 that represents a surgical margin is inverted

with 2001 A11, a representative section of tumor, the potential to erroneously assign a positive margin necessitating reexcision is significant.

When a section has been floated onto the glass slide, the remainder of the wax-embedded tissue must then be removed from the surface of the water bath. As changing and subsequently heating the water in the flotation baths to the correct temperature represents a significant disruption to workflow, this is rarely done in the course of a shift; therefore, failure to carefully remove residual tissue before sectioning the next block can lead to significant opportunity for cross contamination with "extraneous" tissue. This is quite likely an underreported event as most pathologists will ignore non-malignant extraneous tissue fragments. For example, in the large study by Layfield et al., a retrospective review of reports made of extraneous tissue encompassing 521,661 slides examined, revealed a rate of 0.01 % [29]. In contrast, when 1000 slides were prospectively reviewed for contaminants the rate was 1.2 %, of which approximately 60 % were attributable to contaminants from the surface of the water bath. Similarly, in the earlier Q-Probes study, when extraneous tissue was specifically sought in a review of the entire slide the rate was 2.9 versus 0.6 % in routine practice [9].

In the final step of microscopic slide production, the tissue is deparaffinized and stained with hematoxylin and eosin, which in most laboratories is accomplished through manual or automated staining in a series of baths. This represents a final opportunity to introduce extraneous tissue onto a slide. A surprising study by Platt et al. using blank slides to demonstrate contaminants identified only one contaminant on the surface of a water bath, but in contrast identified 26 tissue fragments/bath in the staining set with the most contaminants occurring in the early xylene and alcohol baths. The rate of cross contamination of tissue fragments onto blank slides in that study was 8 % [30].

## *Error Reduction Strategies*

- Institute a strictly enforced cutting protocol that requires manipulation of only one block and slide at a time, and a visual comparison of the block and slide labels before and after cutting.
- Ensure that two identifiers, case number and patient name (minimally last name and first initial), are present on blocks and slides, and that the matching protocol includes visual inspection of both elements.
- Best practice is to generate microscopic slides one at a time by scanning a bar code on the paraffin block at the cutting workstation. In laboratories where this system is not possible, an automated slide labeler located centrally within the laboratory should generate the slides. The labeler should receive data directly from the laboratory information system (preferred) or, when that is not possible, from manual input. Handwriting of slides should be avoided to the greatest extent possible within the local setting.
- The laboratory protocols should include strict adherence to a carefully defined method for cleaning of the water bath surface between blocks and between cases.

Best practice includes random testing for contaminants with blank slides. There should also be a protocol that defines the frequency with which water in the bath is changed.
- To the greatest extent possible, the microtomist should handle a mixture of biopsy and resection cases of varying tissue types. This minimizes the potential for erroneously matching slides and blocks.
- Staining baths should be changed at a defined interval. Best practice would include random screening for contaminants with blank slides inserted at a proscribed interval.
- Poorly/underprocessed tissue presents the greatest likelihood for contamination as these tissues tend to "explode" into small fragments in the water bath, and to detach from the slide during staining. These tissue blocks should be reprocessed or "quarantined" to the end of a run, whenever possible.

## Slide Sign-out

### *Potential Sources of Error*

Completed microscopic slides are paired with the typed description of the specimen (gross description) in a process commonly referred to as "sign-out." Typically, the slides are also matched against a "tech sheet" completed at the time the sections were submitted to ensure that all slides from the case have been completed. Two potential errors can be made at this point. Single slides can be placed with the wrong case, and a set of slides can be matched with the gross description from another patient. The latter can produce a significant misdiagnosis if two cases of the same type (e.g., breast needle biopsy) are involved.

### *Error Reduction Strategies*

- All tissue sections should be visually inspected prior to release. The technician should confirm, through use of the tech sheet, that the sections appear to be appropriate to the tissue submitted. In addition, there should be a visual check for histologic quality at this time to ensure that no slides with poor staining, significant microtomy artifacts, or incomplete sections are released.
- The case number and a second patient identifier, typically patient name, should be carefully matched between the typed "protocol" containing the gross description and the slides. All slides should be matched to each other to exclude the possibility that one block has been cut onto the wrong slide.
- With needle biopsies of breast, lung, and prostate, in which malignant and benign biopsies are frequently juxtaposed, best practice dictates placing only one

case of each type in a slide tray. In some cases, this may be appropriate for larger tissues as well (e.g., transurethral resection of prostate or bladder, excisional biopsies of breast).

- Additional sections cut from a block on request from the pathologist present a unique situation. These cases add the complexity of pulling a paraffin block from the file; therefore, additional potential for error exists in the form of pulling and cutting the incorrect block. For these cases, the specimen number on the requisition should be carefully matched against the block and slides. In addition, best practice dictates that the tissue on the slides should be matched to the paraffin block at the time of sign-out to ensure that no mix-up has occurred.

## The Role of Control Tissues in Error Reduction

One of the most effective strategies to minimize diagnostic errors is to ensure that no inappropriately stained slide leaves the histology laboratory. Routine hematoxylin–eosin stained slides are rarely a problem with the near-universal use of automated staining systems. In contrast, histochemical "special" stains and immunohistochemical stains can vary considerably, particularly if they are performed manually or on tissues that vary significantly in size or tissue processing. An understained section can lead to a false negative result. An overstained section can result in a false positive by misinterpretation of staining that is in fact nonspecific. An obvious example of the former would be the absence of staining for microorganisms that are in fact present. A clear example of a false positive would be overstaining with a tissue-specific antibody like prostate specific antigen (PSA) leading to misinterpretation of a metastatic carcinoma as of prostatic origin, when in fact it is not. Routine use and careful examination of tissue controls to ensure that there is staining of the intended structures and absence of nonspecific staining by both the histotechnologist, before releasing the slide and again by the pathologist in the course of interpretation, will greatly reduce the risk of a misinterpretation.

### *Best Practices in the Use of Tissue Controls*

- To the greatest extent possible, controls should be present on every slide. This practice ensures that the stain is appropriate in that section. Obviously, this is not an obtainable goal for routine hematoxylin–eosin stained sections; however, this practice is possible for special stains and immunohistochemistry in all but the largest laboratories.
- Control tissues should be clearly identified either by placement within a preprinted box on the slide or with a line between the control and patient tissue accompanied by a "C" to designate the location of the control. This practice avoids misinterpretation of a positive control as a positive patient tissue, a significant possibility if the two tissues are of similar size and type.

- Each slide should contain control tissues that are known to be positive and negative for the tissue component or antigen being stained. In some cases, this can be accomplished by the use of a single tissue section. More commonly, a 2- or 3-tissue group or a multitissue array is employed for this purpose.
- Positive controls should contain relatively low amounts of the target structure or antigen in order to ensure adequate sensitivity of the staining procedure. For example, a stain for acid-fast bacilli should contain only sufficient organisms to be readily detected on high magnification. Tissues with numerous organisms visible at low magnification are not useful for the detection of subtle shifts in stain intensity. Similarly, controls for immunohistochemistry involving tumor antigens should be comprised of tumor tissues. The significantly greater amount of antigen present in normal tissues will be unstained only with a grossly inadequate technique.
- Positive controls should address all potential targets of the stain. For example, if a trichrome stain is used to assess both collagen and smooth muscle then both should be present in the control. The control for an immunohistochemical stain like p63 that identifies two or more cell types (e.g., squamous carcinoma, myoepithelial cells) should contain appropriate tissues for those applications.
- Negative control tissues should readily detect nonspecific staining. Tissues that are rich in proteins or organelles (e.g., mitochondria) prone to binding antibodies nonspecifically, such as kidney, partially necrotic, and collagen-rich tissues, are particularly useful in this regard.
- For immunohistochemistry, when a patient tissue contains large amounts of endogenous or exogenous pigment, large numbers of inflammatory cells, or high levels of endogenous biotin (the latter applicable only when immunohistochemical procedures include biotinylated antibodies), a section of the patient tissue should be subjected to the entire staining procedure except application of the primary antibody. This practice, commonly referred to as a "negative tissue control," allows the pathologist to readily distinguish a true positive result from spurious sources of apparent immunoreactivity.

## Extraneous Tissue as a Source of Error

Extraneous tissue is defined as a tissue in a microscopic section or paraffin block that does not originate from the patient whose tissue is under examination. As indicated earlier, extraneous tissue is an inevitable consequence of tissue processing and may arise from: (1) carryover at the time of macroscopic examination and dissection, (2) free floating tissue fragments in automated tissue processors, (3) carryover at the time of embedding, or (4) residual tissue on the surface of flotation baths.

The Q-Probes study published in 1996, using data from 275 laboratories, provided benchmark data regarding the frequency of this problem (0.6–2.9 %), and reported that only 6.1 % of laboratories had written protocols for documenting extraneous tissue in pathology reports [9]. Fortunately, in that study 87.3–94 % of contaminants

were non-neoplastic, 90.1–98.8% of the cases presented no diagnostic difficulty, and clinically significant cases causing severe diagnostic difficulty, such as malignant tissue that could have arisen from that site in an otherwise benign biopsy, were rare, comprising only 0.4% of the slides with extraneous tissue. However, although significant contaminants are uncommon, they require intensive investigation and a high degree of clinical suspicion to avoid a serious misdiagnosis [31, 32]. In most cases, the source of the extraneous tissue can be identified and is clearly not from the patient (endometrium in a prostate biopsy) or is clinically irrelevant (placenta in a colon biopsy). In those rare cases in which further investigation is needed, various techniques, including immunohistochemistry using blood type-specific antibodies, fluorescence in situ hybridization using probes to X and Y chromosomes, and molecular assays, most commonly using probes that identify single nucleotide polymorphisms or HLA-associated loci, can be employed [31, 33–35]. The procedure below provides a systematic method for investigation in the rare event that clinically significant extraneous tissue is observed.

## *Recommended Stepwise Investigation of Suspected Extraneous Tissue*

Upon discovering suspected extraneous tissue, the pathologist should:

- Immediately contact the histology laboratory manager, providing the case number, the type of tissue that comprises the case and the histologic diagnosis and/or organ source of the extraneous tissue, to the extent that it can be determined, so that investigation may begin.
- Contact the submitting physician to apprise them of the diagnostic difficulty and the likely delay in the sign-out of the case.
- The pathologist should NOT issue a final report; if appropriate, a preliminary report may be issued indicating that additional study is pending.
- The pathologist, pathologists' assistant, or grossing assistant should examine the grossing logs from the day the index tissue was submitted. If a candidate case for origin of the extraneous tissue is identified, the slides and report of that case should be examined for histologic similarity with the index case.
- If no candidate cases are identified, the pathologist should refer the slides and the histologic diagnosis of the extraneous tissue to the histology laboratory manager for further investigation.
- The histology manager, in consultation with the medical director of the laboratory, should examine the grossing logs for candidate cases, examining at least 3 days before and after the index case was submitted for histology. The medical director or the pathologist initiating the investigation should examine the slides and reports from any candidate cases.
- If no candidate cases are identified, the histology laboratory manager or their designee should initiate a search of the anatomic pathology laboratory information system using as a search criterion the diagnosis of the presumptive contaminant (e.g., "serous carcinoma") with a window of 1 week before and after the date of

tissue submission from the index case. The medical director or the pathologist initiating the investigation should examine the slides and reports from any candidate source cases.

- When one or more potential source cases for the extraneous tissue are identified, the histology manager or their designee should visually inspect the paraffin block of the index case or cut a superficial section to determine whether the extraneous tissue is present in the paraffin block. If the contaminant is present in the block the manager or designee should then:
  - Determine whether the potential source case was grossed before the index case and, if applicable, at the same grossing station.
  - Identify the histotechnicians that embedded the potential source tissue and the index case and whether the embedding occurred at the same station.
  - Determine whether control tissues were embedded proximately to the index case and, if so, whether the histology is similar.
  - Identify the processors on which the index and potential source cases were processed and whether they were on the same processing run.
  - Alternately, if the contaminant is present in the initial microscopic section only, and not in the paraffin block, the histology manager or designee should then determine the histotechnicians cutting sections from the two cases.
- When a potential source case has been determined to be histologically identical to the contaminant and the investigation above has concluded that contamination from this source is logistically possible, the pathologist initiating the investigation should contact the submitting physician and issue a final/addendum report documenting: (a) the nature of the clinical concern, (b) a summary of the investigation, and (c) the date and time of the phone call to the submitting physician.
- In the very rare case when no source tissue is identified or when there remains uncertainly regarding the identity of the suspect tissue from contaminant or the index patient, the slides and blocks from both possible source and index cases should be forwarded to an appropriate molecular diagnostics laboratory for micro dissection and analysis of short tandem repeat sequences by polymerase chain reaction. Prior to submitting the cases, the initiating pathologist should contact the medical director of the molecular diagnostics laboratory to discuss the case. When the final report is received, the results of the molecular identity studies should be documented in a final or addendum report, a copy of that report should be sent to the submitting physician and medical records, and a copy should be appended to the file copy of the pathology report.

## Conclusion

It is apparent that lack of appropriate quality assurance practices and strict adherence to established tissue handling protocols in the histology laboratory can result in significant misdiagnosis. Errors can occur at any stage of the histology process;

hopefully, laboratories that have adopted many of the error reduction strategies outlined in this chapter will experience low error rates. One of the most important overall error reduction strategies is to carefully document any "near miss" occurrences, most commonly recognition of an erroneous requisition/tissue label at the time of accessioning and recognition of an inappropriate section at the time of slide sign-out by the histologist or review by the pathologist. Identification of "near miss" practices at the time of grossing and embedding can be challenging and are likely best addressed by observational studies similar to those of Raab et al. [18, 23]. While administratively difficult to achieve, the ability to retrospectively identify the histologist performing each of the major histology functions (i.e., loading processors, embedding, and cutting) is essential to an ongoing program of error reduction through education. Finally, the most essential error reduction strategy, and the key to avoiding a misdiagnosis, is effective communication between the pathologist and the histology laboratory.

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# Chapter 5
# Application of Lean Principles to Preanalytic and Analytic Processes

**Anil Vasdev Parwani, Seung Lyung Park and Liron Pantanowitz**

## Introduction

Production processes are pathways by which raw materials are progressively converted into end products. Manufacturing industries such as the automotive industry have applied workflow analysis and quality management tools to their production processes, resulting in an increase in efficiency, consistency, and decreased waste. The production processes in healthcare exhibit features designed to take clinical data via pathways and procedures that generate observations, which in turn get converted into knowledge that culminates in decisions to support patient-centric care. In pathology, due to extensive generation of computerized data and easier access to electronic medical records (EMRs) coupled with new technologies (e.g., instrument automation, tracking systems) being embedded into our workflow, we have begun to see tremendous innovation and advancement in quality management and performance improvement [1].

Surgical pathology workflow is very similar to industrial production processes, because we are converting raw materials (e.g., specimens) into an end product (e.g., pathology report) [2, 3]. The process follows a series of steps, the majority of which have traditionally been manual batch processes. These steps include accessioning, grossing, processing (formalin fixation and paraffin embedding), glass slide generation (sectioning, staining, and coverslipping), transport (case assembly and delivery to pathologists), and reviewing slides (by a pathologist), as well as archiving and sometimes retrieval (of specimens, slides, and blocks). This workflow is somewhat

A. V. Parwani (✉) · L. Pantanowitz
Department of Pathology, University of Pittsburgh Medical Center, Pittsburgh, PA 15232, USA
e-mail: parwaniar@upmc.edu

L. Pantanowitz
e-mail: pantanowitzl@upmc.edu

S. L. Park
Department of Pathology, University of Alabama in Birmingham, Birmingham, AL, USA



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similar to an industrial production line. As a result, surgical pathology workflow has evolved towards adopting industrial quality management and improvement initiatives [2–4]. The focus of this chapter is to review the application of Lean initiatives in the preanalytic and analytic phases of the anatomical pathology (AP) laboratory, giving special emphasis to new technologies and use of informatics tools aimed at error reduction in surgical pathology.

## *Incorporating Lean Process in the Laboratory: Lessons from Industry and Industrial Workflow*

Much can be learned about the Lean process by understanding the industrial workflow [2, 4]. Technological advances of the Industrial Revolution and the widespread acceptance of the concept of standardized end products resulted in the development of industrial workflow, which is characterized by homogenization of the production process, standardization of components, and exploiting economics of scale [4]. The modern industrial workflow has continued to advance with the advent of the Internet coupled with advances in computing power. Utilization of automation and computer-enabled technologies is now part of the industrial workflow. As a result, industrial workers are now able to become experts in the areas of their craft. This has led to the success of many companies, particularly in the technology sector [5, 6].

## *Toyota Production System (TPS)*

There exists significant variability and often quality in the end product of a company, mainly due to lack of a standardized approach to workflow. In addition, there may be inefficiency of these processes. The TPS [2] is founded on concepts brought into Japan by an American statistician named W. Edwards Deming, who initially came to Japan in 1951 to participate in the Japanese Census. Deming was an expert in quality control techniques, and subsequently received an invitation to work with the Japanese Union of Scientists and Engineers (JUSE). Deming trained several Japanese engineers, managers, scholars, and even top management in concepts of quality and quality control. His concepts have been widely recognized and are referred to as the "14 Points for Management" [7, 8].

Several Japanese manufacturers such as Toyota and Sony adopted these management principles and as a result experienced significant improvements in both quality and productivity. Toyota created a workflow, now widely referred to as the TPS [2, 9]. The TPS has been described as an integrated sociotechnical system that, by design, minimizes overburden (*muri*) and inconsistency (*mura*), and eliminates waste (*muda*). This depends, in turn, on the creation of a very agile and flexible production workflow that is fine-tuned and improved upon by rapid iteration, with each iteration encoding more knowledge into the process [10].There are eight subcategories of waste in the TPS, which include transportation, inventory, motion,

waiting, overprocessing, overproduction, defects, and human capital. The TPS is successful primarily if there is buy-in from the leadership at the top, ensuring that the following principles are adhered to: [2, 9]

- Long-term thinking
  - Management decisions are based on a long-term philosophy.
- Creation of the correct production process
  - Creation of a continuous process flow.
  - Use of a system of just-in-time (JIT) production to avoid overproduction.
  - Leveling out the workload so as not to stress any specific part of the system (heijunka).
  - Building a culture of stopping production to fix problems, so that the quality is not compromised.
  - Ensuring that tasks are standardized for continuous incremental improvement (kaizen) and employee empowerment.
  - Using visual indicators (kanban) to reveal problems.
  - Using only reliable, thoroughly tested technology.
- Adding value by developing people and partners
  - Growth of leaders who thoroughly understand the work, live the philosophy, and teach it to others.
  - Development of exceptional people and teams.
  - Respecting partners and suppliers by challenging and helping them improve.
- Organizational learning by continuously confronting root problems
  - Assess the problem to thoroughly understand the situation (genchi genbutsu).
  - Making decisions slowly by consensus, and by considering all options; however, implement decisions rapidly (nemawashi).
  - Focus always on relentless reflection (hansei) and improvement (kaizen).

Today, the TPS system is widely used as a model by many corporations, particularly in the manufacturing industry [9]. By following these production principles, Toyota was able to reduce cost and lead time while significantly improving quality over time, and in so doing became one of the leading car companies in the world [11].

## Lean Process

An offshoot of the TPS is known as the “Lean” method [12]. It is not as rigidly defined as the TPS, and is best understood as a generalization of TPS principles into industries other than manufacturing. As such, it has only two key differences in practice [12]:

- While seeking profit is perhaps the key focus of the TPS, Lean implementations tend to de-emphasize this, instead seeking process improvement for other reasons specific to the industry or organization.
- In the TPS, the area of skills development is that of the work team leader, and not a trained TPS specialist. In Lean, this is often reversed: emphasis is placed on developing the specialist, while work team leader skill development is less emphasized.

### *Six Sigma Process*

Like the TPS/Lean, Six Sigma is a Deming-inspired business management strategy that seeks to eliminate defects and reduce process variation. The name "Six Sigma" itself comes from recognition of the fact that if one has at least six standard deviations between the process mean and the nearest specification limit, zero items will fail to meet specifications. Six Sigma, however, differs from TPS in the following ways [10]:

- All Six Sigma projects must achieve a measurable and quantifiable financial return.
- Six Sigma requires a special infrastructure of Six Sigma experts (named after belt colors in martial arts) to lead and implement projects.
- Decisions are made only on the basis of verifiable data, rather than on assumptions and guesswork.

Six Sigma is driven by *data*, not *knowledge*. The end goal of a Six Sigma project is to produce the vast majority of end products within specification. This is accepted to mean less than 1 defect per million opportunities (DPMO) in the short term, and approximately 3.4 DPMO in the long term. Six Sigma techniques have focused on increasing efficiency and cutting costs, and have been widely applied across industries such as retail and financial services [10, 13].

## Applying Lean Principles in Pathology Workflow

The specifics of any given production process are largely dependent on the nature of both the raw materials and desired end products [2]. Hence, different pathology specialties have somewhat different associated workflows. However, all pathology workflows have the following three phases in common:

- Preanalytic
- Analytic
- Postanalytic

Pathology workflow is highly variable depending on the type of specimen being processed and the place of processing, and may consist of a series of intermediate steps with a range of complexity [3]. Some of these steps can be automated, such as printing of labels. Other steps may be algorithm driven, such as assembling a case and matching paperwork with corresponding glass slides. Many steps require a large amount of manual work by a skilled technician, such as gross examination of specimens or tissue sectioning by a histotechnologist. A significant amount of the workflow is supported by laboratory information systems (LISs).

Currently, many anatomic pathology laboratory information systems (APLIS) are rigid legacy systems that offer minimal end-user flexibility, customization, or interoperability. This negatively impacts quality assurance (QA) projects in pathology. Typically, one of the major barriers to perform QA projects is the extraction of relevant data from these LISs for further assessment, and possibly merging these data sets with other data sources [3, 14]. The overall goal is to mine this data to analyze key quality indicators, such as turnaround time and errors in diagnosis.

AP laboratories have lagged behind clinical pathology laboratories with respect to quality management. Newer technologies such as barcoding, synoptic checklists and electronic bidirectional interfaces with the EMR are providing new avenues for quality improvement in the AP lab. Several pathology laboratories have implemented quality management programs that are based on Lean principles and the TPS [3, 15, 16]. These quality management programs have improved aspects of their workflow and reduced some of the errors in the laboratories. These measures are being adopted by other AP labs, in concert with the deployment of new technologies to augment their quality management programs [3, 17, 18]. The next sections review key steps in the AP workflow, focusing mostly on the preanalytic and the analytic phases.

## Preanalytic Phase

The AP preanalytic phase involves the handoff of a specimen (e.g., biopsy, surgical resection, and cytology sample) from one to another system. Often times, in the operating room or clinic, information about the specimens is recorded on requisitions (paper and/or electronic) by individuals who are usually not physicians and have no training or background in pathology. Preanalytical errors that occur at this stage are usually beyond the control of the pathology laboratory, unless they are actively involved in the training and triage of specimens being sent to the laboratory. This preanalytical encounter may be less error free if the specimen containers at submitting sites have preprinted labels (and barcodes) on them generated by the APLIS with proper positive patient identification steps in place [3].

The first encounter that the AP lab usually has with the specimen is either in the gross room, accession area, or in the frozen section room. The specimen is received with a requisition. Once the case is received, someone in the pathology lab has to manually accession the case, during which (1) the APLIS assigns it a unique

**Table 5.1** Potential sources of error in the preanalytical phase of surgical pathology workflow

| |
|---|
| Patient identification |
| Patient history |
| Specimen loss |
| Specimen identification |
| Specimen adequacy |
| Specimen handling |
| Specimen transportation |
| Accessioning data misentry |

accession number and (2) related information from the requisition is entered into the APLIS. Cases with multiple parts require that each part is entered and documented separately in the APLIS. Table 5.1 lists some of the errors that may arise during the preanalytical phase.

Many of the errors in the preanalytic phase occur before the specimen ever reaches the pathology lab. To avoid these types or errors, the LIS has to be ideally closely linked to the hospital system's EMR. This permits electronic computerized provider order entry (CPOE) to take place. In addition, employing positive patient identification technologies (e.g., barcoded patient wristbands and biometrics) at the specimen submitting sites can help to thwart some of these errors from the outset [3, 17, 18].

## *Patient Identification*

Positive patient identification technologies have had an impact on error reduction in medicine. Such technology helps to reduce errors even before specimens arrive in pathology laboratories. One of the barriers in using the same patient identification system for the EMR and LIS is the lack of standardized barcodes. Hence, barcodes used for patient identification are rarely compatible with those required by the LIS or middleware laboratory tracking system. This results in diverse patient identification data, and not surprisingly is a common source of preanalytical errors. This problem has been the focus of much effort in recent years, which has decreased identification error rates [19].

Positive patient identification technologies that are independent of printing include radiofrequency identification (RFID) tags [20]. RFID is becoming more affordable and accordingly being leveraged to help solve problems encountered with the use of printed barcodes [3, 18]. Another failure in the patient identification process is related to patient demographic data not being available when needed (e.g., at accessioning), as occurs when the Admission-Discharge-Transfer (ADT) feed from the Hospital Information System (HIS) to the LIS is down. Most EMRs are built atop client-server architecture with routinely scheduled downtime for backup and maintenance. In addition, there are unscheduled and unexpected downtimes. Modern EMRs are evolving toward more evenly distributed architectures to minimize scheduled downtimes [21].

**Table 5.2** Potential sources of error in the patient identification process

| |
|---|
| The identification medium deteriorates (e.g., damaged barcode labels) resulting in "read-type" errors or failure to read |
| Use of technology which may not be compatible with downstream systems (e.g., RFID) |
| Patient data are not accessible from an offline or incompatible system |
| Lack of standardized barcodes resulting in either no scans or errors in scanning of barcodes |
| Incorrect patient identification data from an unverified source |
| Manual entry errors |
| Wrong wristband printed and applied to wrong patient |

Lack of standards in barcode technology and labels may be an important contributor to preanalytic errors. For instance, there may be some overlap of symbologies used at the patient registration point and in the lab, which would present a problem if the barcode scanners used in the lab were able to scan either type of barcode. Standardization of barcodes in AP is important, and needs to be addressed, similar to what has been achieved in transfusion medicine and blood banking [3, 18, 22].

Many of preanalytical errors can also be traced to manual steps and processes, especially when these are not standardized and the lab utilizes workarounds for special instances. In general, a process that is more lean and that involves verification at each step will be less error-prone. Each step in the specimen life cycle should be part of a standard workflow process, and ideally follow that of an industrial workflow, with minimal involvement of humans and more emphasis on automation. The resulting Lean processes will help with error reduction [12, 14]. Table 5.2 lists the types of errors that may occur in the patient identification process.

## *Patient History*

A major source of error in the preanalytical phase is a lack of relevant clinical history or incorrect clinical history on paper or electronic requisitions [23]. A large number of requisitions received by the AP lab often have inadequate or no clinical history on the accompanying requisition [24]. There is no question that appropriate and accurately provided clinical history can provide the AP lab with important background information about the specimen type, and further guides the appropriate triage of the specimen. For example, a cancer specimen will receive appropriate grossing and perhaps taking specific sections (e.g., tumor margin) versus a non-neoplastic specimen with inadequate clinical history. One of the strategies employed by AP labs to improve the adequacy of clinical history supplied on their requisitions is to reject requisitions with no or illegible clinical history [23, 24].

Another strategy the laboratory may employ to obtain clinical history is to directly access this data from the EMR or other information systems, to electronically extract any pertinent information from patient charts. Some EMRs can directly transmit this information into the LIS via an electronic interface [22]. This electronic

**Table 5.3** Potential points of error during the accessioning process

| |
|---|
| Illegible handwriting |
| Keying errors |
| Transposing numbers/letters |
| Wrong blocks printed and matched with wrong case |
| Excessive time spent for manual verification |
| Lack of a standardized workflow and reliance on a batch process |
| Lack of relevant clinical information on the requisition |

dump of information may not always contain data that is relevant to the specimen and pathological evaluation that is being performed. Accordingly, it becomes more time consuming in such cases to sift through this superfluous information. Advances in technology are still required to ensure that AP labs are able to routinely receive relevant information for all cases as part of a standardized workflow [22].

In summary, in the preanalytic phase, an ideal state would be achieved when the right specimen is taken from the right patient, an event that is typically beyond the control of AP lab staff. This would be followed by traceable steps in which this specimen is properly identified, labeled, handled, and transported in a timely manner to the AP lab. The AP lab, upon receipt of this sample, needs to accession the specimen without errors [21, 24]. Table 5.3 lists multiple potential points of error that may occur during the accessioning step.

### Computerized Provider Order Entry

Many of the orders received by a clinical pathology laboratory information system (CPLIS) are handled by a CPOE system/interface [22]. However, in the APLIS, a similar CPOE system is not widely used. In many APLIS systems, the order entry is predominantly manual with the majority of "orders" supplied on paper requisitions. There are many advantages of CPOE, most notably the potential to diminish order-related errors. CPOE implementation for surgical pathology has unique challenges, mainly because surgical pathology orders need additional information when compared with clinical pathology (CP) orders. For example, ordering a serum PSA test only requires selecting this lab test in the electronic order set. By comparison, a surgical pathology order is more complex as the order also requires additional information to be relayed to the pathology lab such as anatomical location, organ/tissue type, relevant clinical information, and often pertinent information about the procedure [22]. In addition, a single order may include several parts from the same organ (e.g., margins versus tumor) or multiple parts from different organs. Table 5.4 lists some of the benefits of using a CPOE in the AP laboratory.

**Table 5.4** Key advantages of using computerized provider order entry (CPOE) in the AP laboratory

| |
|---|
| Reduced turnaround time |
| Reduced manual steps, including transcription, label writing, and accessioning |
| Elimination of ambiguous/indecipherable orders |
| Improved compliance with laboratory testing and/or clinical guidelines |
| Improved test utilization and appropriateness of test ordering |
| Direct feed of patient clinical information (e.g., history, problem list, etc.) into the APLIS (i.e., reverse flow of data from the EMR) |

## *Pathology Asset Tracking*

As mentioned, laboratory misidentification errors may be preanalytic or due to post-analytic errors in the test cycle [3, 24]. Asset tracking solutions in pathology continue to evolve, and provide labs with a scalable solution for quality management and error reduction [22, 26–29]. Misidentification errors in the AP laboratory may result in an adverse event causing unnecessary subsequent procedures or even death [25]. A Q-Probes study from the College of American Pathologists (CAP) involving 136 institutions provided information on a total of 1811 mislabeling occurrences, showing that overall mislabeling rates in participating labs were 1.1 per 1000 cases. Interestingly, 21% of these errors occurred before accessioning, 12% at accessioning, 22% at block labeling, 10% during gross pathology, and 30% in histology [31]. As pathology laboratories become more subspecialized, coupling asset tracking technologies with Lean processing methods has the potential to reduce these errors, drive the workflow, and simultaneously make the process more efficient [18, 29]. Table 5.5 lists some of the advantages of barcoding and tracking solutions.

In the pathology lab, tracking begins with adding an identifier to each asset that needs to be tracked. Some examples of assets in the laboratory include specimen requisitions, patient specimens, and their derivatives such as tissue/cell blocks and glass slides (Fig. 5.1). Tracking of machine-readable identifiers such as barcodes and RFID tags has the ability to rapidly and accurately record the asset's identifier into a tracking system (e.g., LIS and middleware [34]). The types of barcodes that

**Table 5.5** Advantages of barcoding and tracking

| |
|---|
| *Asset management* (identification and tracking) |
| *Data input* into the LIS is immediate and reliable: lower potential for data-entry errors than key entry |
| *Standardized workflow* processes: |
| Supports lab automation |
| Just in time printing (e.g., labels) |
| Promotes Lean processing and patient safety |
| Improves overall turnaround time |
| Drives the workflow process |


**Fig. 5.1** Example of a matrix (2D) barcode and its application in assets (tissue blocks and slides) in the anatomical pathology (AP) laboratory

can be used can be of either linear (1D) or matrix (2D) type. Linear bar codes have bars and spaces and can be either numeric (e.g., UPC) or alphanumeric (e.g., Code 128). Matrix (2D) barcodes (Fig. 5.1) have the following advantages [18]:

- Higher data density (more characters and scalable)
- Smaller barcodes, which is better for smaller labels
- Allows omnidirectional scanning
- Associated with less scan failures
- Higher tolerance for printer failure/damage

Tracking systems have a variety of applications and capabilities ranging from identification of the location of the assets in the lab (or storage area) to real-time and dynamic monitoring of their status (i.e., what phase they are in of the workflow process) [18, 29]. This allows a tracking solution to be designed to help in controlling the speed of specimen flow within the lab, as well as in controlling various parts of the workflow of the laboratory. It also allows for collection of QA data to monitor such quality indicators as turnaround time. The functionality of the tracking system dictates what system requirements are needed (e.g., complex interfaces) and what type of an investment in infrastructure will be required (e.g., wired versus wireless networking). As technology matures, so too will the complexity and functionality of these asset tracking systems (Table 5.6) [18, 26].

An asset tracking system significantly contributes to reduction in labeling errors and thereby contributes to patient safety [3, 27]. Implementing a tracking solution to support work process standardization in the AP laboratory has been shown to resolve such issues. For example, at Henry Ford Hospital in Detroit, Michigan,

**Table 5.6** Spectrum of functionality within pathology asset tracking systems [18]

| Function | Tasks |
|---|---|
| Auditing | Track asset events (what, when, and who) |
| | Audit trailing (when was asset last seen) |
| | QA indicators and analysis of workflow |
| | Creating dashboards |
| Workflow control | Prevents batch workflow |
| | Creates locks/gates on steps (e.g., if the right asset is not in association with the right patient) |
| Workflow functions | Barcode driven processes such as case triage |
| | Provide status alerts to recipients about the location of an asset |
| | Create flags for retrieval of interesting cases or cases for a specific function (e.g., such as tumor boards). |

pathologists reported a 62% decrease of their overall misidentification case rate, 92% decrease in slide misidentification defects, and 125% increased technical throughput at their microtomy workstations after barcodes were introduced [15].

Even though the benefits of an asset tracking system are manyfold, there are challenges and barriers in the implementation of a tracking system. One of the major barriers is the immense cost, which in turn depends on the overall scope of the project [30]. Several software and hardware vendors offer customized solutions that will work with the LIS of your choice, or work as an independent tracking system outside of the LIS. Costs associated with the implementation of an asset tracking solution are not limited to hardware and software, but also require human resources, particularly from IT and laboratory teams, as well as consultants from the vendor (Table 5.7). In addition, there may be some indirect costs associated with configuring the implementation to change or accommodate the workflow needed for tracking and optimizing [3, 18].

Implementation of an asset tracking solution may be complex, as it involves installing software and hardware, configuring interfaces, and establishing network connectivity (Fig. 5.2). All hardware deployment, software installations, and establishing of network connectivity have to be carefully validated and documented before moving from a production (test environment) to clinical ("go live") environment. The IT and vendor teams will have to work closely with laboratory staff during the implementation. Some customization may be required. Even after implementation, some of the instruments in the laboratory may not be compatible with the tracking solution that was implemented [18, 28]. This will need to be addressed by incorporating different workflows in to the lab that rely on these devices and/or budgeting to change/upgrade them to more interoperable instruments.

Even after implementation of the tracking solution, the laboratory may continue to see some errors due to workarounds and human errors. This may occur with noncompliant employees and/or when staff makes "small" changes in the workflow

**Table 5.7** Costs that may be incurred in implementing an asset tracking solution in the laboratory

| |
|---|
| Software costs of the tracking solution |
| Software cost for customizing the LIS |
| License and maintenance fees |
| Dedicated lab and IT human resources |
| Vendor consulting time |
| Barcode readers/scanners |
| Label printers |
| Cassette labelers |
| Slide engravers |
| Computers, including: |
| Monitors, keyboards |
| Networking, storage/servers |
| Customization/installation (e.g., mounted arms to support monitors) |

to accommodate a particular scenario (e.g., unique type of staining process or workflow step that is not part of the standard workflow). For example, cutting extra sections or additional control slides which are not part of the protocol and that the tracking solution is not aware of [32]. The tracking solution has to be implemented with all users willingly participating. It is critical to train staff and ensure that all policies and procedures (e.g., downtime procedure) are in place and adhered to by staff. Every step must be taken to ensure that there is good compliance because


**Fig. 5.2** Examples of hardware (computer monitor and barcode reader) to be implemented as part of an asset tracking solution

often times, the latter and not technology issues are the cause of errors, even with a well-implemented tracking solution [22].

## Error Reduction in the Analytic Phase of Surgical Pathology

### *Gross Examination*

The analytical phase in surgical pathology begins once the case is accessioned. The LIS can perform many of the tasks that drive the analytical phase, such as printing tissue cassettes for the case. One of the first steps in the analytic phase is the gross examination of the surgical specimen. This may involve several steps such as obtaining images of the specimen, dissection of the specimen, obtaining tissue sections, annotation of these sections, and dictating a gross description to be recorded in the LIS. Gross specimen digital images are commonly acquired during grossing, and some APLISs have modules to accommodate and manage those images, and if desired even embedded into the final pathology report [22].

Although gross descriptions in several labs are mainly free text based, it is possible to incorporate structured and standardized templates for this task to avoid errors as well as to use voice recognition technology [22, 33]. The gross examination ends with the completion of the gross report. During the gross examination, there are potential for errors to be made, particularly if batch processing is done. This can be somewhat alleviated by incorporating a Lean process and employing a tracking system. During this phase of the test cycle, cassette engravers may be interfaced with the APLIS to print labeled tissue cassettes for each case to ensure minimize identification errors and help drive downstream workflow (e.g., the barcode can include instructions, such as the number of sections to be cut on a particular block or tissue type) [18, 22].

To avoid errors, ideally a standardized workflow should be followed in the gross room for all specimen and services, including rush cases. Even though each surgical specimen is unique, if a standardized approach to labeling, examination, and sectioning is followed, this leads to reduction of errors. In addition, incorporating tracking into this workflow will further help in minimizing errors, and hopefully improve efficiency. The APLIS can be programmed to routinely create the appropriate type and number of cassettes on demand or "just in time" basis (Fig. 5.3). Similarly, barcodes on the specimen requisition or the specimen container may be used to identify the specimens, and by matching these with the printed cassettes will add a step into the workflow that with reduce misidentification errors [35]. Of course, if the surgical staff placed a patient's specimen into the wrong container labeled with another patient (e.g., as may occur in a busy clinic where lots of biopsies are undertaken), this type of error is very hard to detect and rectify. Standardized checklists or synoptic reports may be used instead of free texts to capture standard data elements,


**Fig. 5.3** Use of asset tracking system begins in most labs when the specimen gets accessioned into the LIS (*left*), and includes the use of barcodes on specimen containers and requisitions (*middle*), which are matched up in the gross room (*right*)

further contributing to error reduction and making sure that all required data are at least being recorded. Employing a Lean process from specimen collection to accessioning and then gross examination helps to establish a standardized and hopefully error-free workflow [35, 36].

## *Tissue Processing*

Once the gross examination is complete, the tissue blocks are then sent to the histology laboratory where the next part of analytical phase begins. The histology laboratory is akin to a manufacturing plant where the tissue blocks enter into a production line and the end result are glass slides, with different stains (H&E, GMS, and IHC) performed on these sections. Slide labels can be autogenerated based on scanning the barcode on the tissue cassette that encodes data previously entered by the prosector. Specimen tracking and barcoding are both being increasingly used in this phase, with the LIS providing the ability to update specimen status and location based on the scanning of a barcode (Fig. 5.4) [22, 35].

Implementing a Lean production system in the histology lab, akin to a manufacturing plant, requires tight integration of the various steps undertaken in the lab with the APLIS. Some systems are capable of autogenerating barcoded and labeled slides at individual histotechnologist stations, encouraging them to process only one case at a time. This leads to a reduction in case misidentification, but not necessarily always an improvement in histotechnologist efficiency [15] (Fig. 5.4). Once the slides have been created and are ready for distribution to pathologists, the slides are paired with the specimen worksheet (printed working draft). This contains all the relevant information such as patient's demographics, clinical history, procedure type, the gross description, and reference to any relevant past reports [15, 29]. In an effort to go paperless, several labs have given up using printed working drafts

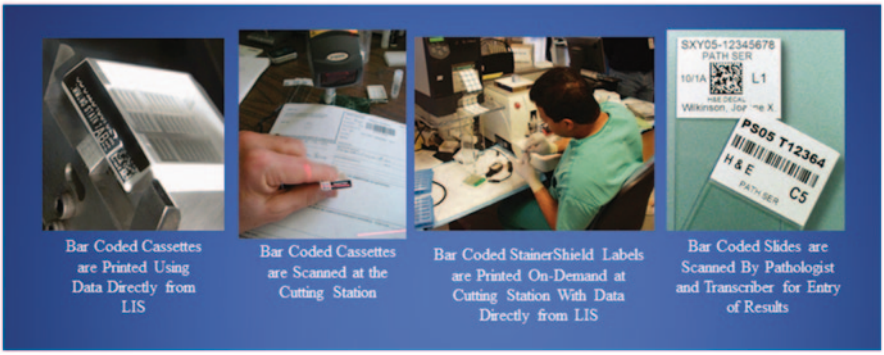


**Fig. 5.4** Use of specimen tracking software and implementation in the histology laboratory to drive a Lean workflow. Barcoded cassettes (*far left*) are scanned at the cutting stations (*left*). This identifies the case, opens the correct case in the LIS, and initiates what happens next. Barcoded labels are then printed "just in time" (*right*) at the microtomy workstation either on to adhesive labels or (*far right*) directly etched onto glass slides

and instead scan the barcode on their case's slides to view all of this information in the LIS. For pathology labs preparing to go slideless and adopt digital imaging for primary diagnosis, it is at this stage that their workflow will need to be carefully restructured to accommodate large-volume digitization of glass slides on whole slide scanners. Fortunately, most whole slide scanners are capable of reading barcodes.

A properly implemented tracking solution can provide additional opportunities for QA activities, such as turnaround time monitoring and error reduction. The LIS can provide data for each event in the workflow as assets (specimens and their derivatives) flow through the laboratory [22]. This scanned data can be used to track who and when they processed a case, the status of the case in the test cycle, and other quality indicators (Fig. 5.5). The AP lab workflow can be made even more efficient by creating checkpoints at each step in the process from receipt of blocks to the point where the glass slides and/or blocks of a case get filed or archived (Fig. 5.6) [22, 36].

## *Final Analytic Phase: Microscopic Examination and Sign Out*

One of the final stages of the analytic phase of surgical pathology is to review the slides and render a diagnosis. If at this point the pathologist needs to order recuts, special stains, immunohistochemical stains, or other studies before making a diagnosis, this can be accomplished either through paper requisitions or through a CPOE interface built into the LIS interfaced with instruments [22]. In most labs, a final pathologic diagnosis is rendered as free text. This is often accomplished by transcription of a pathologist's dictation. Many opportunities exist to incorporate new technologies or standardize workflow in the final diagnostic step of the

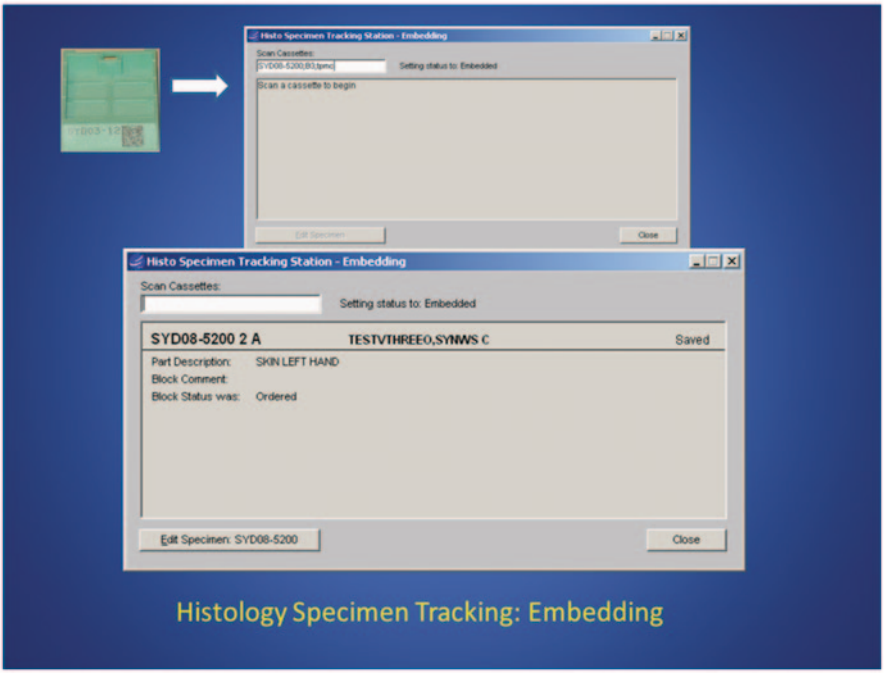


**Fig. 5.5** These screenshots from an LIS demonstrate an example of integrating tracking software with the LIS where a scanned block (*green* cassette in the *upper left*) can drive the downstream workflow. The case number and block identification stored in the small, square matrix barcode on the tissue cassette triggers subsequent printing of the appropriate slides at the histotechnologist's workstation, eliminating the need for manual intervention

analytical phase. Predefined templates or quick text for frequent diagnoses may be used [35, 36]. Voice recognition may also be used to convert speech-to-text as part of the workflow [32, 33, 35].

Because of its importance, the surgical pathology report must be clear, accurate, and comprehensive. Unfortunately, traditional narrative and descriptive pathology reports, although reflective of a given pathologist's style, may show significant variability in format, context, and content. With the increasing complexity demanded of the modern surgical pathology report, important data elements are occasionally omitted (e.g., margin status and tumor stage). Zarbo et al. studied 15,940 pathology reports of colorectal cancer and reported that basic yet crucial elements such as gross tumor size, depth of tumor invasion, resection margins, and tumor grade were often absent [37]. Rosai proposed standardized reporting of surgical pathology diagnoses for major tumors [38]. In 2002, the American College of Surgeons Commission on Cancer (ACOS COC) reiterated this mandate by recommending mandatory cancer protocols. Considerable work by pathologists, researchers, and informaticists was performed to develop mechanisms that ensured quality and uniformity among pathology reports, regardless of the institution of origin, leading to the development of CAP Cancer Protocols and Checklists [39].

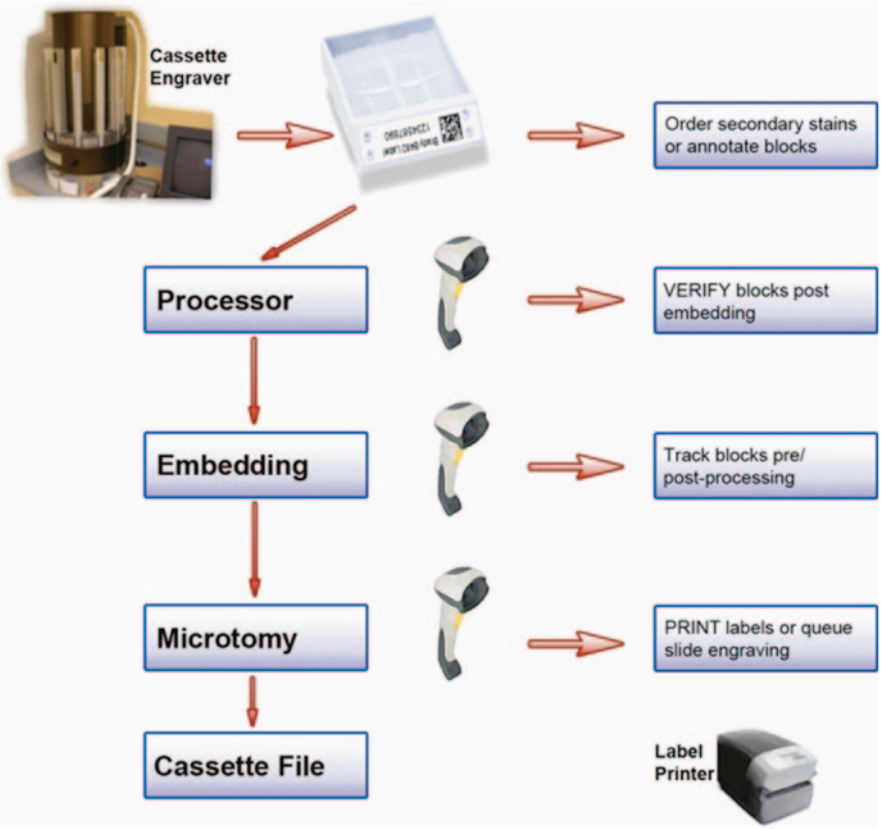


**Fig. 5.6** Standard workflow in the AP laboratory has several points where barcoding and automation can be introduced. When the steps shown here for histology processing include scanning of barcodes the data at each captured within the laboratory information system (LIS)

Checklists or synoptic reporting, as in the CAP cancer protocols, provides a structured and preformatted method for entering clinically and morphologically relevant details of surgical specimens [20, 40]. A checklist (synoptic) format makes reporting efficient, uniform, and complete, especially for the major tumors (Fig. 5.7). Use of synoptic checklists makes reporting efficient, uniform, and complete. Synoptic checklists can be customized by individual laboratories to incorporate, and thus potentially track, data elements important to their practices. Several LISs offer synoptic reporting modules, and there are also third-party synoptic reporting programs that interface with the LIS if it does not have those capabilities built-in. The discrete data elements contained in synoptic reports can theoretically be analyzed at will, facilitating QA and research initiatives. [35] Once a final diagnosis has been entered for a case, this case is marked as "final" in the APLIS, and placed on the pathologist's work list for final edits and electronic sign out. The synoptic report allows the report appearance to be for customized, making it possible to only display

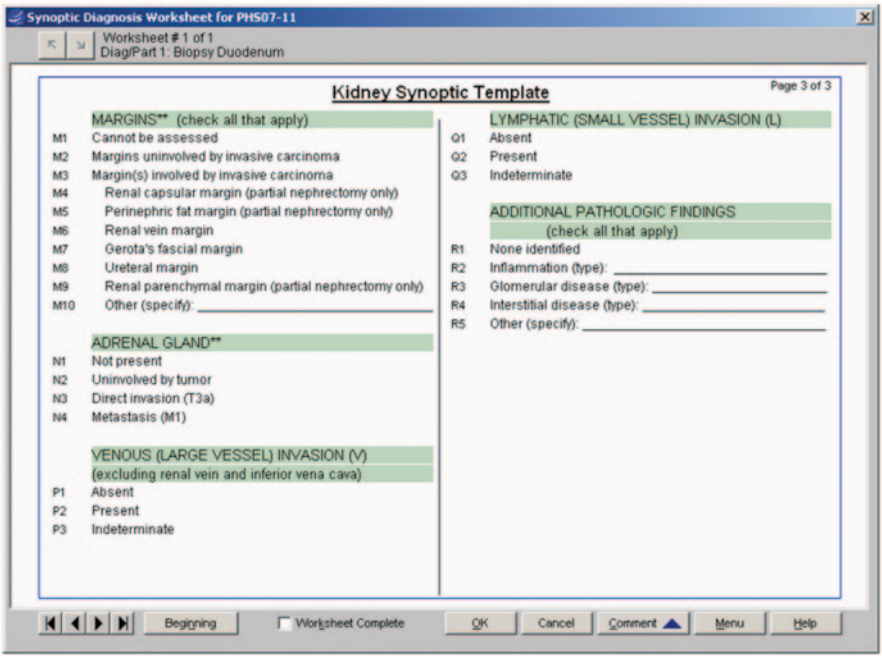


**Fig. 5.7** Synoptic report template for kidney cancer is shown. Note the organization of discrete data elements into groups. This organization makes it easier to enter data relevant to the case. This standard checklist presented to all pathologists, forces them to choose relevant data points, which thereby leads to fewer errors and omitted data in their reports

relevant data items (Fig. 5.8). Billing and other diagnostic codes (e.g., SNOMED) are often entered automatically at this point based on part type, stain orders, and natural language processing of the final diagnostic report [22].

## Presign Out QC Tool

The postanalytic phase in surgical pathology is usually the phase where most QA and research initiatives occur. In many institutes, all or a subset of cases are reviewed routinely by a second pathologist (e.g., consensus conference, over-reads) within the same department as a method of QA. Studies have shown that error rates range from 0.26 to 1.2% for global in-house prospective review and 4.0% for retrospective blinded review [3]. These errors may be major, minor, or clerical. In the postsign out period, there is relatively less time pressure since the case is already signed out; however, decisions to manage patients may have already occurred if an amendment is required to correct a report. Technology can be incorporated into the LIS for automated flagging of cases for randomized QA review within the APLIS, doing this prior to the case being signed out [41]. This creates opportunities to

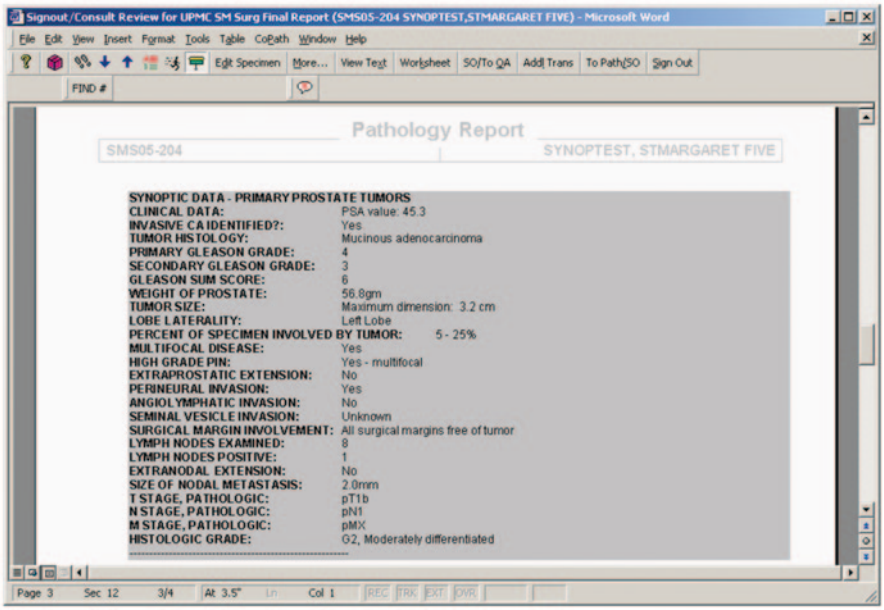


**Fig. 5.8** The output of the synoptic report is highly customizable and as illustrated in this report the user can select the type of font, style, and output location within the report (e.g., top of the report or at the end), making the pathology report visual and patient centric

perform QA during the analytic phase [22]. This is typically done in cytopathology labs where CLIA demands that a proportion of Pap tests be screened in real time by another cytotechnologist. At the University of Pittsburgh Medical Center, a Presign out Quality Assurance Tool (PQAT) was developed that allows the LIS to automatically select a certain percentage of cases for each pathologist for prospective QA purposes, which then goes to a second pathologist for review (Fig. 5.9) [42, 43]. In order to allow for such random QA of cases prior to sign out, several software modifications were required with the help of the LIS vendor. The sign out pathologist has up to 8% of their cases randomly selected by the LIS just prior to sign out. The pathologist does not know ahead of time which case will be selected for QA. As soon as the case gets selected, it is sent to a QA work list where an assigned QA pathologist reviews the case and either agrees or disagrees with the original diagnosis (Fig. 5.10), and then enters their comments into the LIS. At this point, the case is returned to the original pathologist and it is resolved if there is a discrepancy or signed out if approved by the QA reviewer [42].

The PQAT has been in successful operation since January 2009. The number and level of disagreements identified using the PQAT was similar to that reported during the previous 14 months using a 5% postsign out QA audit system. Additionally, the proportion of cases actually reviewed using the PQAT (8.4%) achieved the target review level, while the retrospective method fell short of the 5% goal, with

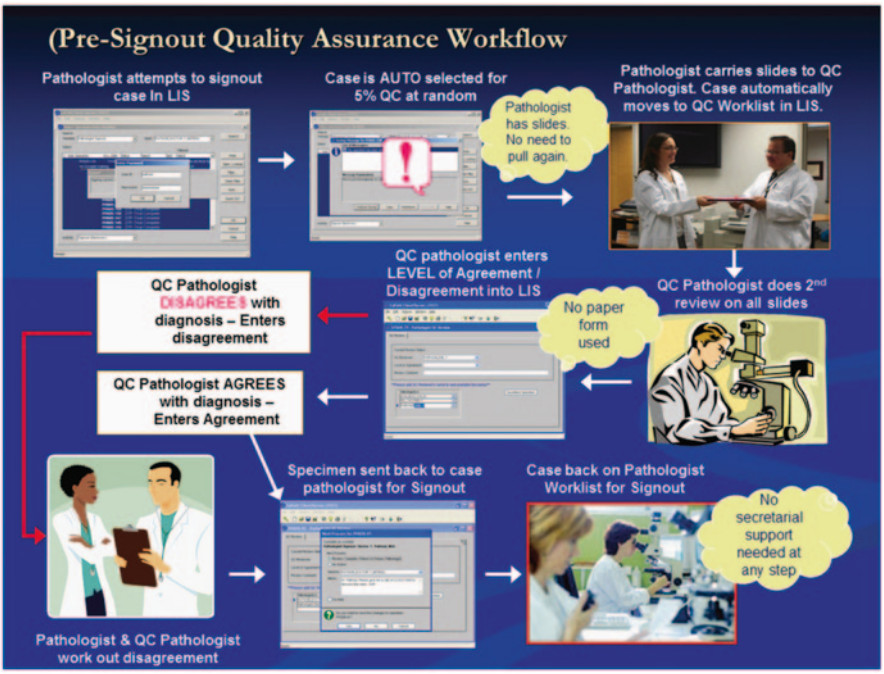


**Fig. 5.9** Novel workflow that facilitates review of surgical pathology cases in the analytical phase in a Lean (just-in-time) process. This prospective, random quality assurance (QA) process relies on the LIS to prospective guide the process

only a 3.7% review rate [42, 43]. The PQAT and the designed workflow allows for corrective action and re-review of cases in real time, allowing for reduction of any serious errors before patient harm may occur.

## Conclusion

New advances in technology and improved standardization of the workflow are being increasingly adopted in the AP laboratory. As a result, we are beginning to witness a decline in the error-prone and inefficient manual and batch type production processes that typically occur in the AP lab. This is because pathology laboratories are starting to implement informatics tools to improve their workflow, efficiency, and overall quality of specimen handling and pathology report production. As a result of this shift, more automated and standardized processes that include traceable steps are starting to take shape. New and innovative methods of transferring data and recording data are making the process of gathering quality data a less surmountable task.

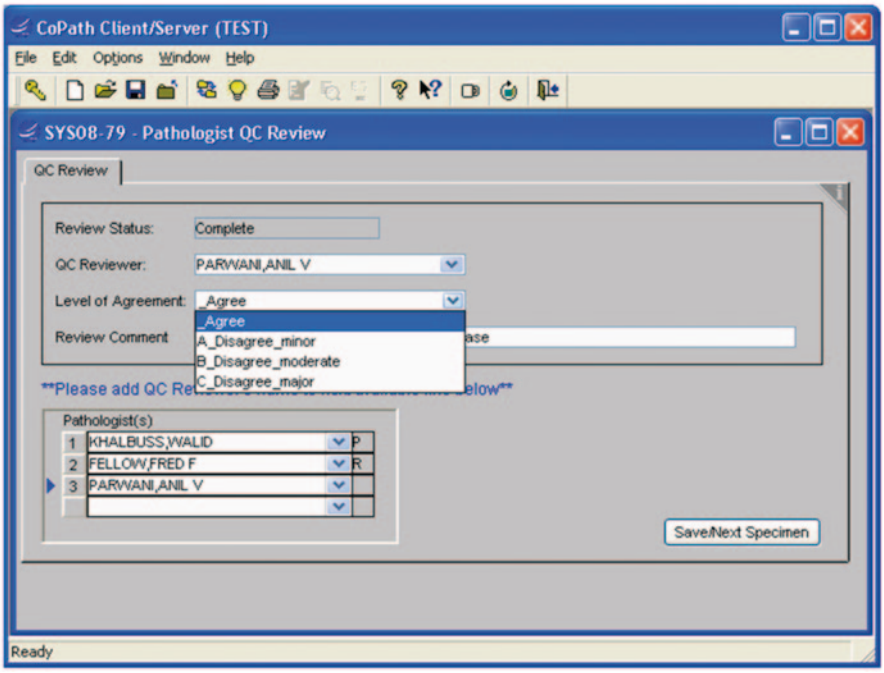


**Fig. 5.10** Screenshot from a laboratory information system (LIS) where presign out quality assurance (QA) allows the reviewing pathologist to agree or disagree with the intended diagnosis in real time and also add review comments prior to the case being signed out

Software, either built into the LIS or as part of middleware, is increasingly providing pathology laboratories with better business intelligence data, rich with information that can be leveraged to monitor a variety of quality and performance indicators [22, 32]. These informatics tools offer many opportunities to now more easily capture, analyze, and leverage these data to promote Lean labs. As in clinical pathology laboratories, there is an emphasis in AP labs to eliminate human intervention and batch processing as much as possible and instead substitute these workflow processes with more standardization and automation. AP laboratories that have adopted automation and shifted to a more continuous "pull" system have experienced more efficient workflows with reduced errors [32, 36]. Newer software technologies such as asset tracking solutions, synoptic reporting modules, business intelligence platforms, bidirectional interfaces, and computerized order entry systems are examples of emerging informatics tools that are creating more opportunities for labs to adopt a Lean workflow, similar to the TPS, and in so doing contributing to error reduction in surgical pathology. As pathology moves toward a digital workflow, and as new tests in pathology emerge such as next-generation sequencing, in order for AP laboratories to continue their march toward more automation, standardization, and better quality they will need to look for new informatics solutions. This transformation has been more rapid in clinical pathology laboratories that employ fully

automated robotic lines, akin to manufacturing plants, allowing them to deal with high volumes and complex tests and seamless integration of information systems. AP is not quite there yet, but progress towards such Lean transformation has already begun and labs have started sharing their success stories. These improvements will undoubtedly continue to pave the way for fewer errors and better care for the patient of tomorrow.

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# Part II
# Analytic Factors Contributing to Errors and Error Prevention

# Chapter 6
# Clinical History and Clinical Correlation

**Keith E. Volmar**

## Introduction

A surgical pathologist's first responsibility is towards the patient from whom a specimen has been taken. The importance of clinical information and clinical correlation in surgical pathology evaluation is recognized by regulatory agencies and is self-evident to the practicing pathologist. Unfortunately, pathologists commonly lament the lack of clinical information on surgical pathology requisitions, and it is likely that every pathologist can recite a few memorable cases for which such information made a dramatic difference in diagnosis. The importance of clinical information and correlation is referenced, at least in passing, in standard pathology textbooks. A few surgical pathology texts go the extra distance to devote a full section to the importance of the subject [1, 2]. It is encouraging to find that an occasional clinician-directed text also contains a significant discussion of such issues [3, 4].

In the introductory section of his widely used text [1], Dr. Juan Rosai includes the following passage:

> By its very nature, surgical pathology depends heavily on the input of clinicians and surgeons who are fully aware of the potentials and limitations of the specialty. They should know that a microscopic diagnosis is a subjective evaluation that acquires full meaning only when the pathologist is fully cognizant of the essential clinical data, surgical findings, and type of surgery. The requisition slip for pathologic study should ideally be completed by a physician familiar with the case; too often the task is delegated to a medical student, a nurse, or the surgery resident who was requested to perform the biopsy. One of the most frustrating and potentially dangerous experiences that a pathologist can suffer is that of the requisition form lacking adequate clinical information.

Indeed, this is not a new problem, as noted by O. N. Rambo [5] more than 50 years ago:

> Incomplete communication between the clinician and pathologist may make diagnosis difficult or impossible. To perform intelligently, a consultant must know all the facts that have

K. E. Volmar (✉)
Rex Pathology Associates, 4420 Lake Boone Trail, Raleigh, NC 27607, USA
e-mail: Keith.volmar@rexhealth.com



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> any bearing on the case. To render a diagnosis from an inherently puzzling bit of tissue with only vague knowledge of its source and no concept of the clinical problem is as foolhardy as to undertake an appendectomy on the basis of hearsay evidence that the patient has a pain in his belly.

Considering the increasing complexity of medicine, the growing list of disease types and subtypes, and the expanding technology of ancillary testing and imaging, the difficulty in obtaining a coherent and accurate clinical history has grown. Add to these factors an increasingly mobile patient population and physicians must piece together medical and surgical history from multiple institutions as well as any history of travel to endemic areas and exposure to occupational and environmental toxins. Perhaps the greatest challenge is in following the growing number of cancer survivors with relatively indolent disease. Such patients may end up not only with a neoplastic history, but also with a lengthy longitudinal record filled with follow-up procedures, toxic therapeutic exposures, and secondary diseases.

## Regulatory Considerations

The importance of clinical history is emphasized by a number of regulatory agencies and accrediting bodies. These agencies include, but are not limited to, the College of American Pathologists Laboratory Accreditation Program (CAP-LAP) [6–9], the Joint Commission Laboratory Accreditation Program [10], Clinical Laboratory Standards Institute [11], International Organization for Standardization [12], and the Centers for Medicare and Medicaid Services through the Clinical Laboratory Improvements Amendments of 1988 (CLIA) [13, 14]. Regulatory aspects are more fully summarized in other texts [15]. Herein are listed the 2013 CAP-LAP checklist items that pertain either directly or indirectly to the adequacy of clinical information and clinical correlation in surgical pathology:

- *General Checklist GEN.40100 Specimen Collection Manual Elements.* The specimen collection manual is to include instructions for all of the necessary elements, including the obtaining of appropriate clinical data, when applicable, such as preoperative and/or postoperative diagnosis. These instructions must be included in the procedure manuals at all sites where specimens are collected.
- *General Checklist GEN.40750 Requisition Elements.* The requisition includes all necessary elements, including appropriate clinical information, when applicable.
- *Anatomic Checklist ANP.10050 Previous/Current Material Review.* Whenever appropriate, pertinent previous cytologic and/or histologic material from the patient is reviewed with current material as sequential analysis of specimens may be crucial in patient management. It is also recommended that such reviews be documented in the current report.
- *Anatomic Checklist ANP.12400 Correlation of Results.* There is a mechanism to correlate results of ancillary studies (e.g., flow cytometry, cytogenetics) with the morphologic diagnosis. Reconciling information from different sections of the laboratory can aid in the avoidance of potentially conflicting diagnoses.

- *Anatomic Checklist ANP.12175 Significant/Unexpected Findings.* There is policy regarding the communication, and documentation thereof, of significant or unexpected surgical pathology findings. Such diagnoses should be determined by the pathology department in cooperation with medical staff.
- *Flow Cytometry Checklist FLO.30790 Final Report.* The final report includes information about the immunophenotype of the abnormal cells, and ideally, direct morphologic correlation should be performed.
- *Hematology Checklist HEM.36250 Fixed Tissue Correlation.* Unified reporting of bone marrow aspirates and biopsies is strongly recommended. Such data correlation is essential for diagnostic consistency and effective patient management.
- *Hematology Checklist HEM.36325 Correlation of Results.* The pathologist should correlate all of the special studies (e.g., flow cytometry, cytogenetics) with the morphologic diagnosis and render a final interpretation of all correlated studies when appropriate.

The CAP-LAP checklist items imply two additional points. First, knowing what is an unexpected finding or diagnosis may require knowing the preoperative impression or other clinical history. Second, not all clinical and correlative information is the responsibility of the submitting clinician. Pertinent ancillary studies that are appropriately included in a comprehensive surgical pathology report may be unknown to the clinician, and are therefore the responsibility of the pathologist.

## Basic Clinical Information Necessary for Surgical Pathology Diagnosis

A properly completed requisition form should include a brief clinical history and preoperative and/or postoperative diagnosis [16]. It is important to recognize that not all clinical information is contained in the "clinical history" space on the surgical pathology requisition form. The basic elements of clinical and demographic information that are necessary for surgical pathology evaluation include:

- *Patient age and sex*. Certain diseases and certain tumors have favored age groups and some are sex specific.
- *Indication or purpose for the procedure performed*. Some procedures are performed for a diagnosis, while others may be for debulking of disease for palliation (e.g., small bowel obstruction caused by known carcinomatosis).
- *Physical exam and intraoperative findings*. It may be necessary to know the character of a lesion (e.g., well-defined versus ill-defined), as well as other physical signs that may be helpful (e.g., the distribution of a skin rash, location, size and number of lesions present, and gross appearance if unusual in any way). Occasionally, one may receive an International Classification of Diseases (ICD) code in lieu of a textual clinical diagnosis; these codes may not be specific enough to be helpful to the pathologist.
- *Specific location of the sampled lesion* (and locations of any other unsampled lesions). For example, a "neck mass" at the level of the thyroid raises a differential

that is different from the one at the angle of the jaw. The differential diagnosis of a "mediastinal mass" depends a great deal on what specific part of the mediastinum is involved. The presence of solitary versus multiple lesions is also useful when considering primary versus metastatic tumor. Knowledge of the specific location may also be useful in avoiding specimen mix-ups and alert the pathologist to potential contaminating tissues from nearby structures.

- *Specific type of specimen and/or method of sampling* (e.g., core biopsy, incisional biopsy, radical resection, etc.). Knowledge of the specimen type may be useful in avoiding specimen mix-ups.
- *A thorough oncologic history, if applicable*. Ideally this includes the diagnosis, location, and stage of each neoplasm. For example, "history of lymphoma" is vague and may not be adequate for the pathologist to appropriately triage a specimen for ancillary studies.
- *Any prior diagnoses or prior biopsy findings*. Knowledge of prior workups may avoid rework, duplication of studies, and potentially conflicting diagnoses.
- *Prior or current treatment*. In many conditions, therapy has shown to change the histologic appearance of tissues and lesions, potentially leading to misdiagnosis. Some examples include inflammatory bowel disease (e.g., steroids), prostate cancer (e.g., hormone or radiation), and allograft rejection in various organs.
- *Urgency level* (e.g., RUSH or STAT specimen).

## Other Elements of Clinical History Potentially Needed for Diagnosis

Depending on individual patient circumstances and particular surgical pathology specimens, there are many other pieces of information that may be necessary for an accurate diagnosis. Which specific elements are vital may vary by tissue type, biopsy technique, specimen size, or by other considerations specific to a given case. Potential additional elements of clinical history include:

- Temporal relationship between symptoms and signs, particularly any unusual features.
- History of other medical diseases or illness that may be associated with specific long-term complications, including neoplasia (e.g., Hashimoto thyroiditis complicated by lymphoma).
- History of immune compromise or immune suppression will likely prompt the pathologist to look more carefully for infectious disease.
- Current or recent pregnancy.
- Family history of inheritable or potentially inheritable diseases including neoplasia syndromes. Some examples include hemochromatosis, familial adenomatous polyposis, and medullary thyroid cancer.
- Imaging findings may be important for many diseases, not just tumors. For example, evaluation of non-neoplastic lung disease often requires correlation with disease distribution on imaging studies.

- Prior studies on the institution's file are important. The ability to recognize that prior pathological material exists is dependent on the laboratory's information system and its ease of use by pathology staff. Laboratories that are part of larger hospital systems may have difficulty in cross-referencing various parts of the patient's record.
- Tracking of "split" specimens within anatomic pathology may be difficult, particularly when there is independent accessioning of cytology and surgical pathology. Some procedures yield both surgical pathology and cytopathology specimens, and a concurrent review of those specimens may lead to a more accurate diagnosis. If accessioning is carried out independently by various divisions of the laboratory, one component from the patient (e.g., transbronchial biopsy) could conceivably be signed out before another component (e.g., bronchial brush) has been accessioned. Possible consequences include duplicate special stains and discordant diagnoses.
- Ancillary studies performed in other sections of the laboratory may provide vital correlative information. Examples include flow cytometry, cytogenetics, and various molecular studies that can be diagnostic, therapeutic, or prognostic. Other examples include chemistry and serology in workup of medical liver disease, and correlating serum tumor markers to ensure adequate histologic sampling of a testicular tumor. When special studies are sent out to a reference laboratory, tracking and reconciling all information for a case can be challenging. The pathologist bears responsibility for constructing a comprehensive report encompassing appropriate ancillary studies. Poor communication between various divisions of the laboratory and a poor laboratory information system may make this a difficult task.
- Ancillary information that the submitting physician obtained from a third party can be critical. Examples include imaging studies, prior biopsies, or clinical labs that were evaluated at other institutions. Such information must be handled with care. The pathologist must be attentive to correct patient identification, reference intervals (when applicable), and the timing of the provided information (e.g., were the provided liver function tests from last week or last year?). Again, knowledge of prior biopsy diagnoses may avoid rework and contradictory diagnoses.
- Contact information for submitting physician and other interested parties may aid in obtaining additional information as needed and may alert the pathologist that a diagnosis is unexpected and likely warrants a phone call to the physician. Also, the treating physician may not be the one who submitted the specimen. Lack of appropriate contact information may delay the transmittal of information to the appropriate personnel.

## Pitfalls and Potential Consequences of Inadequate or Incorrect Clinical History

Inaccurate or misunderstood clinical history can be as problematic as having no clinical history at all (Table 6.1). In a rushed work environment, abbreviations are common and miscommunication may result. Examples include the history entered

**Table 6.1** Pitfalls and potential consequences of inadequate or incorrect clinical history

| Pitfalls of clinical information in surgical pathology | Potential consequences of inadequate clinical information and correlation |
|---|---|
| • Ambiguous abbreviations | • Inappropriate treatment or management |
| • Clinical working diagnosis relayed as definitively established or historical | • Misdiagnosis |
| • Inaccurately presumed clinical history | • Inadequately specific diagnosis |
| • Omission of imaging findings | • Inappropriate specimen triage for ancillary studies |
| • Site and sampling method information | • Lack of necessary ancillary studies |
| • Omission of prior biopsy findings | • Performance of unnecessary ancillary studies or duplication of studies |
| • Insufficiently detailed oncologic history | • Additional time and rework for pathology staff and clinical staff |
| • Omission of immune compromised state | • Delayed case turnaround time |
| • Omission of treatment history | • Delayed notification of significant or unexpected results to treating personnel |
| • Omission of contact information for interested parties | • Diagnostic Overcommitment based on sampling error |
| • Level of urgency not indicated | • Contradictory diagnoses in patient record |
| • Inaccurate or unconfirmed third party data | • Medicolegal consequences |
| • Lack of communication of ancillary studies either inside or outside of the laboratory | |
| • Difficulty in accessing EHR information | |
| • Inaccurate cross-referencing of prior patient specimens in the LIS | |

as “MM,” which could be malignant melanoma or multiple myeloma, or the history of “RCC” (i.e., renal cell carcinoma) that should be “HCC” (i.e., hepatocellular carcinoma). Clinicians and pathologists can also be separated by a medical language barrier. Terminology and jargon that is commonplace to the clinician may not be known to the pathologist (and vice versa). In one study [17], surgeons misunderstood pathologists’ reports 30% of the time. In some instances, a patient may be labeled with a history of disease that has not actually been established (e.g., “history of lung cancer” on the basis of imaging findings or a working clinical diagnosis, but no tissue diagnosis). In some cases, a history may be assumed by either the clinician or the pathologist. For instance, if a patient has a history of nephrectomy, it may be assumed that he had renal cell carcinoma when he actually had urothelial carcinoma (or even a benign process). Consequences of inaccurate or inadequate clinical history include misdiagnosis, inadequately specific diagnosis, inappropriate specimen triage for special studies, lack of needed ancillary studies, or performance of ancillary studies that were not needed. All of the above may result in the ultimate negative consequence: inappropriate management of the patient.

Inadequate clinical information can also result in customer dissatisfaction with pathology services. A 2012 CAP Q-Probes study [18] of turnaround time for large or complex cases in surgical pathology revealed that cases requiring various forms of special handling had a longer turnaround time. Among the forms of special handling were review of operative report or other clinical records (2.2%), review of prior material (6.5%), and delay due to missing information (0.6%). Clinician surveys indicate that, in addition to timeliness, communication of relevant information and notification of significant abnormal results are important customer satisfiers [19, 20]. While many critical values are recognized in surgical pathology, the concept of "unexpected" results is more difficult to define, and such results are more readily identified when either clinical information or a preoperative impression is stated.

Inadequate clinical information has been the underlying cause of medical malpractice claims brought against pathologists. One review of pathology legal cases included a case in which there was failure to notify a surgeon that a colon resected for diverticulitis contained a carcinoma, and a second similar case involving a cholecystectomy [21]. Another review of malpractice claims by Troxel and Sabella [22] indicated that failure to obtain all relevant information contributed to one-fifth of diagnostic errors. Indeed, Troxel has emphasized the importance of clinical history in several legal case studies, including the importance of close examination for bladder carcinoma in situ in bladder biopsies and transurethral resections of prostate, especially in patients with a known history of bladder cancer [23]. Troxel has recommended that clinical information always be entered into the clinical diagnosis or preoperative diagnosis section of the surgical pathology report, and, if no such information is provided that fact should be documented [24, 25]. It is also recommended to report a differential in uncertain cases as this may prompt the clinician to provide additional information that can lead to a different diagnosis [24, 26]. In the case of skin specimens, clinicians frequently do not provide information on prior biopsies or attempts at treatment, so the pathologist must be familiar with the appearance of scar [27]. System errors can result in patient mix-ups and legal issues when the cancer diagnosis is given to the wrong patient [23]. Such errors are potentially avoided with adequate clinical information. Regarding lack of vital clinical history, Rosai wrote [1]:

> The possible medical, financial, and legal consequences of this negligence are enormous, and there are not enough immunohistochemical stains or computer programs that will fully protect the pathologist and the patient against them.

## Special Considerations and Site-Specific Issues

Biopsies and frozen sections are particularly dependent on accurate clinical information and correlation (Table 6.2). When evaluating small biopsies, the pathologist must consider the size of the lesion in order to account for lesional heterogeneity. The location of biopsy sampling relative to other structures or organs may provide clues to contaminating tissues and/or adequacy of sampling. Deep-seated lesions,

**Table 6.2** Special considerations and site-specific issues for clinical information

| | |
|---|---|
| Small biopsies | • Correlation with imaging is especially important for some sites, particularly breast, interstitial lung disease, musculoskeletal lesions |
| | • Size and depth of the lesion (heterogeneity considerations) |
| | • Relationship to adjacent structures (recognize contaminants) |
| | • Polarization for calcifications in breast biopsies |
| | • Evaluation of additional levels for focal findings |
| | • Ancillary studies may be indicated by clinical history |
| | • Treatment history (radiation or drugs) |
| | • Clinical laboratory data (liver and bone marrow) |
| Frozen sections | • Limit use to accepted appropriate applications |
| | • Establish presence or nature of a lesion |
| | • Assess margin adequacy |
| | • Determine if adequate lesional tissue is present |
| | • Determine purpose of the procedure and goal for frozen section |
| | • Prior biopsy findings and/or oncologic history |
| | • Treatment history (radiation or drugs) |
| | • Mishandling may hinder optimal permanent section evaluation |
| | • Risks include loss of small lesions, compromise of margins and staging elements |
| | • Triage material for appropriate ancillary studies |

for instance, may have a "rind" of reactive prominent tissue reaction [1]. For core-needle biopsies of the breast, pathologic–radiologic correlation is essential in every case, and every attempt should be made to resolve any discrepancies. For biopsies taken for calcifications, this may include deeper levels, polarization for calcium oxalate, and obtaining radiographs of the paraffin blocks. In cases of a mass lesion, this may include deeper levels [28]. In a 1997 CAP Q-Probes study [29] of breast needle-core biopsies, participants reported that only 45 % of cases had a radiographic report submitted to pathology, and only 62 % of pathology reports documented correlation between histology and mammography. A more recent Q-Probes study [30] of breast biopsies revealed that despite continued emphasis on mammographic correlation, radiologic images were reviewed in only 22 % of cases, and radiology reports were reviewed in only 48 % of cases. Furthermore, in cases with noncorrelation, 46 % of those pathology reports did not indicate there was a lack of correlation, and 46 % also did not indicate what additional steps were taken in evaluating the specimen. The adequacy of clinical information or provided radiologic information was not specifically addressed in the study.

Clinical information and operative findings can also aid in identifying the biopsy specimen mix-ups. Specific information regarding the character of the sampled lesion can be very helpful. For example, a bladder biopsy sampling from an area

of mucosal erythema should not have the same histologic appearance as sampling from a gross papillary lesion. Likewise, sampling of polyps in the gastrointestinal tract should look different from flat mucosal sampling. Specific information regarding the location of the sampled lesion can also be helpful. In the breast, a sampling from the subareolar region or nipple complex should contain bundles of muscle, and thus, appear histologically distinct from sampling in the more peripheral breast. Any noncorrelations must be investigated in order to rule out specimen mix-ups.

Intraoperative frozen section interpretation requires a close interaction between the pathologist and the surgeon [31]. Appropriate indications for frozen section fall into three categories: (1) to establish the presence or nature of a lesion, (2) to determine margin adequacy, (3) to determine if adequate lesional material is present and if additional sampling is warranted [1]. Frozen section should not be performed to simply satisfy curiosity, to identify normal structures, or to allow expedient communication with the patient and/or patient's family members [1]. Knowledge of the reason and the purpose for frozen section is necessary for appropriate handling of the tissue, and potentially to avoid unnecessary attempts at diagnostic overcommitment by the pathologist. Each organ site has unique indications for frozen section and unique limitations to consider, and the reader is referred to standard texts for a thorough discussion. Inappropriate frozen sections may risk loss of small lesions through rough facing of the block (e.g., focal findings such as giant cells in a temporal artery biopsy), or may compromise margins and staging elements. Mishandling may also hinder the permanent section evaluation (e.g., sectioning a lung wedge taken for interstitial disease, rather than inflating the intact specimen with formalin). Intraoperative triage of material for ancillary studies can be vital in appropriate surgical pathology workups, and this process is aided by accurate clinical information. For example, some lymph node biopsies may require only routine permanent sections (e.g., rule out metastatic disease), but other cases may require flow cytometry (e.g., lymphoma workup), or cultures for infectious disease. Cytogenetic studies may be indicated for a number of specimen types, ranging from placenta to bone marrow. Inappropriate triage of tissue may result in loss of vital ancillary study information.

Specific organ types have other requirements for clinical information and clinical correlation, which are detailed in appropriate texts. Only a few organ sites are mentioned herein. Musculoskeletal pathology is dependent on imaging studies and clinical findings, as nicely summarized by Kilpatrick [32]. In some instances, histologically identical soft tissue neoplasms have different names and different prognoses depending on specific anatomic location or depth (e.g., lipomatous tumors). In the liver, clinical and laboratory data is essential in narrowing the differential diagnosis toward a specific cause [33]. For bone marrow evaluation, necessary information may include duration of symptoms, physical findings, occupation, travel and exposure history, and family/personal medical history, and the marrow biopsy should be correlated with the complete blood count, peripheral smear, and aspirate smears. Ideally, an integrated report is generated that includes not only these elements, but also any flow cytometry findings, and any follow-up ancillary studies [34]. Neuropathology biopsy workup also relies on clinical and radiological fea-

tures such as age/gender, duration and tempo of disease, character of signs and symptoms, prior diagnoses, prior radiation or other treatment, travel or residence in endemic areas, known systemic disease (e.g., immune compromise), and family history. Radiologic characteristics, such as circumscription, infiltration, location, and enhancement features, can all be helpful. The imaging can also aid in determining if the sampling is representative during frozen section evaluation [35]. Investigation of interstitial lung disease requires communication between the clinician, radiologist, and pathologist, and consideration of all factors aids in planning an appropriate biopsy approach (i.e., transbronchial biopsy versus wedge biopsy) [36]. Some histologic patterns of lung disease require that the clinician go back and reassess the patient for occupational exposures, potential sources of hypersensitivity and systemic diseases such as collagen vascular disease. In such cases, a histologic differential diagnosis may be helpful to the clinician.

## Potential Barriers to Communication of Clinical Information

The list of potential barriers to effective communication of clinical information is lengthy, and includes clinicians, pathologists, technology, logistical issues, and at times, the patients themselves. The easy portability of many surgical pathology specimens, particularly small biopsies, allows easy physical separation from their points of origin. This minimizes face-to-face interaction with the receiving laboratory and may be a barrier to communication. The increasing mobility of patients, both geographically and among local healthcare systems, may make the clinician's construction of an accurate clinical history very difficult. For example, a breast cancer patient may have her core biopsy performed in a radiology center, receive neoadjuvant therapy at one hospital, and then undergo subsequent excision at a second hospital. Consequences for such a patient might include inaccurate diagnosis, multiple contradictory diagnoses, and duplication of studies. Technology, including laboratory information systems, radiology information systems, and electronic health records (EHRs), can be important sources of clinical information but are limited by interfacing capabilities, ease of use, by the accuracy of the information entered, and the personnel using them. Computerized provider order entry (CPOE) may be complex enough that the physician relies on ancillary personnel to enter vital information, potentially resulting in the entry of inaccurate information. Even when adequate technology is available, the surgical pathologist must be motivated to make use of it, and to construct integrated reports that reconcile all available information.

Perhaps the most important barrier is a combination of overconfidence in the capabilities of the specialty of surgical pathology, and an apparent growing lack of knowledge of pathology among newly trained clinicians. Due to technological changes and budgetary constraints, many medical schools now employ virtual laboratory exercises rather than traditional hands-on microscope work, and clinical

resident rotations through pathology have all but disappeared. Consequently, clinical resident pathology exposure is generally limited to review of "pre-packaged" surgical pathology cases at tumor boards. The words of O. N. Rambo [5] still ring true a half-century later:

> …because the teaching of pathology used to be relegated primarily to the long-forgotten pre-clinical phase, pathologists traditionally have been regarded to be more scientific than many of their colleagues. A mystic perversion of this assumption prevails among those clinicians who believe that the pathologist, given only a piece of a patient's tissue, has all of the other ingredients necessary to produce a statement of absolute truth at the end of his report. More dangerous to mankind is a pathologist with the same concept.

## Measures of Adequacy of Clinical History

The importance of clinical information may be self-evident to the pathologist, but there is little literature regarding the frequency of its absence or the impact of its absence. A CAP Q-Probes study [37] of surgical pathology accessioning processes reported a number of accessioning deficiencies. Among the deficiencies were: 40% "no clinical history or diagnosis present on requisition slip"; 9.4% "no tissue source indicated on container or requisition slip"; 6.7% "no name of submitting physician." In total, 2.4% of cases had no clinical information on the requisition slip. In the majority (74%) of the cases with missing or incorrect information not related to patient identification, laboratories chose to do nothing about the problem. Accessioning error rates were lower in laboratories with a formal plan for error detection. A review [38] of histopathological cases in the United Kingdom revealed that clinical information was inadequate in 6.1% of overall cases. Statistically significantly higher rates of inadequate clinical information originated from surgeons (9.4%) compared to non-surgeon clinicians (1.4%). In addition, surgeons were less likely to provide a differential diagnosis when compared to other clinicians (38.8 versus 74.4%). Interestingly, there was no significant difference between trainees and consultants for either clinical history or differential diagnosis. Also, surgeons were less likely to provide contact information when submitting a specimen to pathology (27.5 versus 42.0%). An internal quality audit [39] of histopathology reporting in the United Kingdom revealed that 15% of the reports contained inadequate or absent clinical details and 19% contained incomplete or inaccurate clerical details. Similarly, an Australian internal quality audit [40] of surgical pathology reports showed inadequate clinical history in 1.2% of the audited cases and clerical inadequacies in 3.0%. Lack of sufficient clinical and clerical details is not only potentially dangerous, it wastes the time of clerical staff, pathologists, and others.

Another CAP Q-Probes study [41] investigated the extent and severity of problems arising from inadequate clinical information in surgical pathology. In the context of this study, inadequate clinical information was defined as the pathologist's need for additional information before a diagnosis could be rendered, regardless of the amount of information already submitted on the requisition slip. Importantly, if a case had no clinical history and the lack of information did not hinder diagnosis,

the case was not counted as inadequate. Data submitted from 341 participating laboratories revealed that 0.73% of cases required additional clinical information for diagnosis (10th through 90th percentile range, 3.01–0.08%). A higher rate of inadequate clinical information was associated with smaller hospitals and smaller labs, perhaps due to the more general nature of practice in smaller settings and the corresponding lack of specialists, both in pathology and in the clinical realm. Once additional history was obtained, the information led to a substantial change in diagnosis in 6.1%, confirmed the initial diagnostic impression in 59%, and was deemed not relevant to the final diagnosis in 25%. Diagnostic changes or report revisions were more often associated with either malignancy or therapy-induced changes. Additional clinical data were associated with higher rates of diagnostic change in the ovary (15%), small bowel (12%), and lung (10%), and in endoscopic biopsies (7%), and incisional biopsies (7%). The authors concluded that therapy-induced changes in biopsy tissue best exemplify the pathologist's need for clinical information. Only 61% of the study participants had a written policy requiring documentation of clinical history on the requisition form. The most common methods of obtaining additional information were through direct communication with physician (50%), followed by use of the EHR (12%), communication with nursing (10%), prior surgical pathology reports (8%), communication with other healthcare personnel (6%), chart review (5%), and other (9%). Finally, this study also showed an effect on turnaround time, as 32% of such cases experienced delay (15% were delayed at least a day).

Studies of amended reports in surgical pathology do not specifically focus on the impact of clinical information on report amendments, but relevant information can still be gleaned from them. Amended report studies tend to focus on preventing misinterpretation through various mechanisms, among which are clinicopathologic conferences and review at the time of referral to another institution for treatment, both of which often involve additional clinical information. Typically, when clinicians ask for case review they also provide previously unknown information. One Q-Probes study [42] showed that 10% of amended reports directly resulted from additional clinical information that was previously unknown to the pathologist, and an additional 20% of cases were brought to the pathologist's attention because of a clinicopathologic discrepancy recognized by the clinician. A more recent Q-Probes study [43] of report defects found that 5.5% of the defects were discovered following review of additional clinical information and 11.4% were discovered following clinician requested case review. McBroom and Ramsay [44] reported that clinical information affected 7.5% of the reports that were amended as a consequence of review for clinicopathologic conferences. Meier et al. [45] found conference review detected 10–20% of the overall report defects and 42–83% of the misinterpretations during a 4-year-period of tracking amended reports. Nonconference post–sign-out case reviews are also typically initiated by clinicians and include consideration of additional information. A CAP Q-Probe [46] on post–sign-out case reviews in surgical pathology and cytopathology found that clinician-directed reviews were associated with both higher diagnostic discrepancy rates and higher rates of discrepancies with potential for patient harm. Conferences and tumor boards are a time-honored

process allowing pathologists to review cases, often with new clinical and radiographic information, and may constitute an important quality assurance opportunity that allows assessment of diagnostic accuracy in a clinical dialogue [47].

## Means of Obtaining and Documenting Clinical History and Other Pertinent Information

The most common source of clinical information in surgical pathology is the requisition slip. Beyond this, the pathologist is left to either make phone calls to doctor offices, catch up with physicians in person, or attempt to use the EHR. For specimens received from within the pathologist's home institution this may be relatively easy. Pathologist access to the health system EHR allows viewing of the admission history and physical, operative notes, imaging studies, and consultation notes from other subspecialty providers. The laboratory information system (LIS) should provide easy access to prior pathology reports, as well as access to clinical laboratory values. Each institution must work out a process for tracking "shared" specimens so the sign-out pathologist is aware of the pending ancillary studies that are performed in other parts of the laboratory. For example, separate specimens may have been submitted for histology and flow cytometry. Without knowing of the flow cytometry specimen the pathologist may unknowingly release a pathology report that does not represent the complete workup of the specimen. The result may be conflicting diagnoses in different parts of the patient's medical record. It is also vital that patient demographics are consistently accessioned so cross-referencing in the LIS and EHR is correct. It is common for hospital systems to use photo identification for the patient's demographics, while some physician offices use insurance identification cards. Add to this inconsistency, the issue of multiple name changes and it is easy for even a good LIS, manned by good personnel, to inaccurately cross-reference patient specimens.

Renshaw and Gould [48] tracked the use of the EHR during sign-out of surgical pathology and cytopathology cases, and assessed the effect on the final diagnosis. Over an 18-month-period a single pathologist accessed the EHR for 1.8% of surgical pathology cases, and assessed that the information obtained affected the diagnosis in 48% of those cases. EHR information was used to make a more specific diagnosis in 35%, to make a less specific diagnosis in 1.8%, to evaluate a critical value in 9%, and to make a systemic rather than localized diagnosis in 1.8%. Cases involving therapy-related changes were overrepresented. Organ sites most often requiring EHR information were the liver, parathyroids, and lung. The pitfall of finding *incorrect* information in the EHR was noted in one case.

Computer data entry, with use of constraints and forcing functions, can aid in the completeness of information and has shown some success in pathology cancer reporting [49]. However, the pathologist is still vulnerable to variable input. For example, for computerized provider order entry (CPOE), the "P" is not necessarily the physician, particularly if documentation takes place during a surgical procedure.

**Table 6.3** Potential solutions to pitfalls in clinical information

| |
|---|
| • Constraints and forcing functions with computerized entry |
| • Avoidance of ambiguous abbreviations |
| • Avoidance of presumptions of clinical data |
| • Collection of specific information regarding the character and location of the lesion |
| • Easy access to EHR, including specialist consultation notes and operative notes |
| • Easy access to radiology information system data |
| • Accurate laboratory information system cross-referencing of patient specimens including clinical laboratory data |
| • Efficient tracking of ancillary studies and shared specimens including reference testing and concurrent cytology specimens |
| • Pre–sign-out conferences and correlation activities |
| • Inclusion of any clinical data that are not readily confirmed (i.e., "reported history of …") |
| • Pathologist construction of a comprehensive surgical pathology report that reconciles all available information |

The result is entry of what an assistant thinks the physician states as the clinical history or what the assistant understands the history to be and this can be problematic. For example, a circulating nurse in an orthopedic operating room may default to submitting "osteoarthritis" as a clinical history as that is the most common case one deals with. If the patient actually has a pathologic fracture and a known cancer history, such inaccurate information could result in improper handling of the specimen and in missing metastatic disease. Regardless of how the information is obtained, documentation of clinical history on the final surgical pathology report is important. It is likely that all pathologists have fallen victim to the incorrectly reported history. Thus, if the information is "hearsay," then it may be prudent to cite the information as such (i.e., "reported history of…" or "imaging studies reportedly show…") (Table 6.3).

Integration of surgical pathology and clinical data may not be merely a good idea or an academic exercise. New data streams available to clinicians are in competition with the diagnostic evaluation of pathologists. If anatomic pathology computer systems remain isolated entities, they will contribute to the marginalization of pathology as a specialty. Sinard and Morrow [50] envision an evolution to the "Pathologist as Diagnostic Specialist," where pathology is at the hub of medical information. In this scenario, the pathologist uses an advanced pathology information system that integrates histologic interpretation with clinical findings, past medical/surgical history, clinical laboratory data, ancillary studies, genetic data, pharmacogenomics, proteomics, and other data sources, in order to arrive at a data-driven and outcomes-based therapeutic decision. The vital role of pathology informatics in this evolution is obvious.

## Conclusion

The surgical pathologist's highest priority is his responsibility to the patient. Reducing error in surgical pathology is of the utmost importance, and it often involves correlating histologic findings with clinical history [51–53]. Adequate clinical history is a component of the preanalytic phase of surgical pathology [53] and its importance is recognized by both pathologists and regulatory agencies, but its importance is not always fully appreciated by clinicians. Each organ site, each disease process, and each specimen type may be affected to different degrees by various forms of clinical information, but in general terms adequate clinical history is necessary for accurate and appropriately specific diagnoses in surgical pathology. Barriers to obtaining a coherent clinical history include fragmentation of care, disjointed clinical records, lack of access to electronic medical records (EMRs), and other difficulties in communication. Clinical information may also aid in triage of material for ancillary studies, allowing for more efficient and economical workup of complex cases. With the ever-increasing use of ancillary testing in surgical pathology, clinical correlation is becoming more dependent on the construction of comprehensive surgical pathology reports that reconcile all available laboratory data. Thus, the pathologist bears some responsibility for obtaining and documenting clinical history and clinical correlation. Failure to do so may have diagnostic, therapeutic, and legal consequences.

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# Chapter 7
# Knowledge, Training, and Experience

**Amelia Huck and Vania Nosé**

## Introduction

Errors in the interpretation of diagnostic surgical pathology specimens are only one of the many forms of error that may occur in surgical pathology; multiple factors are responsible. A diagnostic error represents "the assignment of a pathologic diagnosis that does not represent the true nature of disease (or lack of disease) in a patient." However, as the practice of pathology is subjective, involving interpretation of complex data sets, it is very difficult to define a true value or a true/correct diagnosis for any given specimen. Because of the subjective nature of interpretive diagnoses, the pathologist's knowledge and experience play a major role in preventing errors. Multiple studies demonstrated that interpretative diagnostic errors may account up to 25 % of all errors in surgical pathology [1, 2].

Errors have been classified in a number of systems. One simple way to categorize errors is to divide them into major and minor errors. Major errors are those with an impact on treatment or a marked change in prognosis. Minor errors have no impact on treatment and have, at most, a minor effect on the patient's prognosis [3].

With diagnostic errors in surgical pathology affecting at least 1.2 % of all cases, without apparent significant variation by department size, identifying and reducing these errors is imperative [4]. Proposed mechanisms to detect misdiagnoses and errors include secondary, blinded, targeted, consensus, or specialist/expert review; prospective or retrospective case review; study of amended reports; correlation of cytology with subsequent histology; or correlation of frozen sections with final paraffin section diagnoses [3–7]. All these reviews are heavily dependent on the knowledge

A. Huck (✉)
Department of Pathology, Massachusetts General Hospital, 55 Fruit Street,
Boston, MA 02114, USA
e-mail: ahuck@partners.org

V. Nosé
Anatomic and Molecular Pathology, Massachusetts General Hospital, Boston, MA, USA



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and experience of the pathologist involved in managing the case as well as of the reviewing pathologist. The optimal mechanism for error detection varies by practice size and type. Academic departments that are large enough to have a completely subspecialized system will inevitably use a different approach than a smaller hospital with a general sign-out. Currently, the most common reason for diagnostic error detection in clinical practice is case re-review on clinician's request when the results do not fit with the clinical picture. When errors are detected in this way, they are particularly likely to be clinically significant [8]. In the world of subspecialization, the pathologist is very familiar with clinical situations and is usually integrated with the clinical team on a routine basis. This offers great advantage over a pathologist who is not clinically integrated and is not knowledgeable of the precise clinical situation.

All instances of error detection are essentially due to case review. A study from the College of American Pathologists of 45 laboratories revealed that 6.6% (median, by laboratory, 8.2%) of cases contained documentation of secondary review prior to sign-out [9]. Most pathology departments also review a proportion of cases after sign-out that leads to corrections in the reports. The true number of reviewed cases is likely higher than the documented number. Most of these cases were reviewed either because the primary pathologist requested a second opinion on a challenging case (46%) or because the laboratory required audit (43%). The reviewed cases were most likely to be malignant (45%) or malignant mimics (16%) [9]. Secondary review in a timely manner of biopsies diagnostic of malignancy, prior to issuing a final report, has been suggested to improve the accuracy of diagnostic histology reports [6]. However, secondary review also adds time and expense to cases, so it is important to optimize which ones are reviewed.

Regular consensus conferences are one approach to regular secondary review, particularly of challenging cases. Regularly scheduled consensus conferences have three considerable advantages. First, a predictable consensus conference reduces the sense that one is taking up another pathologist's time when sharing a case. Second, difficult or unusual cases are often excellent educational opportunities, and sharing them is a valuable exercise. Third, this is a way to tap into the collective knowledge and experience of pathologists within the department [10].

Ideally, internal case review done for the purpose of error detection and for following error rates should be done promptly after (or before) sign-out to allow any detected errors to be corrected while still clinically relevant [5]. Different practices have varying approaches for internal case review. Groups that use random case audits generally review between 2–4% of cases, which generates discrepancy rates of less than 3%. However, random case audits can be quite time consuming for a relatively low yield of discrepancies [5, 11].

## Error Prevention by Subspecialty Target Review of Cases

In response to the sentiment that random case audits detect few errors for the time required, many groups use a targeted review approach. These reviews focus on specific types of cases, which can include all malignant cases, malignant cases in

specific organ systems that are subject to higher variability (e.g., prostate, breast, pigmented skin lesions), or medical cases that are thought to benefit from specialist review (e.g., liver, renal, inflammatory skin reactions) [12]. More importantly, these types of review use the selective expertise of pathologists who have additional interest in specific areas of pathology. These individuals also understand the clinical situation to greater extent and are more adept at diagnoses with meaningful nuanced interpretations. One group that had previously used random review for error detection transitioned to a system where they chose targets (by specimen type or diagnosis) with high rates of variability (chondroid lesions, stomach biopsies, bladder biopsies, and well-differentiated liposarcoma) within a subspecialized system. They found that targeted review led to higher rates of error detection (13.2%; 3.2% major) than in random review (2.6%; 0.36% major), though this is clearly dependent on appropriate target selection [11]. Malignant diagnoses may seem like an obvious target, but many warn that reviewing only malignant diagnoses fails to detect false-negative diagnoses, which are more common causes of error causing patient harm [13].

To attempt to identify discrepancy rates without slide review, one group tracked diagnoses by pathologist to track whether individuals were under- or overdiagnosing different types of cases relative to their peers. While tracking diagnoses can be very helpful on the most common types of specimens (e.g., tracking atypical squamous cells of uncertain significance (ASCUS) rates in Pap testing), natural variation can make interpretation of these data difficult. The same group revisited rates of variability before and after changing to a subspecialty sign-out. In their experience, the rates of different diagnoses in gastrointestinal biopsies were unchanged after transitioning to a subspecialty system; however, it is possible that rates of unusual or difficult gastrointestinal biopsies (e.g., assessment of low-grade dysplasia in Barrett's esophagus) are too low to appreciate significant improvement when reviewing in broad strokes [14, 15].

## Impact of Specialist Expertise in Error Detection

Secondary review, including internal or external specialist review, and central review of cancer cases by specialist pathologists at cancer centers are very important for reaching the precise diagnosis. One could rely on an acceptable standard or a diagnosis rendered by a general, but experienced, pathologist. However, this will also have bias determined by practice patterns, training, experience, personal anecdotes, and human error. One cannot rely entirely on expert opinions or expert diagnosis, as they may harbor significant bias in themselves [3, 7, 14, 16].

Intuitively, expert opinion should improve diagnostic accuracy and error rates. In practice, defining expertise is challenging. Expertise could be defined by fellowship training, board certification, volume of cases seen, publication record, affiliated academic institution, or, more likely, a combination thereof. In some situations, expertise may be the product of collaboration rather than only from in-

dividual knowledge. Subspecialization has been increasing across medical fields. Just as surgeons and oncologists, particularly in large, academic practices, have narrowed their scope to maximize efficiency and knowledge of their chosen system, many pathology departments have moved to a subspecialized system, where each pathologist has one (or, commonly, two) specialties (by organ system) that he or she signs out. Often, one of the specialties is their primary expertise. This allows individual pathologists to focus broadly within a narrow scope. Correlating the gross and microscopic appearances to the broader clinical context, molecular and laboratory data, radiologic appearance, and even suggest potential associated syndromes can maximize the value of the pathology report. Developing relationships with the corresponding clinical subspecialist can maximize the value of the pathologist. In addition, to master the breadth of information available in one subspecialty may be intimidating; mastering that breadth across subspecialties is closer to impossible. Of course, subspecialization is an option available only to the largest departments. Small groups continue to practice as general pathologists and may rely more on outside consultation. Medium-size groups may take an intermediate approach where each pathologist acts as a "point person" for a given specialty, but everyone signs out general cases [10].

On a grand scale, any type of second opinion (expert or nonexpert) is likely to result in a more definitive diagnosis (fewer "atypical" or "suspicious" diagnoses) [8] and a lower error rate, even when the case is reviewed because it is perceived as difficult by the primary pathologist [17]. Case referral for external second opinion is common and happens primarily for one of two reasons: at the primary pathologist's request or at the request of a clinician at a referral center where the patient is being seen. If the external opinion is requested by the primary pathologist, the case is sent to someone who is perceived to be an expert in the field.

## Impact of Subspecialty and Knowledge in Error Prevention

Specialist review at the primary pathologist's request is dependent on the primary pathologist recognizing what he or she does not know, and is therefore less likely to avoid false-negative diagnoses [10]. A survey of 180 laboratories revealed an outside consultation rate of 0.5%, with the specialist adding significant information approximately 16% of the time. The most common specimen types were found to be skin (16%), hematolymphoid (12%), and breast (10%). Groups with a lower volume are more likely to request outside opinion than those with a higher volume, which presumably reflects either experience with uncommon entities or the likelihood of having an internal specialist available to review the case [18].

It has been suggested that there are some types of cases that should always be referred to a specialist (external or internal), which include, but are not limited to, any biopsy for medical reasons (e.g., liver, renal, and inflammatory skin conditions) [12] and breast cases with a diagnosis of ductal carcinoma in situ [19].

Current recommendations encourage review of pathology cases by the hospital to which the patient has been sent for treatment or second opinion. The overall rate of changed diagnosis due to these reviews is approximately 2 %. Globally or locally, tracking what types of specimens or diagnoses are changed more frequently than others can lend insight into problematic areas. In addition to providing a second opinion, these reviews allow clinicians to understand the pathology of the patient as fully as possible, as they are generally most comfortable with the diagnostic threshold and wording used by the pathologists at their hospital [12]. A number of studies evaluating the value of these second opinions have been done and provide a glimpse into the circumstances where second opinions may be the most critical.

In error detection, there are potential ramifications (to the patient, pathologist, and clinician) to a change of diagnosis particularly when slides are sent for a second opinion after the patient has already received treatment (especially chemotherapy), accentuating an advantage of an early second opinion, especially when an eventual referral is anticipated. These changes, even in cases where the medical significance of the change is limited, can have marked psychological ramifications for the patient. It is not uncommon for the second pathologist to have the advantage of subsequent information that the primary pathologist did not have, and this should be reflected in the report. Overall, when a major discrepancy is found, it can be helpful for the second pathologist to be in direct communication with the primary pathologist [20].

The dermatopathology group at the Massachusetts General Hospital (MGH) reviewed referral cases of melanocytic lesions from 1996 to 1997 and from 2010 to 2011, comparing the MGH diagnosis to the diagnosis from the referring institution. They found, on follow-up, that patients were generally treated according to the more severe diagnosis regardless of which diagnosis (first or second) was more severe. Overall, they found that they changed the diagnosis 35 % of the time, but that the discrepancy rate was different when cases were sent in from a dermatopathologist (32 % discrepancy rate; 12 % were major discrepancies) rather than from a general pathologist (51 % discrepancy rate; 21 % were major discrepancies). The fact that pathology groups have become progressively more subspecialized over time was also highlighted by the fact that in 1996–1997, 26 % of the cases were from generalists, whereas in 2010–2011, only 11 % were from general pathologists. These data do suggest that specialist sign-out does reduce discrepancy, but also emphasize that discrepancy still exists amongst specialists [21].

The University of Iowa reviewed all cases that were referred for a second opinion when the patient was sent for treatment between 2003 and 2006. The referred cases were reviewed by at least two general pathologists with the exception of medical renal, neuropathology, and bone marrow cases, which were reviewed by specialists. They found a 2.3 % major discrepancy rate (1.1 % resulted in a change in treatment) and a 9.0 % minor discrepancy rate, which are similar to published error rates in surgical pathology. Long-term follow-up was available for 59 cases with major discrepancies, and they found that the follow-up supported the original diagnosis in 8 cases, the second diagnosis in 49 cases, and was indeterminate in 2 cases. These data serve as a reminder that while second opinion often yields a more accurate diagnosis, the last opinion is not inevitably the correct one [22].

Pathologists at the Ohio State University examined reports from gynecologic specimens sent over the course of a year for a second opinion and found approximately a 15% discrepancy rate, 4.7% of which were major discrepancies. All the cases at the Ohio State University were reviewed by a gynecologic pathologist, and it is possible that the increase in discrepancy rate relative to the general baseline reflects an advantage to specialist review [23].

## Impact of Specialist in Comparison with General Pathologist on Error Rates

It has been suggested that medical liver biopsies are commonly misinterpreted when they are not reviewed by a liver pathologist. A study of medical liver biopsies referred for a second opinion to several institutions in 1996–1997 revealed a 28% major discrepancy rate, with many errors due to missing cases with changes of chronic cholangitis, and a 38% minor discrepancy rate. These figures reflect the importance of identifying types of cases with high error rates and handling them appropriately [24]. Others have also noted that specialist review of transplant liver biopsies can be helpful, but that if the specialist pathologist is external, it is critical to ensure that he or she has adequate clinical history, as review of a medical biopsy without relevant history can introduce, rather than reduce, error [16].

Ductal carcinoma in situ (DCIS) can be a challenging diagnosis with significant treatment implications, and it has been recommended that cases with a diagnosis of DCIS are reviewed by a specialist in breast pathology [19]. Pathologists at the University of Toronto evaluated 350 cases of DCIS referred for a second opinion prior to the patient being treated from 1982 to 2000. They found that concordance was high for tumor size, the presence of necrosis, and margin status, but that a third of the outside cases were missing data on key points: nuclear grade, tumor necrosis, or tumor size. While there was some improvement over time and synoptic reporting may help improve rates of missing data, they did find that 29% of cases had a discordance that changed the estimate for local recurrence, which may have an effect on treatment. These findings may reflect a high baseline rate of disagreement in breast epithelial lesions, but may also support the recommendation for secondary review by breast specialists in these challenging cases [25].

Review of soft tissue tumors in patients referred for treatment to the University of Utah highlights both the importance of pathologist experience and subspecialty expertise in handling difficult, rare cases where diagnostic discrepancies can range from 17 to 48% as well as the importance of subspecialty teams across medical fields. Orthopedic surgeons also rarely encounter soft tissue sarcomas, and inexperience in the evaluation of gross margin status by the surgeon followed by inexperience in sarcomas by the pathologist can lead to undertreatment. In this series, they found that there was a 49% rate of change in margin status from negative to positive on review [26]. These examples in handling difficult cases highlight the importance of subspecialty training and subspecialty expertise and reducing and preventing errors.

Investigation of the effect of a multidisciplinary subspecialist approach on the treatment of patients with liver tumors found that bringing together multiple specialists, including specialty (liver) pathologists, radiologists, oncologists, etc, resulted in a change in treatment plan for nearly 42% of patients. Pathology review resulted in a change of 10% of diagnoses, many due to a revision in interpretation of immunohistochemical stains. The most common (21%) change was from an indeterminate diagnosis to a malignant diagnosis, but 14% were changes from malignant to indeterminate. This evidence also underscores the value of specialist review and knowledge, but it particularly reaccentuates the importance of communication across medical fields as well as clinical input in pathology diagnosis [27].

Maximizing specialist knowledge and impact at the local level can be valuable as well. Expertise from a distance can offer influence on individual cases, but it is harder to affect change in reporting style or grossing protocols from a distance. Reviewing periampullary adenocarcinoma diagnoses from Whipple specimens that were grossed according to a specific protocol revealed variability in the classification of these adenocarcinomas amongst gastrointestinal pathologists. More accurate classification can affect the patient prognosis as well as data collection for treatment and prognostic studies. In this evaluation, they found that using consensus classification revealed a significant survival difference between bile duct adenocarcinoma (median, 22 months) and pancreatic ductal adenocarcinoma (median, 12 months) [28].

These examples of studies of secondary review confirm that secondary, particularly specialist, review can be a valuable addition to diagnostically difficult or unfamiliar cases. A subset of these studies also highlights, to some degree, levels of baseline interobserver variability, which is accentuated in certain types of specimens, such as breast, soft tissue, and melanocytic lesions.

## Subspecialty Diagnostic Threshold and Error

Subspecialized sign-out and specialist review may improve error rates and help to optimize patient care, particularly in challenging diagnoses. However, the threshold of certain diagnosis may differ amongst experts in the subspecialty. It is known that soft tissue tumors, melanocytic tumors, and breast epithelial lesions are common sources of discrepancy, not only between general pathologists and specialists but also amongst subspecialists.

To examine variability between academic specialist pathologists further, we reviewed surgical pathology reports (167) on 119 patients who were first seen at the MGH and subsequently seen at the Brigham and Women's Hospital (BWH). Amongst the 119 patients, there were 13 major discrepancies (11%), which included changes in tumor grade, stage, or margin status. One case was a change in the type of sarcoma. One case was downgraded from malignant (melanoma) to having uncertain malignant potential, one from atypical (flat epithelial atypia of the breast) to benign, and one from suspicious (lymphoma) to benign with the aid of hindsight after resection done at the BWH (Table 7.1).

**Table 7.1** Discrepancy rates between academic hospitals by subspecialty

| Specialty | Reviewed cases | Major | Minor | Major discrepancy rate |
|---|---|---|---|---|
| Breast | 29 | 3 | 5 | 0.10 |
| Bone and soft tissue | 13 | 3 | 2 | 0.23 |
| Cytology | 2 | 1[a] | 0 | 0.50 |
| Dermatopathology | 5 | 2 | 0 | 0.40 |
| Head and neck | 5 | 0 | 0 | 0.00 |
| Eye | 4 | 0 | 0 | 0.00 |
| Gastrointestinal | 12 | 1 | 2 | 0.08 |
| Genitourinary | 12 | 0 | 3 | 0.00 |
| Gynecologic | 12 | 0 | 1 | 0.00 |
| Hematopathology | 10 | 0 | 0 | 0.00 |
| Mixed | 5 | 0 | 0 | 0.00 |
| Neuropathology | 5 | 0 | 1 | 0.00 |
| Pulmonary | 5 | 1 | 0 | 0.20 |
| Total number | 119 | 11 | 14 | 0.09 |

Mixed subspecialty refers to cases where the patient had multiple specimens that spanned different organ systems

[a] The interpretation of the discrepant cytology case reflected the findings in the excised lymph node

Breast cases are the most likely to be re-reviewed, and along with bone and soft tissue cases, are where most of the discrepancies lie. Smaller numbers of cytology, dermatopathology, and pulmonary cases were reviewed, but also had major discrepancies. These findings support the sense that soft tissue tumors, melanocytic tumors, and breast epithelial lesions are common sources of discrepancy—not only between general pathologists and specialists but also amongst specialists. These findings additionally emphasize the importance of communication with clinical teams, which should understand which areas are most subject to variability.

While subspecialized sign-out and specialist review may improve error rates and help to optimize patient care, particularly in challenging diagnoses, it is not always practical, and the advantages must be weighed against its disadvantages. Long-term patient follow-up has shown that up to 8 % of diagnoses rendered on second review were inferior to the original diagnosis [29]. Broad use of specialist consult could lead to excess specialized testing, provide a false sense of certainty, and devalue the role of the general pathologist [12]. Even large departments are rarely specialized to the point of one specialty/pathologist, and it is important to be able to maximize knowledge and education in secondary areas or general pathology as well.

## Minimizing Errors by Standardization of Reporting

There are multiple approaches to improve standardization of pathology reports: synoptic reporting, national guidelines, and pathologist education are all beneficial. Keeping up with new information and recommendations often falls to the individual pathologist or group, and there are different approaches to optimizing this knowledge diffusion [10, 30].

The development and circulation of formal criteria are critical steps in improving uniformity of pathology diagnoses. After a small study that involved sending slides of epithelial breast proliferations out to specialty pathologists revealed unacceptably high levels of interobserver disagreement (no case exhibited 100% concordance) [31], a second group first distributed criteria for the diagnosis of epithelial breast proliferations and then also shared slides to determine concordance rates between six breast pathologists. They found that the addition of the first distributing criteria for diagnosis resulted in a higher concordance rate amongst the group, with complete agreement in 58% of cases and near complete agreement in 71% [32]. While these figures are encouraging, the nearly 30% disagreement between experts illustrates that there is additional room for improvement.

The WHO criteria for classification of gliomas have been widely distributed. To evaluate concordance between neuropathologists using the same criteria, a group of neuropathologists gathered four times over the course of 18 months to review glioma cases together after independent review. They found that there were few discrepancies between pathologists about grade 4 tumors, but many between grades 2 and 3 that rely, at least partially, on more subjective criteria such as hypercellularity and atypia or on diligence criteria such as finding rare mitoses. However, concordance between the four pathologists did increase over the 18 months (from 54 to 86%), revealing both that while formal criteria are informative, they will not alone result in concordance and that training through consensus and discussion can be very valuable in creating more consistent diagnoses [33].

Guideline review and discussion is not always as effective. One group investigated the reproducibility of the ASCUS diagnosis using the Bethesda manual by dividing 100 cases (negative, ASCUS, squamous intraepithelial lesion based on five-person consensus) into pre- and post-tests. Eight pathologists (four experienced cytopathologists and four with less experience) first reviewed the 50 pretest cases with absolute agreement between 44 and 62%. Next, they broke into two teams, each with two more and two less experienced cytopathologists, and reviewed together the Bethesda manual. The absolute agreement on the post-test was 40–60%, illustrating relatively weak reproducibility of the diagnosis of ASCUS even with added training and consensus [34].

Pathologists at the University of Oklahoma, noting historically slow adoption of new guidelines, took a more aggressive approach to guideline distribution within their department. They first distributed a pretest about the new guidelines for lung cancer reporting and molecular testing. Pathologists who scored low were required to attend a seminar about the guidelines and were assigned to a second pathologist

who had scored well to review lung tumor cases. Cases that were signed out before and after this intervention were reviewed, and they found a significant increase in the application of the guidelines. The department also moved from a general to a specialized sign-out during this time, which may confound the data; however, only one of the pathologists signing out lung cases in the subspecialized system had passed the pretest. These findings suggest that taking a hands-on approach to distributing new guidelines can be effective, and the authors suggest that including self-assessment tools for use by pathologists or departments when new guidelines are released for pathology reporting may expedite compliance [35].

## Minimizing Errors by Evaluating Pathologist Competence

There are multiple approaches to improve surgical pathology standardization: synoptic reporting, national guidelines, and pathologist education. Board exams and hospital appointment regulations mandate a very basic level of competence. The continuation of pathologists' privileges at a hospital hinges on the quality and safety of care delivered. The review of privileges falls on the medical staff, which monitors the performance of the pathologists who are granted privileges and makes recommendations regarding which medical staff members should receive new or maintain existing privileges.

The American Board of Pathology (ABP), as one of the member boards of the American Board of Medical Specialties (ABMS), is committed to continuous professional development through its Maintenance of Certification (MOC) program. The ABP is working to maintain and improve the knowledge base of the pathologists requiring the MOC. The ABP MOC program consists of four parts, which are described in greater detail under MOC requirements:

Part I—Licensure and Professional Standing: Diplomates must hold a valid, unrestricted medical license.

Part II—Life-Long Learning and Self-Assessment: Diplomates must meet the ABP's educational and self-assessment requirements.

Part III—Cognitive Expertise: Diplomates must pass a secure examination that assesses their pathology-specific skills and knowledge.

Part IV—Evaluation of Performance in Practice: Diplomates must demonstrate their use of best evidence and practices compared with peers and national benchmarks.

The ABP stresses that to successfully complete a 10-year MOC cycle, a diplomate must have the reporting forms approved, complete an approved patient safety course, and pass a secure MOC exam. After successful completion of the first 10-year MOC cycle, the diplomate's certificate will be renewed for the next 10 years.

In 2007, The Joint Commission introduced its Ongoing Professional Practice Evaluation (OPPE) and Focused Professional Practice Evaluation (FPPE) processes. These tools were created to work together to help determine whether the care delivered by a practitioner falls below an acceptable level of performance. The Joint

Commission, in an attempt to regulate the maintenance of physicians' knowledge and competence, requires the OPPE and FPPE. It is important to note that neither tool on its own is capable of making an adequate assessment, but instead, it is the thoughtful and judicious use of both that is required.

The often slow rate at which changes are incorporated into practice highlights the need for continuing education and evaluation of pathologists [10]. The value of expertise is also such that when making hiring decisions, it is crucial to hire the person with the appropriate skill set. Someone with distant or minimal training without more recent experience may not be adequately prepared [8]. In addition to knowledge-based training, it is also valuable to provide initial training in departmental or group-specific idiosyncrasies [2].

## Final Remarks

There is no one magic solution to the reduction of diagnostic error in surgical pathology. These studies of second opinion and information dissemination highlight some approaches to error identification and reduction. Recognition of one's own weaknesses (in either knowledge or experience) and utilization of secondary review (intradepartmental and/or extradepartmental as appropriate) continue to be some of the most powerful tools. Developing a protocol for case review, particularly targeting diagnoses subject to increased variability, can be beneficial for error detection, though the optimal approach will vary by practice type. Sharing of information—cases via consensus or discussion of new guidelines—can be essential for maintaining and increasing the understanding of new or unusual diagnoses.

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# Chapter 8
# Standardization of Diagnostic Terminology and Criteria: A Prelude for Error Reduction

**Raouf E. Nakhleh**

## Introduction

Interpretive diagnoses are subjective as a whole and depend on the pathologist's interpretation of a visual image. Once a lesion is identified, it must be appropriately categorized so that the clinician is able to act on that diagnosis. The terminology used to identify a lesion is as important as identifying the lesion.

It has been said that classifications are the language of medicine.

For pathologists, this is twofold; first there must be agreement as to which terms are used. Agreeing on the terms is like agreeing on the definition of a word in language.

For example, it is widely accepted that a cancer of epithelial origin is termed carcinoma, a cancer of lymphoid origin is termed lymphoma, and a cancer of soft tissues is termed sarcoma. However, there are many subtleties and many exceptions. This also changes with time and our understanding of histogenesis and pathogenesis. For example, a tumor commonly referred to a hemangiopericytoma in the past is now agreed upon to be designated as solitary fibrous tumor [1]. Another example is a group of seemingly unrelated tumors that are now recognized to be histogenetically similar. The tumors, now recognized as PEComa's or perivascular epithelioid cell tumors, have varied terms used in their diagnoses including angiomyeolipoma, lymphangioliomyomatosis, and sugar tumors, etc. [1].

Second, pathologists must agree on what features, morphologic and/or otherwise, are necessary to define a lesion. Once this is determined, a process should be conducted to assure that identification of features and diagnosis of an entity is reproducible. This is particularly important when a lesion is part of a continuum. Grading systems of preneoplastic lesions and inflammatory conditions are good

R. E. Nakhleh (✉)
Department of Pathology, Mayo Clinic Florida, 4500 San Pablo Rd.,
Jacksonville, FL 32224, USA
e-mail: nakhleh.raouf@mayo.edu



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examples of this need. The importance of defining these lesions and demonstrating reproducibility is necessary to best manage and treat these patients [2]. A diagnosis of low-grade dysplasia may be followed up with little treatment, but a diagnosis of high-grade dysplasia may lead to more drastic attempts of resection or ablation in order to prevent progression.

## History and the Need for Standardization

Historically, the practice of pathology was not systematized nor organized. Progress happened because of individuals' efforts to define disease. The discovery and categorization of disease occurred in a very haphazard way. Examples of this type of discovery happened abundantly all the way to the end of the twentieth century.

During the final quarter of the twentieth century, many began to realize that identical disease had been given multiple names by different authors. For example, the lesion commonly found in the thyroid that is currently known as "nodular hyperplasia" has been referred to as: nodular goiter, multinodular goiter, adenomatoid goiter, and adenomatous hyperplasia. In an attempt to put order where chaos exists and help reduce diagnostic disagreement or error, some authors began to develop categorization schemes for tumors of the same site. Differences in schemes became confusing, as different authors devised dissimilar schemes for the same organ system. Clinicians that worked at a center with an established system realized the benefits. But when patients or clinicians moved to another institution, diagnostic discrepancies became apparent.

Lymphoma classification is a good example of how multiple systems developed [3]. While earlier classification schemes existed, few were widely used till the introduction of Rappaport's classification system in 1966. It was the first system to be widely used in the USA and in many other countries till the early 1980s. The development of various molecular, immunohistochemical, and flow cytometry testing lead to the development of classifications that are based on clonal expansion of normal tissues culminating in systems offered by Lukes and Collins in the USA and by Lennert in Germany also known as the Kiel classification. Subsequently, the need to unify these systems leads to the "working formulation." In the mid 1990s, this evolved to the revised European American lymphoma (REAL) classification. REAL was adopted by the World Health Organization (WHO). The WHO classification is currently used. This system is comprehensive in its approach of incorporating morphologic as well as cellular and genetic markers to establish the best classification of disease. Partly because of the complexity of these schemes and the proliferation of terms with seemingly endless changes in classifications, many pathologists routinely consult with a hematopathologist before signing out a case of lymphoma. Without a doubt, there will be evermore modifications to the current schemes with advancement in knowledge and tools used to assess tumor cells.

The problem of lymphoma classification is perhaps the most complex in terms of number of diseases or lesions and number of variables used to classify these

diseases. The history of multiple classification schemes that ultimately coalesce into one unified and widely accepted scheme is a story that can be repeated for virtually every other organ system [4, 5].

Standardization has also taken root in multiple areas of non-neoplastic or inflammatory diseases. Most notable among these is in the area of transplant rejection. In the 1970 and 1980 as technical and pharmacologic improvements were made, transplantation was more widely performed for multiple organs. Traditionally, pioneering centers developed their own grading schemes for rejection to assess and managed their patients. The impetus to improve transplant outcomes depended on multicenter drug trials. This led to the need to standardize rejection grading schemes so that groups could be adequately compared. In the early 1990s, the Banff working classifications for kidney, liver, and pancreas rejection were introduced [6–8]. The International Society for Heart and Lung Transplantation also introduced systems for heart and lung rejection [9, 10]. The classification of each organ has been periodically revised and updated.

## Elements of Standardization

There are three elements necessary in any successful classification schemes (Table 8.1) [2]:

1. Ease of use: a system should be easy to use, teach, and learn. A system should be based on relatively few objective findings. Grading of breast cancer is as complex as a system may be and still be successful. It is dependent on three factors, tubular content, nuclear grade, and mitotic rate. These three elements are graded and combined to achieve the overall grade. This works because each of these elements is a simple three-level choice. Any more elements would probably make this system too complex with loss of ease. Features have to be clear, e.g., "the presence of marked variation in size, prominent nucleoli, and chromatin clumping is nuclear grade 3," "> 75 % of the tumor is grade 1 tubular formation" etc.
2. Reproducibility: the use of any system should be tested for diagnostic agreement between pathologists. This is ultimately the goal in reducing errors and achieving greater diagnostic agreements. Typically, a set of cases that are vetted to cover

**Table 8.1** Factors necessary for successful standardization schemes

| Necessary features | Demonstration |
|---|---|
| Ease of use | Ease of use in all settings, not just tertiary centers; the process should be simple |
| Reproducibility | Sufficient studies demonstrating good diagnostic agreement with moderate or substantial kappa statistical agreement |
| Clinically relevant | Diagnostic categories should have relevance to patient's therapy and prognosis |

the spectrum of findings is circulated among a number of expert pathologists, and diagnostic agreement is calculated using a Kappa statistic. A Kappa value of 0.4–0.6 is considered moderate agreement and is generally acceptable in most systems. The substantial agreement level (> 0.6–0.8) is considered excellent.
3. Clinical relevance: the levels devised by the grading or staging system must be relevant to patient treatment or prognosis if they are to be of benefit to patients. For example, it may be easy to classify a process into ten levels, but this is not helpful, if there are only two treatments that can be used to manage the patient. The only clinically relevant level will be the point at which therapy should be changed.

The failure of any scheme may lie in any of these factors. Pathologists are likely to avoid using a scheme if it is too complex or too difficult to learn. And if they are forced to use it, they are likely to apply the rules poorly. If a system is too vague or dependent on subjective criteria, pathologists will interpret finding in different ways and this will result in poor diagnostic agreement. Lastly, if a scheme is not clinically relevant, clinicians will not ask for it and pathologists will have no incentive to use it.

## The Benefits of Using Standardized Terminology

1. The ultimate benefit is improved diagnoses and improved patient care. In a perfect world using the most relevant terms to describe a person's disease lets the clinician know exactly what to do. And it would not matter where geographically the patient was being treated, if the pathologist is using the same terminology that the clinician understands. Problems occur when pathologists use a system of disease classification that is obsolete and is no longer applicable to current disease treatment recommendations. Problems also occur when there are two or more systems of classification, and it is not apparent which system is being used.
2. Standardized diagnostic information lends itself to ease of use. If the diagnostic categories are predetermined, it is easy to incorporate these categories into menus to choose from. It has been shown repeatedly that synoptic computerized reports are more complete and are preferred by clinicians. Pathologists more easily complete reports with more confidence in having included all the pertinent information needed to manage the patient.
3. Standardized diagnoses enhanced data collection and comparison of treatments. Progress in medicine is dependent on ongoing clinical trials to improve upon current treatment. This process is heavily dependent on having accurate standardized diagnoses. When comparing different treatment modalities, researcher needs confidence that patients enrolled in the study have the same disease and even the same stage of disease. This is the only way to make direct and equitable comparisons regarding outcome of different therapies.

4. Standardized diagnostic terminology facilitates adherence to standards of care. If there is an agreed upon language of terms to use in the diagnosis of a particular disease and a pathologist uses the standardized terms, the clinician is then able to take that information and apply existing guidelines for the treatment of that disease. For example, the pathologist's diagnosis stage II squamous cell carcinoma of the lung, the clinician is able to access current recommendation for that tumor and stage and offer the patient the most current available treatment.
5. Standardized diagnostic terminology facilitates the assessment of care where treatment guidelines exist. If guidelines exist for the use of standardized terminology such as the cancer protocols, then a director of a service may directly assess the appropriate use of those protocols. Lack of compliance with the use of cancer protocols in accordance to departmental or national policies would indicate clear suboptimal practice. The same could be said for clinicians that have practice guidelines for specific disease processes. With the availability of standards or standardized language, these assessments can be made objectively.

## Additional Indirect Benefits of Standardization

When diagnostic as well as grading and staging criteria are agreed upon and published and pathologists start using the schemes, certain aspects of practice related to classification systems are then recognized and addressed. A series of articles published by the Cancer Committee of the College of American Pathologists demonstrate the ongoing evolution of these schemes [11–15]. Subtle deficiencies are identified in the schemes that are addressed with investigations to determine solutions or answers to questions. Examples of this type of work include practical problems in staging of breast cancer, highlighted in an article by Dr. James Connelly [12]. This includes the classification of isolated tumor cells in lymph nodes and the determination of tumor size when multiple tumors are present. Other problems in the lung cancer checklist are addressed by Dr. Alberto Marchevsky [13]. In particular, defining pleural involvement in the staging of lung cancer and defining tumor location with the presence of multiple tumors. He also addressed determination of lymphatic involvement by tumors. Dr. John Srigley [14] emphasized preanalytic aspects of specimen handling in order to maximize the information gained during microscopic examination and synoptic reporting. Dr. Carolyn Compton [15] addresses problems with colorectal standardized reports focusing on the evolving issue of radial margin in colorectal surgery. She also addresses issues concerning microscopic tumor satellites and determination of lymph node metastasis when lymph node tissue is not identified. In summary, establishment of standardized diagnostic as well as staging and grading criteria is not a static process but is continuously evolving with the study and identification of selected problems, leading to further investigation and clarification of criteria.

Agreement on a single set of diagnostic, staging, and grading criteria makes it easier for pathologists to learn a system and use it for patient care. When more than one system is used, confusion exists as to which system should be used. Studies have demonstrated that pathologists' lack of familiarity with an organ system leads to less than adequate pathology reports [16].

Conversely, the use of synoptic reports with standardized grading and staging leads to improvement among nonspecialists as demonstrated by Messenger [17]. He demonstrated that nongastrointestinal pathologists attained a level of report completeness that was comparable with gastrointestinal pathologists.

Meier et al. [18] showed that with standardization of diagnostic criteria enforced through systematic case reviews of breast and prostate cases, there was a reduction of amended reports for diagnostic misinterpretations over a 4-year period.

## Examples of Successfully Used Current Systems

It is difficult to understand the power of standardization without using actual examples. Table 8.2 lists examples of existing classification schemes. Table 8.3 lists areas that generally benefit from classification schemes.

### *Proliferative Breast Disease*

It has long been recognized that a spectrum of neoplastic disease exists in the breast from ductal and lobular hyperplasia to invasive carcinoma. For a long time, multiple diagnostic criteria existed for specific lesions such as ductal carcinoma in situ.

**Table 8.2** List of existing standardized diagnostic criteria and staging

| Disease and tissue type | |
|---|---|
| Cancer protocols | Over 50 cancer protocols have been developed and are used. Available at www.cap.org |
| Barrett esophagus | Illustrates ease of use, reproducibility, and clinical relevance |
| Bethesda cervical cytology and thyroid cytology | Illustrate important aspects of reporting in cytology specimens including report adequacy, risk assessment of borderline lesions, and associate management |
| Banff transplant rejection | Defines forms of rejection and the necessary features/ancillary studies needed for different levels of rejection. This is correlated with treatment protocols |
| Hepatitis grading and staging | Defines active disease as well as chronic sequelae (fibrosis) of the disease. Extent of disease is decoupled from etiology |

**Table 8.3** Lesions and conditions that may benefit from standardizations

| Lesion or situation | Benefit of standardization |
|---|---|
| Limited sample specimens (e.g., cytology, small biopsies) | Define adequacy, limit variability in diagnostic terms |
| Cancer | Determine diagnostic criteria,<br>Standardize prognostic features including grade and stage<br>Suggest useful ancillary studies for diagnosis and prognosis<br>Include and emphasize feature relevant to therapy |
| Borderline lesions (e.g., dysplasia, carcinoma in situ) | Determine thresholds for diagnoses<br>Categorize in accordance with suggested treatment or management decisions |
| Inflammatory conditions | Determine thresholds in accordance with clinical relevance for treatment or management decisions |

This made the diagnosis confusing and likely created disagreement. This is well demonstrated by Dr. Rosai [19], who in 1991 took multiple proliferative lesions and showed them to experts in the field and demonstrated extremely poor agreement. Some experts were consistently more benign and some were more malignant than others. This was countered the next year by Dr. Schnitt et al., who took a larger number of proliferative lesions of the breast and showed them to experts in the field but asked the experts to use one set of diagnostic criteria (those of Dr. Page) [20]. Remarkably, there was dramatic improvement in the diagnostic agreement with complete agreement in 60 % of cases and agreement of the majority in most of the cases. More importantly, there was no bias of any pathologists to be consistently more benign or more malignant. This example demonstrates the power of using standardized diagnostic agreements.

## *Tumor Location Near the Ampulla*

Applying a standardized staging system helps assure uniformity of information but is dependent on identifying the correct starting point. One example that illustrates this pitfall is commonly addressed in the assessment of tumors of the bile duct, the pancreas, and the duodenum [21]. Tumors of the ampulla, tumors of the distal bile duct, and tumors of the pancreas all use different staging systems. Determining where the tumor started can sometime be very difficult because of the proximity of these three sites. This becomes especially difficult when tumors enlarge and destroy the tissues they infiltrate.

## *Barrett Esophagus*

Today, the diagnosis of Barrett esophagus seems to be a straight forward issue. But a look back into history tells us that not long ago three types of Barrett esophagus were previously described: gastric fundic type, cardia mucosa type, and intestinal type [22]. The American College of Gastroenterology simplified the definition to a mucosal endoscopic finding that is confirmed to have intestinal metaplasia in 1998 [23]. This in turn made the pathologist's job simpler and more reproducible to identify Barrett esophagus. Along the same lines, at one point, dysplasia was classified as indefinite, low grade, moderate, and high grade. Reid et al. [22] simplified the categories of dysplasia into low- and high-grade dysplasia but also included three indefinite categories. Montgomery et al. [24] further simplified this system into low- and high-grade dysplasia with only one category of indefinite for dysplasia. Montgomery also validated these categories and helped define the criteria that constitute each of these diagnoses. Montgomery et al. [25] followed a cohort of patients and demonstrated the clinical relevance of these categories.

The significance of the standardization of the diagnosis of Barrett esophagus and dysplasia has increased. In the 1980s and 1990s relatively few esophageal biopsies came to pathologists for examination. As the field of endoscopy advanced and better understanding of disease occurred, a dramatic increase in upper endoscopies has happened with more specimens being produced. The need for a validated usable classification scheme expands with wide spread use of endoscopy.

## *Standardized Cytology Reporting*

Important in the area of standardization are the Bethesda systems for cytologic reporting in cervical/vaginal cytology and thyroid cytology reporting [26, 27]. The cervical/vaginal original workshop serves as the model for subsequent standardization efforts in cytology.

Among the elements that are addressed in these efforts are elements that are unique to cytopathology and must be managed in the report but also with regards to the patient. The question of adequacy is perhaps the most important issue. Having standard for adequacy helps clinicians and pathologist do their jobs better. An inadequate specimen should result in a diagnosis of "unsatisfactory for evaluation" and may result in repeat sampling as opposed to a diagnosis of "negative for malignancy," which may end the pursuit of a lesion. Also, addressed in these efforts are defined categories of results that have been investigated over the years for clinical relevance and reproducibility.

The system for thyroid cytopathology is similar in its scope and also addresses adequacy with inadequate specimens reported as "nondiagnostic" or "unsatisfactory". Also defined in the document are categories of diseases. The category of "suspicious for papillary thyroid carcinoma" was examined recently particularly in relationship with introduction of the Bethesda System for reporting thyroid cytopathology [28]. The introduction of the reporting system correlated with a decrease in

the fraction of cases called "suspicious for papillary carcinoma," while the risk of these lesions actually being malignant actually increased meaning the specificity of the diagnosis was significantly improved.

As time goes on, these classifications undoubtedly will address the incorporation of ancillary testing similar to what has happened with the work up and classification of lymphoma.

## Problematic Areas of Agreement

### *Endometrial Atypical Hyperplasia*

When the morphologic diagnosis of a lesion is dependent on multiple subjective criteria then reproducibility is poor. Zaino et al. [29] in discussing the factors leading to poor reproducibility of the diagnosis of endometrial atypical hyperplasia identifies the current classification scheme as a potential source of diagnostic discordance in that most features used in the classification are qualitative rather than absolute. This is supported by a prior study by Kendall et al. [30]. Chafe et al. [31] also points out that many changes to the diagnosis of endometrial carcinoma are due to changes in grading, which have a "significant subjective component."

### *Thyroid Carcinoma*

There are selected lesions that are problematic because of a lack of definitive criteria. Follicular thyroid lesions with borderline papillary features are examples of lesion that are unresolved and in need of more definitive criteria. When abundant nuclear features of papillary carcinoma are present, the diagnosis is easily made with a high rate of agreement. On the other hand, when these features are only seen focally, follicular variant of papillary carcinoma (FVPC) is difficult to distinguish from follicular adenoma. Many authors are alarmed that FVPC is dramatically overdiagnosed [32–34]. They feel that because the prognosis of encapsulated FVPC is excellent with cure following simple excision, strict criteria should be used. Major disagreement is seen in this diagnosis between pathologists and even poor self-agreement. Geographic differences can also be seen in the rate of diagnosis of FVPC [35].

## Conclusion

In this chapter, the importance of agreement on standardized classification schemes in pathology is demonstrated. Using a common language in medicine is a basic necessity. Without it advancement in medicine would not be possible.

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# Chapter 9
# Ancillary Studies: Contribution to Error and Error Prevention

**Paul E. Swanson**

Gown's Law: *With sufficient manipulation of tissue or test conditions, any antibody can be made to stain any tissue* [1].

Murphy's Corollary to Gown's Law: *Anything that can be done intentionally can be done accidently.*

A critical assessment of error risk and risk mitigation in ancillary diagnostic testing is particularly well informed by a consideration of immunohistochemical techniques. I suspect that Dr. Allen Gown, one of the small handful of pioneers in diagnostic immunohistochemistry (IHC) who established the value of this testing modality in an evolving diagnostic world, intended his law to be held at arm's length, an inside joke for those who knew the power of play and invention and a (mostly) feigned warning to those not yet experienced in the art. Yet, for those of us experienced with IHC as a manual test, the implications of Gown's Law are real, and relevant to daily practice. Although the use of automated IHC platforms removes the hand of manipulation to a large degree, and thus presumably mitigates the effects of both intentional and accidental alterations of test conditions, variances in test performance persist, both within and between laboratories. The reasons why this should be so continue to inform laboratory practice and provide a useful guide to error prevention at all levels of testing.

While it may seem gratuitous at this juncture, there are two things that must be said about all ancillary testing, not just IHC:

1. Errors associated with testing are best avoided by not performing the test (though not performing the test may itself be a meaningful error), and
2. Diagnostic errors (both analytic and postanalytic) are often not related to the quality of ancillary testing or the quality of the test result

P. E. Swanson (✉)
Cumming School of Medicine, University of Calgary, Pathology and Laboratory Medicine
Calgary Laboratory Services, Foothills Medical Centre, 1403 NE 29th St NW,
Calgary AB T2N2T9 Canada
e-mail: paul.swanson@cls.ab.ca



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It is not our purpose here to address the quality of the physician in this chapter, but it must nonetheless be acknowledged that significant errors will occur in isolated cases because either the wrong tests were ordered or entirely appropriate test results were misinterpreted. Common sense might well be a critical factor, but training, ongoing competency assessment, and meaningful approaches to internal case review/consensus are also important. These broader issues are discussed at length elsewhere in this book.

These important issues aside, how do we approach the matter of error mitigation in the context of the analytic (and preanalytic) variables of ancillary tests? Understanding the limitations of the testing technique affords the user insight into interpretative pitfalls that might help avoid a diagnostic error based on ancillary testing results. Similarly, in-depth knowledge of and facility with the evidence supporting the use of an ancillary technique provide the user with an opportunity to develop testing algorithms, based on the inherent assumptions of test validity and quality that may preclude the types of interpretative error that more commonly occur in the absence of such tests. The latter, for a variety of reasons, are beyond the scope of this discussion, though the subject cannot be excluded from this discussion entirely.

To address some of the more important issues in error and error avoidance in ancillary testing, five specific topics related to IHC (and by extension, to morphology-based testing in general) will be presented:

- Specificity of antibody reagents for their epitopes—an illustration of the difference between expectations and actual behavior of diagnostic and predictive reagents
- The influence of tissue fixation and epitope retrieval on staining characteristics—an extension of the discussion of antibody specificity,
- the use of methodologic, tissue-negative, and reagent specificity controls—an exploration of negative and positive controls as essential forms of risk mitigation
- Reagent/assay optimization—a brief consideration of how limits of detection and clinical relevance are not always the same, and
- Assay validation—perhaps the best way to mitigate risk, assuming it is done properly

Careful attention to these elements of ancillary testing then prepares us for the inevitable question: how do we assess and avoid the error we do not know we are making? A summary of these topics, their associated risks, and suggestions for their mitigation are presented in Table 9.1.

## Antibody–Epitope Specificity

If we use IHC as illustrative of ancillary testing in general, we need to recognize that what constitutes the specificity and sensitivity of an immunohistochemical test is not necessarily the same as it might be for detection of an analyte in the chemistry laboratory. In the latter setting, the technical validity of a reagent is measured

**Table 9.1** Error risk and error avoidance in immunohistochemistry

| Element | Risk | Mitigation |
|---|---|---|
| *Antibody–epitope specificity* | | |
| Cross-reactivity (shared epitopes) and neoepitopes | False or unexpected positives | Be aware of expected antibody specificity and reported patterns of "unexpected" staining; repeat tests with unexplained patterns |
| Conditional epitopes | False positives | Disregard nonspecific or unexpected staining in nontarget cell compartments (e.g., nuclear staining using an antibody to a membrane-based determinant) unless reproducible (idiosyncratic) or documented in the literature; repeat tests with unexpected results |
| *Fixation and retrieval* | | |
| Underfixation | False negatives | Adhere to minimum recommended fixation conditions with aldehyde chemistry in mind |
| Overfixation | No significant risk | If laboratory process and workflow allow, try to allow for at least 12 h of fixation |
| Excess or inappropriate retrieval | Creation of conditional antigens (see earlier in the text), altered limits of detection (false positives) | Review pretreatment protocols on a regular basis; evaluate and confirm retrieval conditions and antibody titers before use |
| *Controls* | | |
| Deletion of negative reagent controls | False positives, especially with the use of nonpolymer detection systems or polyclonal primary antibodies | Repeat test with appropriate controls; if background staining interferes with test interpretation, reinstate negative reagent controls until the issue is resolved; adhere to recommended uses of negative tissue and reagent controls |
| Wrong positive control | Cannot verify a negative test result | Repeat test with appropriate controls |
| *Antibody optimization/calibration* | | |
| Antibody optimized to limits of detection | False positives | Reoptimize with diagnostic or clinical target in mind (use to fit) |
| Antibody optimized to intended clinical use | False negatives | Use appropriate positive and negative controls to test limits of clinically relevant expression |

**Table 9.1** (continued)

| Element | Risk | Mitigation |
|---|---|---|
| *Assay validation* | | |
| Validation of a diagnostic immunohistochemical assay using only normal tissues | Risks relevant for all circumstances relating to validation: false positives and negatives due to unexpected/untested tissue heterogeneity | Use validation targets that reflect the range of clinical utility; normal ones are satisfactory when supplemented with high- and low-expressing diseased samples |
| Validation using only tissue microarrays (TMAs) | Poor overall and positive/negative concordance against a previously validated assay | Supplement TMAs with whole-tissue sections; be familiar with documented use of TMAs for target antigens that are typically heterogeneous or focal in distribution; avoid TMAs when the literature does not support their use |
| Validation against a small set of tissue samples | Failure to recognize nontarget compartment staining pattern that might be revealed by evaluation of a broader validation sample | Consider expanding a small validation set with additional positive cases; internal negatives can be used to provide a complementary increase in negative samples |

quantitatively against a known standard. In IHC, there often is no gold standard, and the technical validation of a new antibody reagent often relies on the expectation of positive and negative results based on histologic and clinical context or cross-validation with a non-IHC methodology that assesses a presumably related phenomenon. The most relevant example of the latter, in current practice, is the comparison of IHC and fluorescent in situ hybridization (FISH) for Her2/neu [2], where one assumes that clinically relevant overexpression detected by IHC can be predicted with high reliability from gene amplification status detected by FISH. In short, technical validation in IHC almost never is based on the known presence or absence of a given marker based on an extramorphologic chemical determination. With that in mind, we need to briefly explore certain elements of the antibody–epitope relationship in the clinical milieu, which for the purposes of this discussion, is the application of antibodies to formalin-fixed, paraffin-embedded (FFPE) tissues.

Antibodies, however prepared for clinical use, are reasonably monospecific for single epitopes, though this statement needs to be qualified. It is a given that commercial polyclonal heteroantisera (of diminished use in today's laboratory, though not without persistent exceptions, including antisera to a variety of polypeptide hormones, selected infectious agents, and immunoglobin heavy and light chains—in both immunofluorescent and IHC applications—selective markers of differentiation (such as prostate specific antigen, Napsin A), and Her2/neu) are not monospecific with respect to a given epitope, though any one of the antibody clones that comprise such reagents will generally target only one epitope. The potential advantage of a polyclonal preparation, apart from being easier to prepare, is that more

than one epitope on a given target is likely to be recognized. However, as the number of clones in such a preparation increases, the likelihood that one of them will recognize an epitope unique to or shared by an unrelated protein will also increase, and the overall specificity of the reagent may be diminished [3]. Taken individually, however, these constituent parts of a polyclonal reagent are not intrinsically less specific for the intended target than a monoclonal antibody raised against the same target. I would note, parenthetically, that this statement is only appropriate to affinity-purified polyclonal reagents, since crude heteroantisera (not uncommonly employed in the early days of diagnostic IHC) probably contained considerably more antibody clones that recognized nontarget than target, though few if any of these were present in sufficient quantity to actually label tissue in a meaningful way.

Murine monoclonal antibodies, the initial product of hybridoma technology and for long the standard for most immunohistochemical applications in clinical practice, are now being supplanted, in turn, by rabbit monoclonal antibodies, in part because the testing environment in medical research and in clinical practice seems to benefit from having quality reagents that are not prone to species-specific adsorption in tissue (particularly relevant to the use of murine monoclonal antibodies in the study of mouse models of human disease). However, the real value of rabbit monoclonal antibodies stems from the immune environment in which they are produced. These reagents, when compared with murine products, often exhibit higher levels of sensitivity and specificity for target proteins and are apparently easier to generate against small molecules, potentially opening a broader set of proteins in human tissue to immunohistochemical study [4].

However, there are potential drawbacks to all such reagents, irrespective of source. Not all monoclonal antibodies are demonstrably monospecific; indeed, under in vitro testing conditions, many presumably specific reagents may, with varying degrees of affinity, bind to more than one epitope, and thus, in clinical practice, potentially label something other than the intended target. This infidelity—indeed, promiscuity (see Parnes [5] and Cohn [6])—is well known even in biological systems. IHC detection methodology that relies on high antibody concentration and low-stringency binding conditions (room temperature or heated environments) is at greatest risk in this regard, as such conditions foster an environment in which lower-affinity binding may occur. It is interesting to muse on the performance of IHC when higher stringency was part of the process (primary incubation with low antibody concentration at cold room temperatures for 18 or more hours) and how, for the most part, even polyclonal preparations performed reasonably well under these conditions. Contrast that with automated staining methods that, given their intended advantages (speed and reproducibility), cannot perform under similarly stringent conditions.

The performance of a selected antibody (or the availability of its epitope) may also change in a variety of disease settings, particularly malignant transformation, where functional changes in microenvironment or protein structure (or the creation of mimics sufficient to allow antibody binding) may yield elements that are not normally exposed to immune recognition—the so called neoantigens/neoepitopes. Perhaps one of the best known of these is the neoepitope on the keratin 18 mol-

ecule that is exposed only after caspase cleavage in apoptotic cells. Recognized by the antibody M30, this neoepitope is a specific marker of apoptotic cell death [7]. We also know that tissue handling and processing—even antigen retrieval methodology—may occasionally be associated with idiosyncratic patterns of reactivity with selected antibodies that may or may not reflect the actual distribution of the intended target [8]. These so-called conditional antigens account for a variety of unexpected results with antibody reagents, including, in my experience, nuclear staining for prostate-specific antigen and membrane-based staining for hepatitis B surface antigen. Even the intended targets of monoclonal antibodies in clinical and investigational samples may only emerge under certain conditions of tissue handling, fixation, or retrieval. A particularly good example of this phenomenon is the detection of keratin 7 in reactive myofibroblasts after heat-induced retrieval, a pattern of staining almost never encountered in tissues more traditionally "retrieved" by enzyme digestion (personal observation). Willingham has argued, in fact, that in the current era of heat-induced epitope retrieval, most stain targets might be seen as "conditional" [8].

## Tissue Fixation and Epitope Retrieval

As just alluded to, heat-induced epitope retrieval, the current standard for enhancement of immunoreactivity in FFPE tissues, generally increases the sensitivity of an assay for a given epitope, and in some cases, is unambiguously necessary for useful labeling with certain antibody preparations [9–12]. Yet, it is also possible that retrieval may change the apparent sensitivity and specificity of a given antibody reagent in its diagnostic milieu. One need only understand that a variety of markers generally assumed to be selective for a given cell lineage or pattern of differentiation are occasionally expressed (with demonstrable gene transcription and translation) in low levels in other cell types. Low-molecular-weight keratins, for example, have been detected in a variety of "nonepithelial" cell populations (a matter we will return to shortly), increasing the likelihood that staining under nonstringent conditions, particularly at high antibody concentration, may yield unexpected results.

As noted elsewhere in this text, standardized protocols, when adhered to, largely mitigate the potential for methodology-sensitive analytic errors [13–17]. This is just as true for histochemical testing as it is for IHC, in situ hybridization, and more specific molecular techniques. Perhaps the most comprehensive source for IHC standards concerning test preparation and performance has been prepared by the Clinical Laboratories Standards Institute (CLSI) [18]. However, established and emerging external quality assurance (QA) programs, including NordiQC [19], cIQc [20], and UK-NEQAS [21] (among others), through the dissemination and interpretation of targeted laboratory challenges, have generated useful data about variance in laboratory practice, the latter forming the basis for credible recommendations regarding the selections of antibody clones, best practices in retrieval methodology, preferred detection options, and objective evaluation of automation platform-based

variance. The College of American Pathologists, through its IHC surveys programs, has the potential to be another important player in the external QA market, but has yet to provide the richness of feedback available through other QA sources. Attention to these recommendations, through participation in the available quality control (QC) challenges and through perusal of web-based summaries of the external QA programs, should result in fewer analytic and interpretative errors in daily practice [12, 13, 15, 22]. And yet, despite these attempts to harmonize IHC practices, many preanalytic and analytic variables remain uncontrolled in current diagnostic and investigative practice, including (and certainly not limited to) cold ischemic time before proper tissue preparation and fixation, tissue processing protocols (both reagents and times), choice of materials for controls (see later in the text), the handling of unstained slides (though this has more recently been the subject of specific recommendations for preparation, handling, and storage [23]), the choice of pretreatment protocols, the use of automated platforms, selection of primary antibody (differing clones, differing product presentation—ready to use versus concentrated), and the use of chromogens.

Fixation remains a particularly important focus of efforts to standardize practice because of the increasing clinical reliance on biomarkers predictive of treatment response that are interpreted in quantitative or semiquantitative terms [12, 13, 18, 24, 25]. Although this subject has been addressed elsewhere in this text, it is important to briefly revisit the impact of fixation on the biomarkers used in the clinical evaluation of breast carcinoma: estrogen receptor (ER) protein , progesterone receptor (PR) protein , and Her2/neu. From a basic perspective, formaldehyde fixation does not impart either particularly destructive or permanent alterations to the protein matrix [26]. Even after fixation to extinction (greater than 48 h), no more than 1 % of total protein is insoluble [27], and the mild cross-linking that occurs is reportedly 90 % reversible [28]. However, when fixation does not progress for at least 18–24 h, these cross-links may be rapidly broken down when the tissue is removed to another medium during tissue processing. This “unlinking” is exaggerated in tissues exposed to formalin for less than 8–12 h. The next step in most tissue processing protocols is exposure to ethanol, a reagent that typically results in extensive protein damage (as a protein coagulant) and loss of up to 40 % of soluble proteins [27].

How does this relate to the immunohistochemical detection of ER protein? There can be no reconciliation of the literature on this point, although the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) Her2 [2] and ER/PR [29, 30] recommendation panels recognized the potential problems of underfixation and at least set a lower limit of acceptable fixation (in this case 6–8 h). That limit, unfortunately, falls within the range of fixation times that are likely to promote protein degradation during processing, and Goldstein et al. [25], in their study of ER reactivity and fixations times in a cohort of breast carcinomas, confirmed the potential susceptibility of ER to underfixation even at these fixation conditions.

Interestingly, two often-cited studies provide contrary evidence to the notion that short fixation times pose a risk for suboptimal staining for ER [31] and Her2/neu [32]. These studies, however, remain problematic in the context of this discussion because each was based on the sequential analysis of a single case, sampled at

regular time intervals, each chosen for its size, lack of neoadjuvant treatment, and known high level of biomarker expression. Though this point will be made again later, the assessment of biomarker IHC in a specimen enriched for that marker and using a highly sensitive detection system (current standard of practice) does not provide a testing environment in which fixation-related changes in accessible analyte concentration (even relatively large changes) can be easily recognized [33].

From the perspective of the practitioner attempting to gain insight into the potential utility of selected immunohistochemical reagents, even the manner in which these variables are reported (particularly in the peer-reviewed literature) are not held to uniform standards. Having said that, it must be acknowledged that considerable effort has been expended trying to provide clarity (through recommended standards) to all preanalytic, analytic, and even postanalytic elements of IHC [16, 17, 34].

Ad hoc and organized groups within the investigative and diagnostic pathology communities have also provided particularly useful recommendations for the reporting of methods and results themselves, providing standards for both immunohistochemical and molecular analyses presented in peer-reviewed forums. The *m*inimum *i*nformation *s*pecification *f*or *i*n *s*itu *h*ybridization and *i*mmunohistochemistry *e*xperiments (MISFISHIE) initiative, a protocol patterned on earlier attempts to define *m*inimum *i*nformation *a*bout a *m*icroarray *e*xperiment (MIAME) [35, 36], should help create an environment that fosters more uniformity of practices, even approaching best practices, in both the investigative use of ancillary methodology and the purveyance of high-quality patient care.

## Controls

Clive Taylor [37] famously coined the phrase “An exaltation of experts” (drawing on the witty and often poignant historical, etymological, fictional, even fantastical rendering of collective nouns offered by James Lipton (of “Actor’s Studio” fame) in his book *An Exaltation of Larks* [38]) to suggest perhaps the implicit dichotomy of both the coherent collective of these graceful birds and the cacophony of their collective voices as metaphor for the value of expert consensus opinion in the practice of pathology. Perhaps the better approach—evidence-based practice—has only more recently taken center stage in attempts to provide clarity to ancillary testing protocols and pathology practice in general. Careful perusal of most recent recommendations of best practices in ancillary testing suggests that the exaltation still echoes a bit more loudly than it should, though one might reasonably argue that this reflects the paucity of evidence supporting elements of standard work in the laboratory practice of anatomic pathology. Nonetheless, careful integration of practice experience and evidence, through ad hoc and more formal associations of experts in the field, have provided important guidance, emphasizing the practical implications of proper selection and deployment of positive and negative controls [39, 40]. While there has perhaps been greater emphasis on reagent selection, methodology,

and interpretative criteria in consensus works dedicated to the task of process improvement and risk mitigation in pathology practice [12, 13, 16–18, 29, 34, 41], attention to controls is no small matter [42]. The proper use of controls is an increasingly important element of error recognition and avoidance in ancillary testing because it is the basis for both the optimization/calibration and validation of these reagents in their clinical testing environments.

The negative control, seemingly almost anachronistic in the current era of polymer-based immunohistochemical detection systems, remains an important element in both test development and clinical application. Generally discussed in terms of negative reagent controls (NRCs: tests performed on serial sections of patient material and subjected to otherwise identical retrieval and detection conditions, further separated into "specific" NRCs that test the vehicle in which the primary antibody is prepared by substituting antibody with species-specific serum (for polyclonal antibodies) or either ascites fluid or nonspecific antibody of the same heavy chain class (for monoclonal antibodies), and "nonspecific" NRCs that test the influence of the detection system itself on the staining result by substituting elements of the detection downstream to the primary antibody) and negative tissue controls (NTCs: specific tissues known or expected to lack the target analyte, either internal to the test tissue or external, mounted on-slide), these elements are effective monitors of the analytic and clinical specificity of a given reagent and the precision and limits of detection of the selected detection method [39]. Because currently employed polymer-based methods only rarely introduce unwanted background staining in most testing environments, the use of the NRC has been largely discontinued (this approach is in fact recommended by several agents of QA, including the College of American Pathologists). Based on recent recommendations from an ad hoc expert panel, however, there are a few important exceptions to this trend [39]:

- NRCs should be utilized as part of the evaluation of any new antibody reagent, retrieval medium, or detection system.
- NRCs should be used at the pathologist's discretion when endogenous tissue pigment interferes with interpretation, when suitable internal NTCs are lacking in a clinical test sample, or when in the absence of an initial NRC, a false-positive result is suspected.
- NRCs should be used if published guidelines for a given testing protocol specifically recommend their use.
- NRCs should be used in the performance of any stand-alone diagnostic test or predictive biomarker unless the stain is deployed in a panel that includes sufficient alternative NTCs, or if the predictive marker is used as a screen for a confirmatory molecular test.

The last of these exceptions explicitly draws a distinction between antibodies applied in routine diagnostic practice and those that are used as predictive or prognostic biomarkers in clinical practice. I highlight this distinction because it reflects an impression that has driven consensus guidelines for the detection and interpretation of selected biomarkers in recent years and was perhaps the critical driving force in the FDA's decision to classify predictive biomarkers and other stand-alone IHC

tests separately from analyte-specific reagents (ASRs) and IHC in vitro diagnostic devices (IVDs) used to corroborate histologic diagnoses [43]. The underlying assumption is that IHC methods for predictive biomarkers and stand-alone diagnostic tests need to be more strictly controlled. Indeed, the FDA reasoned that most diagnostic IVDs and ASRs pose only limited risk to the patient, and these were defined as Class I reagents (subject to good manufacturing principles and general controls), whereas predictive markers and stand-alone diagnostic tests, as they provide actionable test results independent of the other elements of the histopathologic evaluation, are of higher risk to the patient. These markers were defined as Class II reagents and were subject to more rigorous premarket documentation of clinical performance characteristics and demonstration of "substantial equivalence to existing validated tests" (premarket clearance). The third category (Class III—of highest risk to patient safety and requiring premarket approval), did not specifically include examples of antibody IVDs, but it is notable that selected vendors have chosen to gain premarket approval of predictive marker IHC test kits as Class III reagents prior to marketing for clinical use.

While I agree that there is inherent risk in the use of Class II and Class III reagents, I am not entirely sure that I agree that there should therefore be a relaxed standard of evaluation for Class I reagents. I will return to this thought later.

Positive controls—tissues known or expected to contain the analyte of interest—are (perhaps counter-intuitively) somewhat harder to define and standardize than either tissue-negative or methodologic-negative controls due to a lack of consensus about how to define an appropriate control in differing clinical settings [40, 42]. Should a positive control for an analyte used to support a diagnosis of malignancy be prepared from representative neoplastic tissue? Should it include tissues expected to contain high, intermediate, or low concentrations of the analyte (or a combination of these)? Should cell lines with documented levels of analyte expression be used or should biologic tissue constructs that mimic the target tissue (the so-called histoids) [44]? Should the control (and its evaluation) be tailored to different uses of the same reagent (for example, ALK-1 IHC testing in lung adenocarcinoma, as opposed to hematopoietic neoplasms or inflammatory myofibroblastic tumor) [41]? Here, consulting consensus recommendations and external QC sources may be of value. NordiQC, for example, has drawn on results from multilaboratory challenges to discern patterns in control selection and staining quality, allowing for specific recommendations for the use of normal tissue with constitutive analyte expression in some settings [19]. These discussions have precipitated more focused consideration of how positive controls can be designed to facilitate a more uniform approach to reagent evaluation within and between laboratories, as a part of internal quality management programs; facilitate the design and creation of tissue microarrays for test and reagent development; and, by extension, facilitate the preparation and maintenance of controls of consistent quality for use in external QA and proficiency testing programs. Such target-specific controls, referred to as "immunohistochemistry critical assay performance controls (iCAPS)," [40] have been proposed recently by an ad hoc expert panel. iCAPS ideally would be prepared from tissues selected for consistent and predictable *patterns* of analyte expression,

*levels* of analyte expression, and *cellular localization* of expression. Such controls, if properly designed and disseminated, might reasonably mitigate error associated with methodologic variance in both translational research and clinical applications.

Recent recommendations regarding the use of on-slide positive controls (see the College of American Pathologists Laboratory Accreditation Program Item ANP22550) also bear some scrutiny in a risk-averse laboratory. In general, the ability to immediately evaluate the quality of the positive control in the context of the clinical test slide improves both the diagnostic accuracy of a given stain and the likelihood that pathologist feedback to the laboratory regarding tests of borderline or unacceptable quality will be both informative and timely. In both settings, the use of on-slide controls are an important element of quality management and error mitigation and ideally would be applied to all forms of morphology-based ancillary testing. However, we also know that certain tissues, especially those comprising collections of small stainable units—such as placenta—may occasionally fragment during cutting, slide mounting, or even during staining, resulting in the displacement of elements to areas of the slide beyond the intended site. This is also true when the target analyte is packaged in a way that allows for actionable positive results confined to single cells—such as cells positive for virus. When such tissues are employed as on-slide positive controls, there is a nontrivial risk that positive elements from the control may overlay or admix with patient materials. At the University of Washington, a small, but disturbing, number of cases have been identified in which cytomegalovirus (CMV)-positive cells have detached from an on-slide control, contaminating clinical gastrointestinal mucosal biopsies from patients suspected of having clinically relevant CMV infection (Florencia Jalakis, MD, personal communication).

## Assay Optimization/Calibration

For a variety of reasons, the quality assessment of reagents intended to support histologic diagnoses seem less dependent on methodological rigor than those intended as predictive markers, yet the literature remains replete with examples of target analytes the apparent distribution of which in normal and abnormal human tissues is broader than expected because the reagent either is not as specific as intended or is used in a testing milieu that does not match the sensitivity of the assay to the expected specificity of the analyte. Examples of the former include TTF-1, where one such reagent (clone 8G7G3/1) binds to an epitope that is not exclusive to the TTF-1 molecule; it also is a part of a mitochondrial enzyme principally upregulated in normal hepatocytes and hepatocellular neoplasms. While one might question whether this is actually a drawback to this reagent (certainly no one has taken issue with the clinical value of the ability of polyclonal anti-carcinoembryonic antigen to specifically bind to a bile-associated glycoprotein in the bile canaliculus), one would probably not argue that the ability of polyclonal antisera raised against pax8 to also selectively bind to pax5 and pax6 might, in fact, represent a significant

diagnostic problem [45]. Examples of the mismatch between assay sensitivity and analyte specificity are discussed in greater detail later in the text. In either event, error mitigation is best served by careful consideration of reagent optimization protocols.

The optimization of an antibody reagent, effectively the determination of appropriate antibody titer and test conditions to meet the intended clinical use of the reagent, is not as straightforward as one might like, as it is not always clear what level of analytic sensitivity is appropriate. The proper selection of positive and negative tissue controls provides a basis for testing a range of anticipated tissue concentrations to determine a titer and testing environment that will be sufficiently sensitive to detect the target analyte in most clinical settings. However, it is also clear that a reagent titered to detect the protein as efficiently as possible without regard to clinical application (optimized to the reagent's limit of detection) may pose serious risks for error in both the diagnostic and predictive realm. And here, two illustrative examples might be considered.

## *Keratins*

Setting aside for the moment the practical value of keratin subtype analysis to the classification of selected epithelial proliferations, there is a body of evidence that keratin-specific reagents may be problematic in the evaluation of the neoplasm of uncertain histogenesis. One might think that this is a problem related to nonspecific or unexpected cross-reactivity that could be resolved by using molecular evidence of keratin gene expression, but in fact, this proves to be an example were such a relationship cannot be relied on. Arguing for the moment that the detection of epithelial differentiation is the appropriate clinical application of keratin IHC, optimization of a pan-keratin regent should be designed with this in mind. A historical reflection on this topic will remind the reader that the initial use of keratins generally met this expectation [46]. It is true that keratins optimized for the detection of epithelial neoplasms also labeled a subset of "nonepithelial" neoplasms, but for the most part, these exceptions proved to be neoplasms with epithelial attributes—synovial sarcoma and epithelioid sarcoma. Miettinen's demonstration [47] of keratins in a subset of leiomyosarcomas, on the other hand, proved somewhat more enigmatic, yet the utility of keratins remained unquestioned. Over time, however, an increasingly diverse range of "nonepithelial" keratin-positive neoplasms were reported in the literature [46]. The difference was not in the quality of the reagent but more likely in the analytic sensitivity of the assay. Papers reporting keratins in pleomorphic sarcomas, ependymomas, and even melanomas, while not commonplace, became more conspicuous in the literature [46]. And then there was an interesting public conversation regarding keratin stains in subsets of angiosarcomas, particularly epithelioid angiosarcomas of deep soft tissue [48, 49]. While keratin reactivity proved to be an important characteristic element of both a subset of normal endothelial cells and epithelioid angiosarcoma (indeed, a diagnostic criterion for this entity [49]), it remains problematic in the other examples cited, not because these lesions do not

express keratin genes but because the amount of keratin in these cells is typically rather small. And that is the point. An assay developed to chase the system's limit of detection may be diagnostically specific, even though the analytic specificity of the assay is high. In this respect, optimization of an antibody-based assay, even with controls selected specifically for the antibody, cannot be sufficient for clinical use.

## *Estrogen Receptor Protein*

Pushing an immunohistochemical method to its limit of detection may also have implications for predictive markers, even when the result of the method forms a reliable basis for therapeutic decisions. My favorite example here, of course, is ER protein. As recounted in greater detail elsewhere, the initial utility of IHC for ER (and PR) was predicated on the relative ease of IHC compared with the ligand-binding assays that defined the clinical relevance of ER and the demonstration that a properly validated immunohistochemical system could recapitulate the linear relationship between "quantity" of ER and response to antihormonal therapies [50]. With the advent of increasingly sensitive IHC detection systems and antibodies, ER (and PR) detection has effectively been dichotomized [51, 52], by generating positive results that fall consistently in a range of optical density that cannot distinguish readily among samples that might, under less sensitive conditions, yield a range of visibly different reaction products. Rather than going into greater detail on the relatively complex notion of dynamic ranges of test systems and their influence on the interpretation of quantitative results [32, 53], one need only be reminded of the potential limitations of quantitative chemical analyses that rely on optical density. Typically interpreted on a log scale because of the relationship between chromogen concentration and optical density, significant changes are readily discernible at lower levels of optical density, but at high concentrations of analyte (and a method that favors intense staining of that analyte), significant differences in concentration are not as easily perceived by either the eye or by optical instrumentation, since the optical density changes do not vary in a linear fashion. Hence, current IHC methodology, while creating an easy-to-use dichotomous (positive/negative) report for purposes of treatment, masks the linear relationship between ER concentration and clinical response. While this may not affect treatment decisions in the current milieu, it diminishes the likelihood that current clinical data can be used retrospectively or prospectively to analyze treatment responses to novel antihormonal therapies [54]. It is also possible, by extension, that such techniques might create sufficient optical density in small subsets of positive cells to convert an Allred score of 2 (weak, $<1\%$) to a 3 (moderate, $<1\%$) or 4 (strong, $<1\%$), creating an actionable, but false-positive, result. The recommendation to limit reportable positives to samples with 1% or more positive cells is a response to this inevitability [30], but not a solution for the problems of overly sensitive detection. The fact is, despite our ability to mask the linear relationship between ER concentration and treatment response, the relationship nonetheless exists, and can be shown by methods that

do not have the inherent limitations imposed by measurement of optical density. Quantitiave immunofluorescence is one of many examples [33]. On the other hand, the recent introduction of an intrinsically more sensitive antibody against ER (the rabbit monoclonal SP1 [55]) raises the possibility that accurate clinical detection of this receptor could be achieved with *less* sensitive (and more representative) IHC assays (though I am not aware of any laboratory that has tried).

## Assay Validation

Validation (in contrast to optimization), when properly performed, allows the laboratory to better define and assess the expected use of the assay and the sensitivity and specificity of the assay in that context [2, 29, 56, 57]. Here, the concept of "analytic" validation becomes problematic, as analytic sensitivity and specificity are terms that assume that the method will detect (and only detect) the target analyte [14, 57]. As noted earlier, IHC is not an ideal analytic environment because for many tissue-based systems we cannot know for certain (without gene expression or proteomic analyses that only rarely exist) that the analyte is actually present or in what concentration. This, needless to say, is a particularly important matter when the target analyte is a predictive biomarker the actual (not inferred) concentration of which in tissue may be important. Even so, sample sets can be generated in most clinical settings that provide a reasonable reflection of actual tissue expression.

Recommendations have been offered over the years for approaches to validation, perhaps the most rigorous of which was the original ASCO/CAP recommendation for validation of Her2/neu IHC assays [2]. This guideline may not have provided specific guidance for important elements of a validation procedure (it did not, for example, make a specific recommendation for the number of samples in a validation set, rather setting the recommendation at 25–100 cases), but it did include a careful statistical assessment of how sample size and expected concordance values affect the likelihood that a laboratory can meet minimum concordance-based validation requirements for negative (0, 1+) and positive (3+) results. These analyses, based on the expectation of 95% concordance between results obtained in the validation set and the comparator values obtained using a previously validated assay, strongly supported the use of validation sets closer to 100 cases than 25, and the recommendations included the requirement that a validation set would include both expected (or known) negative cases and expected (or known) positive cases, the latter including tissues with both low and high concentrations of (or intensity of staining for) the target analyte. A principle driver in the original formulation of these guidelines was the lack of defined validation procedures for biomarkers in most US IHC laboratories and a literature that suggested that interlaboratory testing results for Her2/neu rarely met even a 90% concordance level for positive and negative results [2]. Of course, concordance is a funny thing. Although the lack of gold standards in IHC renders the true concordance between methods unknowable (unlike chemical analytic assays validated against a known quantitative and chemical standard), any

expected concordance less than 100% explicitly assumes discrepancies will occur between two laboratories testing the same material—in effect, acknowledging that at some level, error is unavoidable (and perhaps, even, acceptable). In this respect, the decision to defer validation sample size and expected concordance levels to the discretion of the laboratory director in the updated Her2/neu guidelines is interesting [58]. I would caution the reader to carefully peruse the data supplements to this update, however, since a concordance goal of 95% is still implicitly favored by the consensus panel, particularly when new reagents or methods are being validated.

Proposals for validation of ER and PR IHC assays [29, 30] have retained explicit expectations of concordance, in part because a concordance target can be used as a measure of confidence in the results of the assay, and because monitoring results over time against these standards and other indices of expected staining results (for example, overall ER- and PR-positive rates, ER-positive rates for selected demographic groups, rates of PR-positive/ER-negative cases) provide ongoing, real-time assessment of assay performance. These guidelines also more clearly defined the number of cases that should be included in validation sets. Based on confidence intervals resulting from attaining the recommended 90% concordance for positive results and 95% concordance for negative results when compared with previously validated assay results, samples sets including 20 expected negative cases and 20 expected positive (including both high- and low-reactive) cases were proposed [29]. This recommendation is odd in one respect—the use of a 40-sample validation set was contingent on the FDA status of the assay. If the test/assay kit was FDA approved or cleared (two entirely different things, but both an acknowledgement of a more rigorous premarket evaluation than mere Class I markers), the 40 sample size was deemed sufficient to establish that the assay will perform as expected. This was considered an abbreviated form of validation and referred to as "verification." However, if the assay was laboratory developed (despite often using the same reagents included in a given FDA cleared or approved test kit), a formal validation sample size of 80 was recommended, in part because the performance characteristics of the assay were not vendor defined [29]. This, of course, cannot be regarded as an evidence-based recommendation, since confidence intervals for concordance using 40 cases in a verification or validation set do not change simply because the presumed pretest quality of the assay is different. It may well be that a laboratory-developed test is less likely to meet expected concordance values when compared with previously validated samples, and it is true that it is statistically more likely that concordance can be achieved when a larger sample set is used (see Appendix F of the original Her/neu guidelines [2]), but there is nothing inherent to laboratory-developed tests that should require them to be subjected to more rigorous validation procedures.

Recent projects to define parameters for validation of immunohistochemical assays in general have employed the same basic principles with respect to the composition of validation sets, but recommend an overall sample size of 20 cases (unless previously published recommendations existed for a given marker, and with the caveat that predictive biomarkers should be validated with greater rigor—that assumption again—using a 40-sample validation set), with overall concordance

targets of 90% (including both positive and negative results) [56]. Statistically, 95% confidence intervals for 90% concordance with this sample size are considerably wider than those obtained with a 40-sample set using the same concordance targets, and the overall confidence that concordance reflects the actual accuracy of the assay is thus lower. However, the pragmatic implications of validating a large number of assays, many of which rely on scarce tissue samples for controls and validation challenges, precluded a consensus recommendation for a larger sample size. Laboratory director discretion was also emphasized in the determination of assay validity when testing conditions departed from FFPE materials (such as cytolyte-prefixed formalin-fixed cell blocks in cytology and decalcified specimens in surgical pathology), to account for the absence of clear literature support for a particular approach to validation in these settings [56].

An interesting (and rather more rigorous) approach to antibody validation proposed by Bordeaux et al. [59] uses at its core a tissue microarray (TMA) of selected tissues and cell lines that test signal localization and reproducibility based on known or expected patterns of analyte expression, but does not rely only on the staining patterns that emerge. The antibody subject to validation is first tested against Western blots prepared from cell lysates extracted from cell lines known to express or lack the antigen of interest. If cell lines known to be negative for the analyte are not available, lysates from siRNA knockdowns are used. If appropriate results are obtained in Western blots or if antibodies negative against blots identified specific bands of expected-molecular-weight immunoprecipitation assays, then the tissue microarray is employed. If reactivity is considered appropriate and of expected intensity based on earlier blot analyses, the TMA is retested reiteratively to ensure results are reproducible between runs. Only after reproducibility is achieved does the laboratory accept the reagent as valid. This latter approach has the advantage of establishing that both the testing array and the reagent are appropriate for detection of the analyte without requiring a statistical analysis of a limited sample set but may require a level of investigative rigor that exceeds what is available in most clinical laboratories. Both proposed validation schemes emphasize the need to test an assay against an appropriate collection of known or expected positive and negative cases (however defined), and in this process, by selecting positive cases that anticipate the clinical range of reactivity and negative cases that potentially include lesions that express the gene responsible for the target analyte, but which remain immunohistochemically negative under "optimized" test conditions, the laboratory director can provide reasonable assurance that the test will perform as expected.

The difficulties with validation notwithstanding, nothing the laboratory director can do prior to introducing a test into clinical practice will mitigate the risk for laboratory error more than assay validation. This is a given for novel molecular tests, and is increasingly a focus of IHC practice, though in some respects, anatomic pathology laboratories have been slow to adopt validation guidelines and procedures in their quality management programs [60]. Perhaps as we move forward, the development of on-line resources (such as Antibodypedia [61, 62]) that warehouse and compare validation data for selected immunohistochemical and molecular reagents will become a valuable asset for those contemplating ongoing and future validation attempts.

## The Error we do not Know we are Making

We assume that the information we derive from ancillary testing will necessarily augment diagnostic accuracy and improve patient care. How can we be sure? The most appropriate avenue is the use of evidence-based tools and decision-making algorithms that guide the application of these tests. But what evidence, what tools? There is one question that needs to be asked any time a test is performed for clinical use: Do I know how the result of the test will be used?

It is, of course, first necessary to establish that an accurate and reliable (consistent and reproducible) test result can be obtained, as much of the foregoing discussion has emphasized. However, what is the basis for answering the question? For diagnostic markers, the pathologist must know the significance of both a positive and a negative result, which requires the user to have an understanding of the likelihood that either result will inform a specific diagnosis. For biomarkers, this requires that the pathologist also understands the clinical utility of the test result, and by inference, whether the test performed is actually capable of answering the clinical question [53, 63]. How does one know the significance of a test result? As discussed in detail by Wick et al. [53], this is a matter that requires, for each test or test panel offered by the laboratory, a careful and systematic evaluation and application of the literature in ways that many pathologists are either unfamiliar with or unaccustomed to. Effectively an application of Bayes theorem to the routine practice of diagnostic IHC, the critical elements of this process include a determination of which diagnostic alternatives are relevant to both the test and the clinical circumstance in which the test may be employed, an understanding of the pretest probability that a given diagnostic alternative will occur in the patient population being tested, a consideration of the clinicopathologic features that suggest the most likely diagnosis in the specimen being tested, the identification of the best target analytes for the diagnosis under consideration based on the positive likelihood ratio of each test, and a determination of the best (ideally, the smallest) panel of tests appropriate for the differential diagnosis, using probability ratios or odds ratios. This is clearly not the same as basing test decisions on experience or a casual reading of the literature, and the use of tests without this level of evidence is likely to result in assay values that do not obviously contribute to diagnosis or that leave the pathologist with a less-than-objective decision about how an unexpected positive or negative result should be applied.

Because diagnostic IHC testing should be predicated on rigorous evidence-based principles, and because the risk of misdiagnosis or delayed diagnosis is heightened by poor test selection and poor pretest optimization and validation, it remains unclear to me, as alluded to earlier, why the pretest evaluation of diagnostic IHC should be any less rigorous than that recommended for predictive IHC. Those who have worked with me in the past know that I have not always advocated for such detailed attention to diagnostic markers, in large part because I have perhaps too casually undervalued the significance of evidence-based principles in diagnostic IHC. However, if there is a conclusion to be drawn from the accumulated work of consensus panels and the evidence on which their expert opinions are based, it is

that we can only begin to mitigate the risk of error in ancillary testing through a careful and consistent approach to reagent selection, developmental of appropriate controls, and the consistent and reproducible application of optimization and validation principles prior to the clinical use of any test. Not knowing to use a test or not knowing *how* to use a test in a particular diagnostic setting may be important contributors to diagnostic error, but the real risk in ancillary testing is *assuming* that one knows when a test is appropriate and how to apply the results.

It ain't ignorance causes so much trouble; it's folks knowing so much that ain't so. (Henry Wheeler Shaw, aka Josh Billings, 1818–1885) [64]

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# Chapter 10
# Optimization of Case Reviews in Different Practice Settings

**Raouf E. Nakhleh**

## Background

Because of the potential for disaster the Federal Aviation Administration mandates that every commercial flight has two pilots. This is done for teamwork and cognitive redundancy. The idea is to have redundant combinations or backup, so if a mistake is made by one member of the team, the other has the opportunity to catch it before an accident can occur. One person completes a task and the other independently checks the work [1]. This concept is catching on in surgical pathology. In a recent study, 8 % of cases are reviewed by a second pathologist before the case is signed-out [2].

In most surgical pathology laboratories, an incident or mishap with a diagnostic case occurs that leads to someone in the organization (usually the chairman) to conclude that when a similar situation arises, more than one pathologist should examine the case to assure an appropriate outcome. Typical among these cases are the following: (1) a brain biopsy is sent for frozen section to assure the presence of lesional tissue and is thought a low-grade glioma only to be diagnosed on permanent sections as reactive gliosis. (2) A thyroid lobe is sent for frozen section for a nodule, which is diagnosed as a follicular lesion only to be changed the next day to papillary carcinoma of the thyroid. (3) An esophageal biopsy with Barrett's metaplasia is diagnosed as no dysplasia is sent to another institution where high-grade dysplasia is identified. (4) A breast biopsy is diagnosed as ductal carcinoma in situ but is then sent to another institution where invasion carcinoma is identified.

These examples among others have lead departments to conclude that these seemingly higher risk cases deserve routine second looks to assure accurate reporting. Departmental policies however, vary in the type of case included.

R. E. Nakhleh (✉)
Department of Pathology, Mayo Clinic Florida, 4500 San Pablo Rd.,
Jacksonville, FL 32224, USA
e-mail: nakhleh.raouf@mayo.edu



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## Does Review of Cases Result in Error Detection?

A recent search of the literature reveals over 130 articles that include some type of second pathologist review of cases. In all of these articles, errors or diagnostic discrepancies are detected. Depending on the type of study and the focus on a particular type of tissue or diagnosis, the error rate varied substantially. Some studies claim error rates up to 50 % and more [3, 4].

The studies could be divided into internal reviews (review of cases from the same institutions) and external review (review of cases from other institutions). Most of the external review studies argue that review of cases is worthwhile because the patients' therapy changed for some of these cases [5–7]. The external studies argue that review of cases make sense because of patient safety concerns and from a financial perspective. A few studies actually calculate the financial impact of these reviews and calculate the savings from reduced surgery or more appropriate therapy and conclude that external review justify the expense of doing them [8].

The studies could also be divided by organ specificity. Approximately a quarter of the studies were reviews of multiple organ systems and the remaining studies focused on specific organ systems. The organs most frequently reviewed include the prostate and the thyroid. Additional multiple studies covered lymph nodes, central nervous system, and gynecologic organs. In general, studies of single organs had higher rates of error than multiorgan studies.

## What is the Optimal Timing of Case Review?

If the purpose of reviewing cases is to catch errors and have them corrected before a patient is treated, then it makes sense to review cases before sign-out or immediately after sign-out [2, 9, 10]. The advantage of reviewing cases before sign-out is that errors are caught before the report is generated. This potentially reduces the amount of rework necessary to correct or amend reports. On the other hand, review of too many cases before sign-out adds to the burden of initial work and may impact turn-around time. There are good reasons to have reviews after sign-out that are established. For example, review of cases for a tumor board or for a multidisciplinary conference. There is good evidence that review of some cases before sign-out, at the very least, reduces amended reports and most likely reduces diagnostic errors [9, 11–14]. And there is no reason to stop reviewing cases after sign-out. Review of cases soon after sign-out has the same benefit to the patient when errors are discovered so long as the patient has not been treated.

Renshaw and Gould examined factors that correlated with worse or better performance. Among the factors that stood out, reports that had two pathologists' names on them or more were correlated with a lower amended report rate and a lower diagnostic disagreement rate than cases with reports containing only one pathologist's name [9]. This implies that cases reviewed by an additional pathologist result in fewer errors.

Dr. Novis reported his experience of case sign-out where two different years of quality assurance data are compared. In the first year, one pathologist's signed-out cases [12]. In the second year, all the cases were seen by two pathologists before cases were signed-out. During the year when two pathologists looked at cases, the number of amended reports was reduced by half.

Owens et al. [13] describes a quality assurance method where cases are randomly selected for review by a second pathologist before a case was signed-out. This is compared with a previous method of quality assurance where cases were reviewed after sign-out. In the process with review of cases pre-sign-out, there was a reduction in amended reports by 30% and a reduction of amended reports for diagnostic edits by 55%.

Lind et al. [11] conducted a study that compared prospective review of cases vs. retrospective review as a method of improving the pathology reports. Overall, the major error rate was 1.2% in prospective reviews vs. 1.7% for random retrospection review of cases. The points of emphasis of this article include the following: (1) Prospective reviews prevent errors before a case is signed-out; (2) This review resulted in a small delay in diagnosis (1.62 vs. 1.79 days); and (3) There were benefits from pathologists showing cases in having the opportunity to discuss diagnostic and prognostic features.

Nakhleh and Zarbo conducted a Q-Probes study that identified practices associated with amended reports [14]. Most notable, practices that had a policy of case reviews before sign-out had lower rates of amended reports than those with review policies after sign-out (1.2/1000 vs. 1.6/1000).

## How Many Cases Should be Reviewed?

There are some in the literature that have advocated review of all cases in pathology [12, 15]. Many have dismissed this as an inefficient and costly method to eliminate diagnostic error. A rate that is close to zero is probably inadequate to catch a sufficient number of cases. Review of a substantial percentage of cases leads to a dramatic level of effort requiring additional full-time equivalents (FTEs). There needs to be a balance between the level of reviews and the negative effects of doing reviews [11].

There are a number of reviews that occur in the course of normal practice. This includes review of cases for conferences, review of cases with clinicians for various reasons. Often pathologists seek a colleague's opinion on a case that is unfamiliar to them. Or they may share a case because of a particular interest of a colleague. It is very instinctive for pathologists to show cases to other pathologists. There is a natural need to demonstrate a "great" diagnosis, but at the same time, pathologists seek confirmation of that diagnosis.

Many departments have instituted policies that mandate reviews of selected case types such as brain or thyroid cases. The reasons for these reviews are many. Some have instituted review policies because of demonstrated poor agreement in selected organ systems. The demonstrated poor agreement could be within the institution

itself, locally, or nationally. Others may also institute such policies for cases that are not commonly seen at that institution. Many tend to include review of most initial diagnosis of cancer. Some have determined that all diagnostic breast biopsies should be reviewed by a second pathologist. Table 10.1 lists all the types of case review.

If one could document all of these reviews that occur during the natural course of work, it is not clear what percentage of cases is normally reviewed. A Q-Probe conducted in 45 institutions, measured the frequency of documented case review in surgical pathology. The overall rate of review was approximately 8 % [2]. The range of case was wide and ranged up to 17.1 % for the 90th percentile and 2.0 % at the 10th percentile. It is likely that additional cases are reviewed but are not documented, and therefore it may be that a normal rate of case reviews is higher than 10 %. Institutions that had a policy for review of cases have a higher rate of review, 9.6 %. A single institution's study reports a 13 % rate of documented reviews [9].

Few studies have looked at optimal combinations of cases that should be reviewed by a second pathologist. Renshaw and Gould [16] examined various combinations based on known rates of amended reports. In their study, tissues with the highest amended report rates included: breast 4.4 %, endocrine 4 %, gynecology (GYN) 1.8 %, and cytology 1.3 %. The specimen types with the highest amended rates were breast core bx 4.0 % and endometrial curetting 2.1 %. The diagnoses with

**Table 10.1** Methods of case review by a second pathologist

| Review type | Explanation of process |
|---|---|
| Targeted | Review of specific types of cases either by diagnosis or by organ system |
| Random | Review of cases using a previously outline method of selecting cases randomly (e.g., review of cases with accession numbers ending in 0) |
| Percentage of cases | Review of a predetermined percent of cases (e.g., 5, 10 %) this may be achieved through multiple methods. Some departments do 10 % random review. Others may be happy to achieve 10 % through any and all methods |
| Conference cases | Review and documentation of cases reviewed for conferences such as tumor board, clinical–pathologic correlation conferences |
| Intradepartmental consultation | On request of a pathologist, a case is reviewed by a second pathologist within the same department |
| Extra-departmental consultation | On request of a pathologist, a case is reviewed by a second pathologist at another institution |
| Unsolicited extra-departmental review | A case is reviewed at another institution usually because the patient's care has moved to the other institution. This may also occur because a patient seeks a second opinion |

highest amended rates were nondx 5% and atypical/suspicious 2.2%. Based on these findings, they calculated that reviewing nondiagnostic and atypical/suspicious resulted in review of 4% of cases and detect 14% of amended reports. Reviewing all breast, GYN, non-GYN cytology, and endocrine material resulted in a review of 26.9% of all cases and detected 88% of amended reports. The study authors conclude that the optimal strategy for review is still unknown.

The rate and mix of cases in a review is highly dependent of the types of cases seen at any particular department and the availability of pathologists with specific expertise in any one area. Just as an example, pathologists at a children's hospital will have material that is mostly different from pathologists that serve primarily adult patients.

Raab et al. did not tackle the question of appropriate timing for reviews but conducted a study that compared 5% random review vs. focused organ review. The 5% random reviews resulted in detection of errors in 2.6% of case. The focused review detected errors in 13.2% of cases. This difference was statistically significant and was maintained when looking at major errors as well (random review (0.36%) vs. focused review (3.2%)). This study clearly demonstrates that targeted reviews are a more efficient method of detecting errors vs. random reviews [17].

To sum up this section, it is not clear what the optimal rate of review should be? Studies of pre-sign-out institutional review rates show a current review rate of 8–10%. There is evidence that targeted reviews of selected cases is more effective than random case reviews.

## How Should a Second Pathologist Review be Structured?

How reviews occur is greatly dependent on workflow and individual or group capacity. As stated earlier, the most ideal time for reviews is either before case sign-out or just after. This is to minimize any potential harm from error to patients. This also works in the pathologist's favor and reduces potential liability if and when an error is detected.

The type of cases that need to be reviewed is also greatly dependent on the material that an institution receives. There are some general principles that could be applied to case selection:

1. Cases with known poor diagnostic agreement (statistically low kappa) (e.g., Barrett dysplasia)
2. Cases with high potential for patient harm (e.g., false positive cytology)
3. Cases with high potential for legal claims (e.g., false negative biopsy)
4. Cases with known departmental disagreement
5. Borderline lesions
6. Cases unfamiliar to an individual
7. Rare disease states
8. Cases where diagnostic criteria are subjective

9. Cases where a focal finding may be missed (e.g., prostate biopsies)
10. High-profile cases that may attract significant attention

While this list may seem redundant, it is a checklist meant to remind individuals of potential risk.

In each practice, pathologists should assess the material they see and determine where their risk lies. Then, there needs to be a discussion of how to best capture these cases in a review. If current mechanisms of review make sense from a risk perspective, they should remain in place. If not enough cases with potential risk are being reviewed, then that should be addressed.

The most important factor is to outline a strategy to review cases and implement it. Subsequently, checks should be in place to make sure that the process is being carried out and is effective in detection of errors in a timely manner.

It is important to outline the strategy for case reviews within the annual quality assurance plan. List the reviews that occur naturally within the department and the expected level (e.g., all cases, 5%, etc.) of review. If it is desired to achieve a certain level of review, then there should be a check to assure that that level has been achieved. If too few cases are reviewed, then additional reviews should be added.

## How Can Reviews be Optimized for a Very Small Group Practice?

In a small practice, particularly solo practice, the opportunities for reviews are limited. Most small practices rely on external consultation for difficult or unusual cases but also understand that a significant proportion of patients with newly diagnosed cancers will be referred to another center for definitive treatment. Unless the pathologists have additional training or experience in renal pathology or hematopathology, most small practices will automatically send out kidney biopsies to rule out glomerulonephridites and lymph node biopsies for the diagnosis of lymphoma. Other types of case that may be sent out include brain biopsies as well as soft tissue and bone tumors. In a study of consultations initiated by pathologists, it was documented that 0.5% of cases were sent for consultation to a known expert [18]. The range was 0–2.0% with a median of 0.7%. Smaller institutions more frequently sent cases for consultations than larger institutions supporting the idea that this is a necessity in small practices.

In a small group setting, the most practical and likely more frequent reviews are reviews that are unsolicited because a patient is referred to another center for treatment. Unsolicited external reviews are probably the best opportunity to understand how good a particular department is and identify their potential weaknesses. If for example, report discrepancies are repeatedly identified in a particular organ system, then steps should be taken to understand the source of the discrepant reports and the underlying deficiency. At that point, steps can be taken to rectify the deficiency. It is not always that there is lack of ability on the part of the pathologists, it may be as simple as using an updated diagnostic classification or an indication to refresh one's

knowledge. Sometimes, it may be an indication that a new confirmatory test has been introduced and is being used at other institutions. Depending on the location of the practice and if there are nearby institutions, many pathologists will seek out others to show cases and discuss ways to work up difficult cases. Some localities have active "city wide" case conferences that may be helpful in addressing current cases. The potential impact of telepathology, slide scanning technology, and the ability to share cases electronically is still being explored [19, 20]. These solutions will have a substantial impact on the practice of pathologists in remote areas. With an appropriate network of available pathology experts, it is possible that a pathologist could seek a second review of a case at any time, even at frozen section.

Small group practice posses more difficult challenges with regards to obtaining case reviews, but technology offers potential solutions. Ultimately, pathologists in small group practice must proactively define relationships with other pathology groups to have the support in the need to show cases for formal and informal reviews. Small groups must proactively define their review strategy to consistently assure quality.

## How Can Reviews be Optimized for a Medium Size Practice?

It is difficult to define this group precisely. These are likely groups that contain roughly 6–7 at the low end up to 20 pathologists or so. The essential feature of these groups is that pathologists are generalists, but most groups have individuals that are trained or have strong interests in specific subspecialty fields. This allows these groups to have individuals that serve as the point people for that subspecialty. These individuals serve in several capacities: (1) They tend to be the primary connection with clinical teams of that subspecialty. (2) They take on the responsibility of keeping track of the literature and educating the group of any changes in practice. (3) They generally serve as the main person to review cases in that subspecialty. (4) They usually review cases for discussion at multidisciplinary conferences. When problematic or unfamiliar cases are seen by other pathologist of the group, typically, they are the first individual to show a case in that subspecialty. This practice also serves as a reference point to gage the strength and appropriateness of a diagnosis, but also this reinforces the education of diagnostic criteria and the appropriate content of pathology reports for particular diagnoses.

From the prospective of having a well-rounded group, it is important to hire pathologists with different interests. It is particularly important to be sure that individual interests reflect the points of focus of the institution they serve. At the same time, there needs to be sufficient number of individuals that can cover the service. For example, while practices vary, gastrointestinal biopsies tend to be a large proportion of cases (20–50%); sufficient staff members have to be expert in this area. It is difficult for one individual to serve as a reference point with a large volume of cases because most of the time reviews tend to be disruptive of pathologists sign-out routine. While most cases are routine, the number of cases reviewed by a second

pathologist is variable depending on the specific tissue. Esophageal biopsies with Barrett esophagus tend to be reviewed at a higher rate than others gastrointestinal (GI) tissues. Breast biopsies tend to be a relatively small percentage of cases but are also reviewed at a relatively high rate [2].

Practices must have a good feel for the frequency of review and how long the process takes. Approximately 75% of laboratories have policies that address or recommend the extent of case reviews [2]. It is optimal that departments determine the percentage range that they would like to have reviewed to assure accurate diagnoses. It is also important to measure and document the percent of cases that are reviewed as a demonstration of appropriate practices and assuring quality. Based on our experience, review rates of 5–15% of cases seem to be prevalent among pathology practices. There is no ideal formula or number that has been shown to be superior to others with regards to the percentage and types of cases that departments want to have reviewed. It is also important to check that individual practitioners are also checked to determine the rate of cases that they show to others. Beyond detecting and correcting errors, this practice promotes teamwork, cohesion of the group, and continuing education.

A typical list of cases that may be mandated for review include breast biopsies with proliferative lesions, brain biopsies, selected thyroid nodules, Barrett esophagus biopsies with dysplasia as well as all new cancer diagnoses. However, since the majority of legal claims brought against pathologists are false negative cases, it may be prudent to include some negative cases with the potential to miss a diagnosis such as multipart prostate biopsies that are negative on initial screening [21, 22]. Similarly, breast biopsies or other biopsies that have a high clinical index of suspicion for malignancy could also be included. Areas that are frequently placed in this category include fine-needle aspiration of the thyroid and panceatico-biliary nodules.

## How Can Reviews be Optimized for a Large Size Practice?

Large size pathology practices are the most likely to have developed fully subspecialized models of case sign-out. Still fully subspecialized practice is unusual in the U.S. Hybrid models of practice are more likely than practices where pathologists only work in one organ system. Depending on the volume of material in any one subspecialty area, pathologists may work in one specialty or may choose to work in two or three subspecialty work groups. There may also be a core group of generalists that work in such groups that cover frozen section services.

Large groups are also likely to have redundancy in talent in most areas and the most sophisticated tools to help assure report accuracy and completeness. Because of the depth of knowledge and extent of subspecialization, review of some cases may be more for academic interest, but a scheme of case reviews should be in place to assure sufficient review of enough cases. Large groups are likely to have specialists not often seen in small group practice such as neuropathologists and hematopathologists. And there are likely to be more than one subspecialist in these

areas of sign-out. Added checks on these systems include a higher level of clinical correlation with more close relationships with clinical colleagues as well as frequent multidisciplinary conferences. Larger groups are also much more likely to have ongoing clinical trials and some of their pathologists may serve as reference pathologists for those clinical trials. Because of all of these activities, pathologists in large groups are more frequently the second or third pathologist to examine a case and have the advantage of seeing previous opinions as well as fuller clinical correlation. A recent review of a large tertiary practice indicates that based on follow-up, pathologists in this setting are more often right, but not perfect [23]. This supports the notion that even tertiary large groups should develop a system of reviews and checks for the diagnoses they make.

Unlike smaller groups, larger groups could set up review mechanisms that operate entirely within a subspecialized area of practice. For example, hematopathology or other work groups such as breast or GI work groups could have their own quality assurance programs that include a strategy for case reviews.

Table 10.2 lists potential quality assurance monitors that may be used to check on a department's analytic accuracy and report completion.

**Table 10.2** Quality assurance monitors to check on the accuracy and completion of reports

| Monitor | Description |
|---|---|
| Rate of second review | Determining the percentage of case seen by more than one pathologist. This activity when coupled with mandatory review of specific cases promotes teamwork within a department and gives a general impression of the frequency of reviews |
| Compliance with mandated reviews | If a department has a policy of mandating review on a specific type of specimen (e.g., brain tumors), then it is prudent to check that individuals are complying with this policy. A reasonable target may be 90% compliance |
| Rate of amended reports | The percentage of reports that are changed, this may be broken down into multiple subcategories as listed below: |
| Rate of amended reports for diagnostic change | The percentage of reports that are changed for changes in the diagnosis |
| Rate of amended reports for nondiagnostic report defects | The percentage of reports that are changed for changes in the report other than the diagnosis. Usually, the changes are nonconsequential (e.g., typos, change of date or time, etc.) |
| Rate of amended reports for specimen misidentification | The percentage of reports that are changed due to misidentification of the patient, site, or laterality |
| Rate of amended reports for specimen defects | The percentage of reports that are changed due to problems with the specimen (e.g., lost specimen, inadequate or small, inappropriate ancillary studies) |

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# Part III
# Post-analytic Factors Leading to Errors and Error Prevention

# Chapter 11
# The Complete Surgical Pathology Report

**Michael O. Idowu**

## Introduction

An essential component of the postanalytic phase of a pathology test is a timely, concise, complete, and easy to read and understand report. The information provided in a pathology report is useful for optimal patient management as it provides not only accurate diagnosis but also information that may be prognostic or predictive. The purpose of a specimen procurement may be defeated if the pathology report is inaccurate, verbose, incomplete, difficult to read, or difficult to understand. An incomplete or ambiguous pathology report for cancer resection may not only delay patient management (as clarification of the report may be sought by the treating clinicians), but may be misunderstood with potentially significant consequences. Hence, the importance of a complete report cannot be overemphasized. *The need for standardized reporting was identified more than two decades ago*. The Association of Directors of Surgical Pathology (ADASP) highlighted the importance of standardization of surgical pathology reports, including the use of a "checklist" approach for recording information needed for patient treatment and prognosis [1–9]. While the recommendations by the ADASP have been adopted by most in the pathology community, *there are recent studies highlighting the need for improvement in the standardization and completeness of pathology reports*. For example, a recent College of American Pathology (CAP) Q-Probes study found that almost 30% of pathology reports lacked at least one or more required elements [7, 8].

M. O. Idowu (✉)
Department of Pathology, Virginia Commonwealth University Health System,
1200 East Marshall Street, Gateway Building, 6th Floor, Richmond, VA 23298, USA
e-mail: MIDOWU@MCVH-VCU.EDU



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## The Need for Complete Pathology Reports/Standardization

### *Interest from Accreditation, Governmental and Non-governmental Agencies*

The importance of complete reporting is recognized and recommended not only by pathology organizations but also by other organization such as the National Quality Forum (NQF), American College of Surgeons (ACS) Committee on Cancer (CoC), and governmental agencies like the Center for Medicare and Medicaid Services (CMS) [10–17].

The NQF is a nonprofit, nonpartisan, public service organization that reviews, endorses, and recommends use of standardization. Its membership includes a wide variety of healthcare stakeholders including accrediting and certifying bodies and quality improvement organizations among others. The NQF has been in contract with the Department of Health and Human Services (HHS) since 2009 to help establish quality and efficiency measures for use in reporting on and improving health care quality. While the majority of the measures recommended and endorsed by the NQF relate to clinical practice, standardized pathology reporting is also included as one of the quality measures [10]. The cancer checklists/protocols by the College of American Pathologists (CAP) are endorsed by the NQF, albeit as a voluntary standard [17].

The CMS is also interested in standardized and complete pathology reporting. The CMS Physician Quality Reporting System (PQRS) program will begin to impose penalties in 2015 in the form of reduction in payments for lack of participation in the program [11]. Pathologists who do not participate will face a 1.5% penalty in 2015 based on overall Part B Medicare payments. For pathology, a majority of the five measures developed by the CAP for PQRS—Breast Cancer Resection Pathology Reporting, Colorectal Cancer Resection Pathology Reporting, Radical Prostatectomy Pathology Reporting, Barrett's Esophagus Reporting, and Immunohistochemical (IHC) Evaluation of HER2 for Breast Cancer Patients—revolve mostly around completeness and standardization of pathology reporting. While the proposed use of penalty for lack of participation in the PQRS is unprecedented; it probably highlights the importance of pathology reports as a quality measure.

In fact, following recent approval by the CMS, the American Board of Pathology (ABP) has begun offering Maintenance of Certification: Physician Quality Reporting System (MOC:PQRS) as an additional Incentive Program to ABP diplomates [12, 13]. This program offers eligible pathologists who have satisfactorily submitted data under the PQRS an opportunity to earn an additional 0.5% for covered Medicare Part B services by "combining PQRS reporting with increased activities for Maintenance of Certification." The ABP has defined what "increased activities or more frequently" mean for diplomates with time-limited and non-time-limited certificates [12, 13].

Furthermore, one of the accreditation requirements of the ACS CoC relates to the use of the cancer checklist for reporting of findings on specimens for cancer resection [17]. While cancer program accreditation by the ACS CoC is voluntary,

applying for and maintaining the accreditation will probably speak to the commitment of a program/institution to providing quality cancer care; it enhances the accredited cancer program/institution's reputation, including but not limited to national recognition, quality improvement measures and public awareness. Since January 1, 2004, the ACS CoC "mandated the use of the RDEs as part of its Cancer Program Standards for approved Cancer Center" [17]. The ACS CoC considers the CAP Cancer Checklists as the reporting standard for cancer resection. In fact, the ACS CoC standard 2.1 "requires that 90% of eligible pathology reports that include a cancer diagnosis will contain the RDEs outlined on the currently applicable surgical case summary checklist of the CAP publication" [17]. CoC further recommended that "at a minimum, a random sample of 10% of the pathology reports eligible for the CAP protocols or a maximum of 300 cases are reviewed each year to document compliance with this standard. The cancer committee may delegate this quality control activity to the pathologists who report the quality control activity and a summary of findings regularly to the cancer committee" [17]. The willingness of pathologists to actively participate in such monitoring is encouraged.

Lastly the CAP laboratory accreditation program (LAP) now contains items (ANP.12350 and ANP.12385) that specifically address the issue of complete pathology reporting and formatting [18]. CAP LAP requires that all data elements in the applicable CAP cancer protocols should be included in the surgical pathology report (ANP.12350, a Phase II deficiency) [18]. While the use of CAP protocol or cancer checklist is encouraged, it is not mandatory that these must be used as long as all the RDEs are present in the report. The format of the synoptic report while not currently an accreditation requirement is a checklist item ANP.12385 (currently Phase 0; i.e., for information gathering only) requiring that "all elements required by applicable CAP Cancer Protocol are reported using a synoptic format" [18]. This checklist item indicates that paired required data element (RDE): response format is required. For example, RDE "Tumor size" must be indicated followed by the response (Tumor size: 7.5 cm). Format without the paired RDE: response format is not considered synoptic. Attention needs to be given to formatting because some report formats may be difficult to read and important information may be difficult to locate.

From the foregoing, it should be evident that the issue of completeness of pathology reports/standardized reporting is critical, as it may have not only accreditation implications, but may also be associated with reimbursement and Maintenance of Certification. A pertinent question therefore is: What constitutes a complete pathology report? The answer to this question will be addressed by discussing the following: the use of a checklist, formatting of pathology report, and reporting special stains (predictive/prognostic markers).

## Use of Checklist/Synoptic Report

A complete pathology report may simply be defined as a report containing all the information/interpretation/data obtained from examination of a procured specimen that are necessary for optimal management of a patient. Specifically for cancer

resection, a complete pathology report, *at a minimum*, should contain all the scientifically validated RDE as defined by the CAP [15]. Non-RDEs may be included in addition to, not in lieu of, the RDE. Clinicians may in fact request that some non-RDEs (not yet scientifically validated) should be included in the pathology reports as these may be needed for clinical decision making. Communication between pathologists and clinicians is important to determine which non-RDE needs to be reported without sacrificing conciseness of the report. *There is little or no need to clarify or add data elements to a complete report*.

A complete pathology report for a cancer resection specimen necessarily begins with a good gross description and adequate sampling of such specimens. CAP LAP checklist item ANP.12200 indicated that "all surgical pathology reports include gross descriptions, information essential for diagnosis and patient care, and record-essential processing information" [18]. These include specimen type, weight, dimensions, extent of gross lesions, and summary of sections. Indeed, without good gross examination, it is difficult, if not impossible to generate an accurate and complete report. This is because adequate histological examination of specimens relies on thorough gross examination and sampling.

The findings on histological examinations need to be reported to give a concise but complete summary of the findings. Given, the mobility of patients these days, a patient may transfer care to a center different from where the cancer resection was performed. Standardized reporting is important for smooth and effective transfer and continuation of patient care. Although most centers have a policy to re-review outside pathology materials prior to instituting definitive management, standardized reporting by using cancer protocol checklists makes this process easier. The CAP cancer protocol checklists are free and readily available [15]. The CAP authorizes modifications of the cancer protocols by physicians and healthcare practitioners for individual use. The use of the checklists in a computerized system is also allowed as long as it is for nonprofit purposes. There is a license requirement to use the checklist for any other purpose other than those expressly approved by the CAP. The required elements for some common cancer resections are highlighted in Table 11.1 [3–6, 15].

It may be argued, however, that narrative reporting is adequate as long as all the necessary elements are included in the report. However, while all the required elements may be included all the time by experienced pathologists in subspecialty settings (for example, breast pathologists or gastrointestinal [GI] pathologists), one or more elements may be omitted by a general pathologist in a nonspecialty setting. This is because it is difficult to recall all the required elements for the different cancer resection specimens from memory. The limitations of narrative reporting have been highlighted by many studies that showed improvement in cancer reporting with the use of cancer checklists. However, narrative type comments are acceptable, if used in addition to, not in lieu of, synoptic reporting.

To ensure that all the RDE are included at a minimum in cancer resection reports, it is a useful exercise to periodically monitor a percentage of such reports whether as part of cancer center accreditation or not. Studies have shown that when there is a mechanism by which reports can be monitored for completeness and that provides

**Table 11.1** Required data elements (RDE) of representative cancer resection specimens [3–6, 15]. Additional RDE for cancer resection specimens may be found at the CAP Website [15]

| **BREAST CARCINOMA** |
|---|
| **Specimen laterality**: |
| **Procedure**: |
| **Lymph nodes sampling** (*required only if lymph nodes are present*): |
| [a]**Tumor site/location**: |
| **Histologic type of Invasive carcinoma**: |
| **Tumor focality** (*required only if more than one focus of invasive carcinoma present*): |
| **Tumor size** (*size of largest invasive carcinoma, if multiple foci*): |
| **Histologic grade** (*total score*): |
| Nuclear score: |
| Tubule score: |
| Mitosis score: |
| **Ductal carcinoma in situ (DCIS)** [Present/Absent]: |
| [a]Extent/size of DCIS |
| [a]EIC |
| [a]Grade |
| **Macroscopic and Microscopic Extent of tumor** (only if the structures are present and involved): |
| Skin: |
| Nipple: |
| Skeletal muscle: |
| [a]**Lymphovascular invasion**: |
| **Margins** |
| **Invasive carcinoma** (Involved/uninvolved): |
| Distance from closest margin: |
| [a]Specify closest margin: |
| [a]For positive margins, specify extent (focal, minimal/moderate or extensive): |
| **DCIS** (DCIS not present, Involved/uninvolved |
| Distance from closest margin: |
| [a]Specify closest margin: |
| [a]For positive margins, specify extent (focal, minimal/moderate or extensive): |
| **Lymph nodes** (*required only if lymph nodes are present in the specimen*) |
| Number of Sentinel lymph node(s): |
| Number of Total lymph node(s) (sentinel and non-sentinel): |
| Number of lymph node(s) with macrometastases (*>2 mm*): |
| Number of lymph node(s) with micrometastases (*>0.2 mm to 2 mm and/or >200 cells*): |
| Number of lymph node(s) with ITCs (*>0.2 mm to 2 mm and/or>200 cells*) |
| [a]Size of largest metastasis |
| [a]Extranodal extension: |
| [a]**Treatment effect** (if there is neoadjuvant treatment): |

**Table 11.1** (continued)

| |
|---|
| **Pathologic TNM staging:** |
| **Ancillary Studies/ Predictive Markers #**: (Breast Biomarker Reporting Template now available on CAP website) |
| Estrogen receptor (*%, intensity and interpretation*): |
| Progesterone receptor (*%, intensity and interpretation*) |
| HER2 (*Immunohistochemistry and/or FISH Result*): |
| |
| **CARCINOMA OF THE COLON OR RECTUM** |
| **Specimen**: |
| **Procedure**: |
| **Tumor site**: |
| **Tumor size**: |
| **Macroscopic tumor perforation**: |
| **Histologic type**: |
| **Histologic grade**: |
| **Microscopic tumor extension**: |
| **Margins**: |
| Distance of invasive carcinoma to closest margins (if all margins are uninvolved): |
| Specify margin: |
| Proximal: Uninvolved by invasive carcinoma |
| Distal: Uninvolved by invasive carcinoma |
| Mesenteric (radial for rectal cancers): |
| **Treatment effect**: |
| **Lymph-vascular invasion**: |
| **Perineural invasion**: |
| **Tumor deposits** (*discontinuous extramural extension*): |
| **Lymph nodes**: |
| Number of Lymph Nodes Examined: |
| Number of Lymph Nodes Involved: |
| **Pathologic staging** (pTNM): |
| [a]**Ancillary Studies/ Predictive Markers** (Colon and Rectum Biomarker Reporting template now available on CAP website) |
| Immunohistochemistry studies for Mismatch repair protein (MMR): |
| Microsatellite instability (Also specify testing method): |
| Methylation studies |
| BRAF mutational analysis |
| KRAS mutational analysis |
| |
| **CARCINOMA OF THE KIDNEY** |
| **Procedure**: |
| **Specimen laterality**: |
| [a]**Tumor site**: |
| **Tumor size**: |

**Table 11.1** (continued)

| |
|---|
| **Tumor focality**: |
| **Macroscopic extent of tumor**: |
| **Histologic type**: |
| **Sarcomatoid features**: |
| **Histologic grade** (*Fuhrman Nuclear Grade*): |
| **Microscopic tumor extension**: |
| **Margins**: Tumor present at renal vein margin |
| **Lymph nodes**: |
| Number examined: |
| Number involved: |
| **Pathologic Staging** (pTNM): |
| **Pathologic findings in non-neoplastic kidney**: |
| |
| **CARCINOMA OF THE PROSTATE** |
| **Procedure**: |
| **Prostate weight**: |
| **Prostate size**: |
| **Lymph node sampling**: |
| **Histologic type**: |
| **Histologic grade** (Gleason pattern): |
| Primary pattern: |
| Secondary pattern: |
| Tertiary pattern |
| Total Gleason score: |
| **Tumor Quantitation**: |
| Proportion (percent) of prostate involved by tumor: |
| and/or |
| Tumor size (dominant nodule, if present): |
| **Extraprostatic extension**: |
| **Seminal vesicle invasion**: |
| **Margins**: |
| **Lymph-Vascular invasion**: |
| [a]**Perineural invasion**: |
| **Treatment effect on carcinoma**: |
| **Pathologic staging** (pTNM): |
| |
| **THYROID CARCINOMA** |
| **Procedure**: |
| **Specimen Integrity**: |
| **Specimen Size** |
| [a]**Specimen weight:** |

**Table 11.1** (continued)

| |
|---|
| **Tumor Focality** (*For multifocal tumors: Dominant and second tumor nodules need to have the indented data elements completed separately for both; findings on additional nodules should be recorded in additional findings*): |
| **Tumor Laterality**: |
| **Tumor Size**: |
| **Histologic Type**: |
| [a]**Histologic grade**: |
| **Margins**: |
| **Tumor capsule**: |
| **Tumor capsular invasion**: |
| **Lymph-Vascular Invasion**: |
| **Extrathyroidal Extension**: |
| **Number lymph nodes examined**: |
| **Number lymph nodes involved**: |
| **Pathologic Staging** (pTNM): |
| **Additional findings**: |
| |
| **ENDOMETRIAL CARCINOMA** |
| **Specimen**: |
| **Procedure**: |
| **Lymph Node Sampling**: |
| **Specimen Integrity**: |
| [a]**Tumor Site**: |
| **Tumor Size**: |
| **Histologic Type**: |
| **Histologic Grade**: |
| FIGO Grading System for endometrioid and mucinous adenocarcinomas only): |
| Grading for other carcinomas (well to poorly differentiated): |
| **Myometrial Invasion**: |
| Depth of invasion: |
| Myometrial thickness: |
| **Involvement of Cervix**: |
| **Extent of Involvement of Other Organs**: |
| [a]**Peritoneal Ascitic Fluid**: |
| **Lymphovascular Invasion**: |
| **Pathologic staging (pTNM [FIGO Staging])**: |
| [a]**Ancillary studies:** |
| Immunohistochemistry for Mismatch Repair protein |
| MSI testing |

**Table 11.1** (continued)

| **MELANOMA** |
|---|
| **Procedure** (*optimal evaluation requires complete excision; checklist may be used for shave or punch biopsies, but evaluation of the margins or tumor thickness may be inadequate/ incomplete*): |
| **Specimen laterality**: |
| **Tumor site**: |
| **Tumor size**: (*required only if gross tumor is present*): |
| **Macroscopic satellite nodules** (*required for excision specimens only*): |
| **Histologic Type**: |
| **Maximum Tumor Thickness** (Breslow thickness): |
| [a]**Anatomic level**: |
| **Ulceration**: |
| **Margins**: |
| Peripheral Margins: |
| Deep Margin: |
| **Mitotic Rate**: |
| **Microsatellitosis**: |
| **Lymphovascular Invasion**: |
| **Lymph nodes** (required only if present in the specimen): |
| **Pathologic Staging** (pTNM): |
| |
| **CARCINOMA OF THE LUNG** |
| **Specimen type**: |
| **Procedure**: |
| **Specimen integrity**: |
| **Specimen laterality**: |
| **Tumor site**: |
| **Tumor size**: |
| **Tumor focality**: |
| **Histologic type**: |
| **Histologic grade**: |
| **Visceral pleural invasion**: |
| **Tumor extension** (*outside the lung*): |
| **Margins**: |
| Distance to closest margin: |
| Bronchial margin: |
| Vascular margin: |
| Parenchymal (stapled) margin: |
| Parietal pleural margin: |
| Chest wall margin: |
| Other attached tissue margin: |
| **Treatment effect**: |

**Table 11.1** (continued)

| |
|---|
| ***Tumor associated atelectasis or obstructive pneumonitis**: |
| **Lymph-vascular invasion**: Not identified |
| **Pathologic staging (pTNM):** |
| Primary tumor (pT): |
| Regional lymph nodes (pN): |
| Number examined: |
| Number involved: |
| Distant Metastasis (pM) |

Some optional elements/non-required data elements (non-RDE) are included in the above checklist with an asterisk. Institutions (Pathologists and Clinicians) may include these and other non-RDE data elements not indicated in the above sample synopsis by weighing conciseness with determined clinical importance of such data elements

[a] not required, but may be requested by clinicians/geneticist. If this is standard practice in your institution, report only if available at the time of report completion. If not available, it may be best to report these as addendum, rather than holding up the report. Indicating that these studies have been ordered and pending may be useful

NOTE: Some Biomarker Reporting Templates are now available for free on the CAP website(http://www.cap.org/apps/cap.portal?_nfpb=true&cntvwrPtlt_actionOverride=%2Fportlets%2FcontentViewer%2Fshow&_windowLabel=cntvwrPtlt&cntvwrPtlt%7BactionForm.contentReference%7D=committees%2Fcancer%2Fcancer_protocols%2Fprotocols_index.html&_state=maximized&_pageLabel=cntvwr)

feedback to the pathologists, there is improvement in the standardization and completeness of reporting [19–21]. Although monitoring of completeness of reporting for cancer resection specimens is required by the CoC for cancer center accreditation, there is utility in pathologists working with the cancer center to monitor these reports.

## *Synoptic Reports for Small Biopsies/Non-resection Specimens*

While the cancer protocol checklists primarily apply to cancer resection specimens, there are checklists provided by the CAP for some small biopsies like skin biopsy for melanoma, prostate biopsy, urinary bladder biopsy, transurethral resection of bladder, adrenal gland biopsy, gastrointestinal tumor biopsy, and kidney biopsy [15]. With the exception of skin biopsy for melanoma for which a cancer checklist is generally used, the use of a cancer checklist for most of the small biopsies is optional.

Some institutions have created their own checklists for small/needle-core biopsy specimens for which there are no CAP cancer checklists. There is a need for caution in using a checklist for small biopsies to avoid providing information that may not be clinically useful. An example is using an institution-developed cancer checklist for breast needle core biopsies for cancer [22]. The use of a checklist for needle core

**Table 11.2** Examples of checklist reporting for breast biopsies

| Final diagnosis | |
|---|---|
| *Left Breast, Needle Core Biopsies* | *Ductal Carcinoma In Situ* |
| Maximum size | 3 mm |
| Number of cores involved | 2 |
| Histologic grade | High grade |
| Type of DCIS | Solid |
| Comedonecrosis | Present |
| Calcifications | Not identified |
| Additional histologic findings | Fibrocystic changes |
| Immunohistochemistry | Hormone receptors ordered |
| *Left Breast @ 10 o'clock, Needle Core Biopsies* | *Invasive Ductal Carcinoma* |
| Maximum size | 6 mm |
| Number of cores involved | 3 |
| Combined histologic grade | II |
| Tubule formation score | 3 |
| Nuclear grade | 2 |
| Mitotic activity | 1 |
| Additional finding | Focal ductal carcinoma in situ, intermediate nuclear grade |
| Comedonecrosis | Present |
| Calcifications | Not identified |
| Additional histologic findings | Fibrocystic changes |
| Immunohistochemistry | Hormone receptors, HER2 and Ki-67 ordered |

biopsies for breast tumors (Table 11.2) appears controversial. Some data elements presented in such reports are generally not needed for patient management and may be misleading or inadequate for the following reasons: the maximum tumor size given on such needle core biopsy specimens is often an underestimation of the real tumor size and cannot be used for staging; it is difficult to accurately determine the tubular score when such a score can only be reliably given after evaluation of representative sections of the whole tumor; it is often not possible to count mitosis in 10 high power fields (due to small specimens) or to reliably identify areas with most mitoses for such counting. Rarely, the size of the tumor on needle core biopsy may be indicated in cases of small carcinoma on needle core biopsy, not present in the excision specimen. But these are the exception rather than the rule.

## *Synoptic Reporting in Benign Cases*

The CAP Anatomic Pathology checklist specifies that "a synoptic report is not required for specimens that contain no cancer" (CAP Anatomic Pathology Checklist ANP.12385) [23], however, a pathologist evaluating certain specimens such as

benign liver or kidney specimens may feel that a more standardized report is necessary to ensure completeness in reporting [24]. It is clear that some non-neoplastic surgical pathology specimens require more complex reporting, and standardization of reporting in such cases may be ideal. However, the use of checklists for reporting benign biopsy or resection specimens is entirely optional and dependent on institutional preference.

## Synoptic Report Formatting

Report format often refers to the layout of the report and includes such things as the text font, text size, letter case (uppercase or lowercase), report heading, and so on. Formatting can have significant impact on clarity and readability of pathology reports and the ease of finding the required elements [25]. Two cancer resection pathology reports having all the required elements but with different formats may have different effectiveness in communicating information. CAP provides a list of specific features that define synoptic reporting formatting, including the following: displaying the required cancer data using a format consisting of the required checklist item, followed by its answer (e.g., Tumor size: 10 cm; NOT Tumor measures 10 cm); each required element or diagnostic pair should be listed on a separate line; users may include additional items (optional) as long as all the RDE are included; data elements may be presented in any order; and the location of the synopsis in the pathology report is left to the discretion of the pathologists. Table 11.3 highlights variation in formatting of synoptic reports [14].

Consideration should also be given to the conciseness of the synoptic reporting. Since synopsis generally connotes summary of a text, a condensed statement or outline, a synoptic report that is verbose or too long, is in effect no longer a synopsis.

It must be emphasized that, generally speaking, report formatting applies not only to cancer resection specimens but also to biopsies and noncancer specimens. Effective report formatting, even in noncancer specimens and biopsies improves the clarity of the reports. A review article highlights four principles that can be used for effective report formatting [25]. The principles are as follows:

1. *Use of headlines to emphasize key findings*. This is especially important to communicate the key/most important finding in multiple biopsies specimens.
2. *Maintain layout continuity*. Consistent use of position/chosen format allows clinicians to always know where to find necessary information in pathology reports.
3. *Optimize information density for users*. It is easier for users familiar with the format of a pathology report to group diagnostic terms for easy recall.
4. *Reduce clutter*. This is essentially to minimize unnecessary information or distracters. Too much unnecessary information may result in the report being misunderstood. Although certain information is required by the CAP LAP checklist item GEN.41096 in a pathology report, the location of these items in the report may reduce distraction or clutter.

**Table 11.3** Formatting and location of the synopsis in the pathology report

| | | | | |
|---|---|---|---|---|
| **SURGICAL PATHOLOGY SYNOPTIC REPORT** | | | | |
| a) Synoptic report directly located below the diagnosis. | | | | |
| Breast, left; excision: | | | | |
| | Invasive ductal carcinoma. See synoptic report | | | |
| | Ductal carcinoma in situ | | | |
| | Previous biopsy site changes | | | |
| | **Synoptic Report:** | | | |
| | | **Specimen: Partial breast** | | |
| | | **Procedure: Excision with wire-guided localization** | | |
| | | **Lymph node sampling: None** | | |
| | | **Specimen laterality: Left** | | |
| | | **Tumor size: 2.1 cm in greatest dimension** | | |
| | | **Tumor focality: Single focus of invasive carcinoma** | | |
| | | **Histologic type of invasive carcinoma: Invasive ductal carcinoma** | | |
| | | **Histologic grade: Grade 3** | | |
| | | | **Glandular differentiation: 2** | |
| | | | **Nuclear pleomorphism: 3** | |
| | | | **Mitotic count: 3** | |
| | | **Macroscopic and microscopic extent of tumor:** | | |
| | | | **Skin: Skin is not present** | |
| | | | **Nipple: Nipple is not present** | |
| | | | **Skeletal muscle: Skeletal muscle is not present** | |

**Table 11.3** (continued)

| | | | | | | |
|---|---|---|---|---|---|---|
| | | **Ductal carcinoma in situ: Present, no extensive intraductal component** | | | | |
| | | | **Extent of DCIS: 0.3 cm in greatest dimension** | | | |
| | | | **Architectural pattern: cribriform** | | | |
| | | | **Nuclear grade: Grade II** | | | |
| | | | **Necrosis: Not identified** | | | |
| | | **Margins:** | | | | |
| | | | **Invasive carcinoma: Uninvolved** | | | |
| | | | | **Distance from closest margin: 0.5 cm (to anterior)** | | |
| | | | **DCIS: Uninvolved** | | | |
| | | | | **Distance from closest margin: 0.5 cm (to anterior)** | | |
| | | **Lymphovascular invasion: Not identified** | | | | |
| | | **Estrogen receptor, progesterone receptor and HER2:** | | | | |
| | | | **Performed on another specimen (previously reported)** | | | |
| | | | | **ER: 80% (Positive 3+ intensity)** | | |
| | | | | **PR: 60% (Positive 3+ intensity)** | | |
| | | | | **HER2: Ratio 1.2 (not amplified)** | | |
| | | | | **Proliferation index: 40%** | | |
| | | **Tumor stage: pT2 NxMx** | | | | |
| **b)** No separate diagnostic line before the synoptic report | | | | | | |
| RIGHT BREAST, LUMPECTOMY: | | | | | | |
| | Tumor Histologic Type and Subtype: | **INVASIVE DUCT CARCINOMA** | | | | |
| | Focality: | **ONE** | | | | |
| | Size of Tumor: | **2.3 CM** | | | | |
| | Specimen laterality: | **RIGHT BREAST** | | | | |

**Table 11.3** (continued)

| | | | | |
|---|---|---|---|---|
| | Tumor Histologic Grade: | | | **GRADE 1 OF 3** |
| | Nottingham Combined Tumor Grade: | | | **5** |
| | | Tubule Formation Score: | | **2** |
| | | Nuclear Grade Score: | | **1** |
| | | Mitotic Activity Score: | | **2** |
| | Extent of Tumor Invasion: | | | |
| | | Skin: | | **NO SKIN OR NIPPLE WITH SPECIMEN** |
| | | Nipple: | | **NO NIPPLE PRESENT** |
| | | Skeletal muscle: | | **NO SKELETAL MUSCLE PRESENT** |
| | Carcinoma in situ: | | | **PRESENT, LOW GRADE, CRIBRIFORM** |
| | | Extensive Intraductal Component: | | **ABSENT** |
| | Margin Status: | | | |
| | | Positive for invasive carcinoma: | | **NO** |
| | | Positive for in-situ carcinoma: | | **NO** |
| | | Extent of margin involvement: | | **N/A** |
| | | Distance to closest margin: | | |
| | | | Invasive carcinoma: | **3 MM (TO MEDIAL MARGIN)** |
| | | | In-situ carcinoma: | **2 MM (TO MEDIAL MARGIN)** |
| | Lymph Nodes: | | | |
| | | # of sentinel lymph nodes assessed: | | **7** |
| | | Total # of sentinel and | | 7 |

**Table 11.3** (continued)

| | | | |
|---|---|---|---|
| | | non-sentinel: | |
| | | # with isolated tumor cells: | **0** |
| | | # withmicrometastasis: | **0** |
| | | # withmacrometastasis: | **0** |
| | | Extranodal extension of tumor: | **N/A** |
| | Total # of nodes with metastasis: | | **0/7** |
| | Total # of nodes without metastasis: | | **7 NODES ARE NEGATIVE FOR METASTASIS** |
| | Pathologic TNM Staging: | | **pT2 N0(Sn)** |
| | Ancillary Studies: | | **PREDICTIVE MARKERS PERFORMED ON PRIOR BIOPSY**<br>**(AB-00-00000)** |
| | | Estrogen Receptor: | **99%, Strong Intensity** |
| | | Progesterone Receptor: | **10%, Weak intensity** |
| | | Proliferation Marker: | **21% (Low)** |
| | | HER2 by HERCEPTEST | **1+, negative** |
| **c)** The inclusion of non-RDE should be balanced with the conciseness of the synoptic report. Synoptic reports that are too long may make it difficult to easily find the required elements. | | | |
| **INVASIVE CARCINOMA OF THE BREAST** | | | |
| **Procedure:** Segmental mastectomy with wire-guided localization | | | |
| **Lymph Node Sampling:** Sentinel lymph nodes | | | |
| **Specimen Laterality:** Left | | | |
| **Tumor Site: Invasive Carcinoma:** lower outer quadrant | | | |
| | Position: 3 o'clock | | |

**Table 11.3** (continued)

| | |
|---|---|
| **Histologic Type of Invasive Carcinoma:** Invasive ductal carcinoma | |
| **Tumor Size: Size of Largest Invasive Carcinoma:** Greatest dimension of largest focus of invasion: 1.5 **mm**, residual status post neoadjuvant therapy | |
| **Histologic Grade: Nottingham Histologic Score** | |
| Glandular (Acinar)/Tubular Differentiation: Score 3: <10% of tumor area forming glandular/tubular structures. | |
| Nuclear Pleomorphism: Score 2: Cells larger than normal with open vesicular nuclei, visible nucleoli, and moderate variability in both size and shape. | |
| Mitotic Rate: Score 2 (4-7 mitoses per mm2) | |
| Overall Grade: Grade II of III | |
| **Tumor Focality:** Multiple foci of invasive carcinoma. | |
| | Number of foci: 3 |
| | Sizes of individual foci: 1-1.5 **mm** |
| **Ductal Carcinoma In Situ (DCIS):** DCIS is present<br>Negative for extensive intraductal component (EIC) | |
| Architectural Patterns: Micropapillary, solid | |
| Nuclear Grade: Grade II (intermediate) | |
| Necrosis: Present, focal (small foci or single cell necrosis) | |
| **Lobular Carcinoma In Situ (LCIS):** Not identified | |
| **Margins:** | |
| Invasive Carcinoma: Margins uninvolved by invasive carcinoma. | |
| | Distance from closest margin: 14.0 **mm** |
| | Specify margin: Deep |
| DCIS: Margins uninvolved by DCIS | |
| | Distance from closest margin: 8.0 **mm** |
| | Specify margin: Superficial |

**Table 11.3** (continued)

| | | | |
|---|---|---|---|
| **Lymph Nodes** | | | |
| | Number of sentinel lymph nodes examined: 2 | | |
| | Total number of lymph nodes examined (sentinel and non-sentinel): 4 | | |
| | | Number of lymph nodes with macrometastases (>2 mm): 0 | |
| | | Number of lymph nodes with micrometastases (>0.2 mm to 2 mm and/or >200 cells):0 | |
| | | Number of lymph nodes with isolated tumor cells (≤0.2 mm and ≤200 cells): 0 | |
| | | Number of lymph nodes without tumor cells identified: 4 | |
| Method of Evaluation of Sentinel Lymph Nodes: H&E, multiple levels | | | |
| **Treatment Effect: Response to Presurgical (Neoadjuvant) Therapy** | | | |
| In the Breast: Probable or definite response to presurgical therapy in the invasive carcinoma | | | |
| In the Lymph Nodes: No lymph node metastases and no prominent fibrous scarring in the nodes | | | |
| **Lymph-Vascular Invasion:** Not identified | | | |
| Dermal Lymph-Vascular Invasion: No skin present | | | |
| **Pathologic Staging (based on information available to the pathologist) (pTNM) (Note M)** | | | |
| TNM Descriptors: y | | | |
| Primary Tumor (Invasive Carcinoma): pT1a: Tumor >1.0 mm but ≤ 5.0 mm in greatest dimension | | | |
| Regional Lymph Nodes: pN0 | | | |
| Distant Metastasis: Not applicable | | | |
| **Ancillary Studies** | | | |
| Estrogen Receptor (ER) | | | |
| | Results and interpretation: Negative (no tumor cells with nuclear positivity) (SP-12-17169) | | |

**Table 11.3** (continued)

| | |
|---|---|
| Progesterone Receptor (PgR) | |
| | Results and interpretation: Negative (no tumor cells with nuclear positivity) (SP-12-17169) |
| HER2: | |
| Immunoperoxidase Studies: N/A | |
| In Situ Hybridization (FISH or CISH) for HER2: | |
| | Results: Not amplified (HER2 gene copy <4.0 or ratio <1.8 (SP-12-17169) |
| Other Ancillary Studies: Performed on another specimen: SP-12-17169 | |
| | Name of test: Ki-67 |
| | Results: 65% |
| **Microcalcifications:** Not identified | |
| **Clinical History:** | |
| Palpable mass | |
| Radiographic finding: Mass or architectural distortion | |

Lastly, in this electronic age, most pathology reports are transmitted electronically. It is important to periodically review the electronic reports to ensure the integrity of the transmission by comparing these with the paper reports. It is possible that reports may have been rendered unintelligible or the formatting may be garbled. In fact CAP LAP checklist item GEN.41067 requires that "an individual meeting CAP laboratory director qualifications reviews and approves the content and format of paper and electronic patient reports at least every 2 years" [18].

## Reporting Ancillary Studies

Reporting prognostic and predictive ancillary studies are increasingly becoming important/necessary for optimal patient management. While the focus of these predictive markers is mostly on preanalytic and analytic phases of testing (ANP.22969, ANP.22970, ANP.22973, ANP.22976, ANP.22978, ANP.22983, ANP.22985, ANP.22999, ANP.23002), reporting is also addressed (ANP.23003) [23]. Reporting the results of these predictive markers are required (RDE) for breast cancer reporting, however, the reporting of predictive/prognostic markers is currently non-RDE for other cancer resections. Even if not currently considered RDE, some of these

studies are increasingly being used for patient management (e.g., *KRAS, BRAF*, mismatch repair protein and microsatellite instability testing for colorectal cancer; *EGFR, EML4-ALK, KRAS* for lung adenocarcinoma, etc.). The result of any test is useless if not available for clinical decision making or for patient care. Therefore, standardized reporting of the results of these biomarkers should be a component of complete pathology reports. The results of these tests may be included in the original synoptic report if available at the time of completion of final reports, or reported as an addendum report if not available at the time of finalization of the original report, rather than holding up the cases for this purpose. It is important to have a statement indicating what tests have been ordered and to promptly issue the addendum/supplemental reports when the results are completed, so that valuable time is not spent calling to have the test ordered or tracking down the results.

Of note, CAP has recently released templates for reporting results of biomarker testing for colorectal and non-small-cell lung carcinomas [26, 27]. While the use of these biomarker reporting templates is optional at this time, the templates provide useful guidelines on important elements to include in reports for these molecular tests in surgical pathology. The CAP molecular testing template also provides explanatory information on the rationale for including these elements [26, 27].

## Conclusion

As new technologies such as next generation sequencing become widely available, resulting in massive amount of data/results, pathologists are in a good position to synthesize these results/data and determine what results need to be reported for patient management. The determination of what to report in this setting is best done in collaboration with the clinicians. In the future, it is conceivable that there may be inclusion of additional RDEs for the cancer resection report to be considered complete. However, the broad definition of a complete pathology report will likely remain: a report with all data elements necessary for clinical decision making and patient management.

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# Chapter 12
# Communicating Effectively in Surgical Pathology

**Carolyn Mies**

The key *analytic* tasks of surgical pathology include understanding clinical context; observing and recognizing key microscopic findings; parsing and extending them with optimal ancillary studies; and, finally, integrating this totality of information to form an accurate and complete pathologic diagnosis. Once formulated, this analytic product must then be "packaged" and transmitted—in other words, communicated—to the rest of the team caring for the patient. How to accomplish this *postanalytic* task well, and as error-free as possible, is the topic of this section.

Surgical pathologists have two main communication tasks: (1) convey clear, unambiguous, useful, and complete diagnostic information in a timely fashion to other physicians and health care providers; and (2) create a permanent record of findings to guide patient care and ensure accountability. The surgical pathology report, as the vessel of these interrelated tasks, must be composed with thought and care. In addition, the task of communication extends beyond the report; the pathologist must be available, willing, and prepared to discuss the reported findings with clinicians [1].

The surgical pathology report most commonly serves its functions as a *written* document; as such, pathologists should use strategies to maximize written English comprehension. Less often—for example, when communicating frozen section (FS) findings during surgery—the pathologist transmits a report (a preliminary version) by the *spoken word*, which has different "rules of the road" for safe conduct.

## Written Communication

The main tasks of writing the surgical pathology report are to (1) communicate the results of the pathologist's comprehensive analysis of facts, i.e., the diagnosis; and (2) create a permanent record to guide treatment and ensure accountability, the latter

C. Mies (✉)
Division of Anatomic Pathology, Department of Pathology & Laboratory Medicine, Hospital of the University of Pennsylvania, 6 Founders, 3400 Spruce Street, Philadelphia, PA, 19130 USA
e-mail: carolyn.mies@uphs.upenn.edu



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a medico-legal duty). Clear, succinct, unambiguous, and memorable reporting of diagnostic findings will best accomplish these tasks.

While it is true that "the best report in the world is worthless if the diagnosis is inaccurate," [1] it is equally true that the most astute diagnosis, if communicated poorly, may be misconstrued. Because faulty comprehension can lead to clinical error, surgical pathologists must attend to all facets of report construction that can affect comprehension: design layout, the audience, format, style and language, order, saying too little (incomplete) or too much (distracting).

## *Design Layout*

Absorbing information from a written report is a visual task; those who have studied this issue find that design layout matters [2]. Report layout can make comprehension seem effortless or turn it into an arduous slog. Valenstein [2]showed how four layout principles used by the newspaper industry could be adapted to the report context to aid communication: (1) use headlines to emphasize key points; (2) aim for report-format consistency, across one's institution and over time; (3) optimize information density; and (4) reduce extraneous information ("clutter"). Renshaw [3] showed that applying some of these principles to cancer template formatting could increase synoptic-completion rates in a high-volume pathology practice.

## *Know Your Audience*

On opposite sides of the surgical pathology report is the *writer*, a surgical pathologist (usually, just one) and the *reader(s)*, most of them *not* pathologists: nonpathologist physicians (surgeons, oncologists, etc.), nonphysician health care providers and, increasingly, the *patient*. And, if things go wrong, an attorney may join the crowd. The College of American Pathologists (CAP), American Society of Clinical Oncology (ASCO), and the National Cancer Institute (NCI) have informational websites for patients that describe the pathology report and how to read it [4].

In addition to "know your audience," pathologists can employ other linguistic strategies used by science and other technical writers to communicate complex information to nonscientists. Report-layout aside, the individual practitioner controls the actual content of the diagnostic report and can choose and order words to optimize error-free comprehension.

## *Format*

Narrative or synoptic—which format is better for a diagnostic report? In fact, both are useful, but for different tasks. Narrate derives from the Latin *gnarus* or knowing, akin to the Latin *gnoscere, noscere*—to know, meaning to recite the details of

(a story); synoptic, derived from the Greek *synoptikos*, means affording a general view of a whole [5].

Narrative exposition *tells a story*; because humans are hard-wired to *remember stories*, diagnoses written as complete or partial sentences will be remembered more easily [6]. A synoptic format summarizes facts in outline-form; it is useful because humans are also hard-wired to *forget details*. Thus, in composing a surgical pathology report, narrative and synoptic formats are complementary; combining them, where appropriate (e.g., in reporting results of cancer resections), can facilitate both comprehension and completeness.

## *Style and Language*

The meaning of "style" depends on context. Here, it is used to mean *a manner of expressing information in words*. Style is a tool set for articulating and disseminating complex information in an efficient manner [7, 8]. An effective style in writing surgical pathology reports can make content clear, easy to grasp, and more likely to be understood.

## *Order*

There are two prominent positions in a sentence or paragraph: the *beginning* and the *end*. An axiom of scientific writing is to go from what is known to what is *new,* stating the known at the sentence beginning and the new information at the end [9]. Because reading a surgical pathology report has a different goal and time frame than reading a scientific paper, it is more effective to use the front end of the sentence(s) for delivering critical, new information, i.e., the diagnosis. Context matters—in reports, the most important information should goes first.

## *Completeness vs. Too Much Information (TMI)*

Achieving completeness requires knowing what the clinician needs and expects to learn from the report. Earlier customer satisfaction studies showed lack of surgical pathology report completeness and other communication issues were high on the list of clinician's complaints [10, 11]. Satisfaction with report completeness has improved in recent years, probably because of widespread adoption of cancer synoptics and other checklists [12, 13].

To ensure that complete staging information is recorded for all cancer patients, hospitals seeking American College of Surgeons accreditation must use CAP cancer case summaries or similar for patients receiving initial cancer treatment. The effective cancer summary ensures completeness by putting cancer staging elements for

each anatomic site on "auto-pilot"; when optimized, it is a great communication and learning tool.

Completeness is vital, but reports can also have TMI. Nonpathologist clinicians read reports in a highly focused manner, searching for the "actionable" information. Although it can be tempting (especially for early career pathologists) to record every observation, an exhaustive litany of findings is difficult to sort through and may obscure the most important diagnoses. Avoid TMI in the narrative, so that the critical, need-to-know information stands out.

Checklists and cancer synoptics should also be monitored for TMI. Synoptic templates can be modified, as long as mandatory elements are covered [3]. Some "canned" templates that can be electronically downloaded via a laboratory information system are more comprehensive than is useful in daily practice and can be customized to better meet practice needs. Sticking to the shortest list of essentials will ease pathologist compliance and reader comprehension. Renshaw [3] showed that eliminating all optional items, sequentially numbering mandatory items, and a few other small format changes led to a durable 98 % increase in template completeness in their high-volume hospital practice.

In addition to eliminating nonmandatory elements, it is useful to *order* the essentials in a clinically logical fashion. Prioritize these so that the most clinically actionable information appears at the top-end (the beginning) of the synoptic, where it will be easy to find. Using breast cancer as an example, medical oncologists will focus on the pathologic stage elements—for most patients, invasive cancer size and node status—and predictive marker stain results, because these will dictate systemic treatment. Surgeons care most about margins and results of sentinel node biopsy. Radiation oncologists will focus on margin status, extratumoral lymphatic tumor emboli (LTE) and extracapsular extension of nodal metastasis. Thus, pathologic stage (and its components), predictive marker results, and margin status should lead the synoptic. Invasive carcinoma subtype and modified Bloom–Richardson grade follow, along with LTE. Clinician readers are far less interested in the specimen size and character, the color margins were inked, etc. Where a checklist summary is replacing conventional narrative gross description, these details belong toward the end. Key clinician groups can weigh-in on pruning and reorganizing synoptic templates to make them more useful; this may also ease acceptance of new reporting formats.

## Verbal Communication

Effective verbal communication—like the written type—is a learned skill; the most valued surgical pathologists are comfortable discussing report findings with clinicians and, on occasion, *patients*. In the FS context, the effective surgical pathologist must be able to articulate diagnoses clearly; further, what is said must correspond to the written record of the exchange. Safety, in this context, requires that the patholo-

gist can hear well (using hearing aids, if needed) and both articulate and comprehend spoken English.

Here are three safety maneuvers the pathologist can use in providing intraoperative support to surgeons. These complement operating room safety "time-outs" for patient identification, etc., and will aid clear verbal communication. (1) In reporting gross or FS-findings via phone or speaker, the pathologist should identify the patient by name and then by at least one other identifier—e.g., date of birth or medical record number; (2) say the specimen number and anatomic site written on the FS request; (3) request a "read-back" of the spoken diagnosis. The latter makes it possible to correct misunderstandings in real time, especially those due to word "drop-out" during transmission.

## Ten Tips for Communicating Effective and Error-Free Diagnoses

*1. Use Words for Nonpathologists*

This is the corollary to "know your audience." Mostly nonpathologists will read—and must understand—the report in order to care for the patient. *Pathologists* who may read the report include those who may reference it when signing out a subsequent resection of the same site; those evaluating a later specimen from the same patient, for a separate problem; and pathologists at another institution reviewing slides because a patient seeks a second opinion or treatment at another hospital.

Nonpathologist physicians and other health care providers are educated to understand diagnoses of the common disease states, both benign and malignant; what they do not know are the histological attributes that cause pathologists using a microscope to recognize each diagnostic entity. Examples of breast pathology diagnoses they will know: invasive carcinoma, *in situ* carcinoma, fibrocystic changes, and fibroadenoma. Words that can mystify include: myxoid (describing a fibroadenoma), clear cell and other types of metaplasia, and collagenous spherulosis (a pattern of duct hyperplasia, which is a fibrocystic change). So, avoid pathologic descriptors in the main diagnosis—they are incomprehensible to most nonpathologists and may confuse, rather than illuminate [14].

It is sometimes helpful to convey morphologic information to other pathologists who may have occasion to look at the same slides or other tissues from the same patient. A concise microscopic description or note set off from the main narrative is a good place to "talk" to other pathologists.

*2. Do Not Bury the Lead*

Tips 2 and 3 expand on using style and word order to make diagnoses easy to understand and remember. The *lede* (journalism spelling) line, a.k.a. the "lead," is the most important, significant, attention-grabbing aspect of a story [15]. Failing to put this in the first line in a journalistic report is called "burying the lead"; avoiding this is mandatory in journalism and should be in reporting pathologic diagnoses, too. In the report context, the most attention-worthy, actionable diagnosis is the lead and

should be readily identified by position. This is true, even when a negative finding is "the news." [2]

**Example** *Final Diagnosis*

Right breast, new margin, excision:

Breast tissue with biopsy-site changes; *no carcinoma* is seen.

Rewrite to lead with the most clinically significant diagnosis:

*No carcinoma* is seen; biopsy changes in breast.

*3. Order Words for Clarity*

Word order can help the reader to recognize and comprehend the key diagnoses. Some joke that "surgeons read only the first five words," [16] but there may be some truth to this observation and it may apply to other busy physicians, as well. Therefore, use the first five words to tell the most important part of the story; do not hold the reader in suspense.

Use standard diagnostic terms—examples are as follows: fibroadenoma, fibrocystic changes, carcinoma, and lymph node. Use word order to make the sentence flow logically, so it easy to comprehend. Put critical modifiers up-front—*invasive* carcinoma, *in situ* carcinoma, *negative* lymph nodes, and *no* carcinoma. *Mis*understanding is more likely where decisive modifiers *follow* nouns: carcinoma, *invasive*; carcinoma, *in situ;* lymph nodes *without carcinoma*.

**Example** *Final Diagnosis*

Left breast, core biopsy:

Columnar cell changes with lobular carcinoma *in situ.*

Rewrite to: lead with the most clinically important diagnosis; put the critical modifier (*in situ*) before carcinoma; state an implicit diagnosis (no invasive carcinoma); and omit a pathologic descriptor (columnar changes):

*In situ* lobular carcinoma; no invasive carcinoma is seen.

*4. Omit Unnecessary Diagnoses*

Avoid TMI by omitting unnecessary diagnoses and pathologic observations, which may divert attention from the key message. Examples of what can be omitted safely: benign diagnoses that do not require action or are no longer relevant. For instance, when diagnosing invasive breast carcinoma, risk-associated fibrocystic changes in the adjacent breast are no longer significant and there is no point in mentioning them. The same is true for an incidental fibroadenoma or mammary duct ectasia, etc. Nonessential information can clutter a report and distract from important findings; it should be omitted [2]. Speak to the nonpathologist reader, focus on the critical diagnoses, and avoid word clutter. If you cannot resist comprehensiveness, put the incidentals in a succinct note or microscopic description.

**Example** *Final Diagnosis*

Left breast, core biopsy:

Fibrocystic changes with lobular carcinoma *in situ.*

Rewrite to lead with the most clinically important diagnosis; put the critical modifier (*in situ*) before carcinoma; and omit a diagnosis that requires no action:

*In situ* lobular carcinoma; no invasive carcinoma is seen.

*5. Be Brief*

Whether composing the narrative diagnosis, note, microscopic description (if used), cancer synoptic, or addendum—keep it short and concise. Observing tips #3 (order words for clarity) and #4 (put critical modifiers in front of nouns) will aid concision. The shorter each sentence, the more likely that the reader will make it to the end and understand the complete thought.

**Example A** *Final Diagnosis*

Right sentinel lymph node, biopsy:

One out of one benign lymph node negative for metastatic carcinoma.

Rewrite succinctly, leading with the critical modifier (negative) followed by a readily understood ratio (0/1):

Negative lymph node, 0/1.

**Example B** *Final Diagnosis*

Left breast, MRI-guided core biopsy:

Papilloma with florid, focally atypical ductal hyperplasia, and atypical lobular hyperplasia.

Rewrite to lead with the most clinically significant diagnoses:

Atypical ductal and lobular hyperplasia in a papilloma*

*More description could go in a *note*, but this shortened sentence states the essentials.

*6. Avoid Ambiguity*

*Ambiguous* and *equivocal*, two adjectives, are synonyms that mean "capable of being understood in more than one way or sense." In addition, *equivocal* can imply an intent to mislead [17]. Complete diagnostic certainty (100% probability) at all times is unachievable in surgical pathology; on the other hand, *near*-certainty (a very high degree of probability) is expected in most circumstances. Habitually using ambiguous terminology, therefore, is not appropriate and can be inadvertently misleading.

Examples of ambiguous phrases are: *indicative of*; *suggestive of*; *not excluded*; and *cannot exclude*. Although household-phrases to physicians, such expressions are interpreted inconsistently, which can lead to different actions and outcomes

[17]. Although each of these well-worn expressions is correct, appropriate, and useful on occasion, they should be reserved for these uncommon circumstances.

*7. Proof the Report!*

There is no way to avoid this task—proofreading is essential for safe reporting. Built-in spell-checkers are useful tools, but cannot identify missing words or missing letters that change meaning. Inadvertently omitting a decisive modifier such as "no," "negative," "not," "is," and "is not" can lead to a radically different meaning, regardless of whether the modifier is up-front or follows a diagnosis noun. Omitting "*in situ*" in front of carcinoma may imply to some readers that carcinoma is invasive, when that is not the intended diagnosis.

The pathologist should also make sure the FS diagnosis recorded in the final written report reflects accurately what was transmitted verbally. Be prepared to address discordances by both verbal (see *unexpected, significant finding,* below) and written communication.

*8. Be Timely*

In order to be effective, surgical pathology reporting must be timely, which is context-dependent. The CAP, using broadly distributed surveys, has determined appropriate and achievable expectations for the timely reporting of FSs, routine biopsies and complex specimens. Turn-around time benchmarks for these three contexts are 20 min, 2 days, and 2 days, respectively. The CAP Laboratory Accreditation Program requires 90, 95, and 91 %, respectively, of a laboratory's cases to meet these benchmarks [10, 18].

There are two nonroutine circumstances in which timeliness is crucial. Resembling critical values reporting in laboratory medicine, these two types of actionable diagnosis mandate special reporting-time frames and actions: (1) the *urgent* diagnosis, and (2) the *significant, unexpected* diagnosis. CAP and Association of Directors of Anatomic and Surgical Pathology have published jointly a consensus statement of "timeliness" guidelines for these unusual cases, but recommend that each surgical pathology practice develop its own guidelines for identifying and acting on such diagnoses [19].

An *urgent* diagnosis signifies a medical condition that, while not imminently life threatening—like a "critical value" in the chemistry laboratory—should be directly communicated as soon as possible, certainly before day's-end. In such cases, failure to recognize urgency or communicate the diagnosis to the appropriate clinician can lead to patient harm [19]. Examples are: (1) cytomegalovirus or other invasive pathogen in a tissue biopsy from an immunocompromised patient; and (2) pathologic changes of rejection in a transplanted organ.

A *significant, unexpected* diagnosis is one that is clinically unusual or unforeseen [19]. Examples are: (1) discordance between an FS interpretation and the final diagnosis; and (2) finding carcinoma in a reduction mammaplasty specimen. The surgical pathologist should notify the appropriate clinician of a significant, unexpected diagnosis as soon as practical, so that the matter can be addressed during the patient's clinical course [19].

Effective communication of an urgent diagnosis or significant, unexpected finding requires some form of *direct* person-to-person communication [19]. Phone call is the surest means of direct communication, but STAT reporting mechanisms exist for this purpose in some institutions. E-mail with return receipt may also work for some surgical pathology practices, particularly those in academic centers where there is a "24/7" digital communication culture.

The pathologist must also *document* that essential communication took place; this can become a critical piece of defense, should litigation arise. Many legal experts would say, "If it isn't written down, it didn't happen," so it is important to record, in the surgical pathology report or in the medical record, the date, time, persons involved, and transmission mode (phone, e-mail, etc.) in directly communicating an urgent or similar diagnosis [20].

*9. Be Available to Discuss the Report*

Another facet of effective communication in surgical pathology occurs *after* the report is written and delivered. Comprehension may not be perfect, even when the report provides the information sought [14]. The effective pathologist—or designate, if the pathologist of record cannot be available (out of the office)—must be reachable to discuss and clarify report-findings, as needed [1].

*10. Mind Your Addenda: Notify and Document*

An *addendum* report, by definition, is issued after the final report. It may or may not change the original diagnosis; when following a distributed provisional report, the addendum may be the final report. Some laboratories use "addendum" to encompass any follow-on report including revised, amended, and corrected reports [21]. Regardless of content or intent, it seems addenda more easily "fall through the cracks" than final reports [22]. To avoid this pitfall, the pathologist issuing an addendum should take some form of direct action to make sure the appropriate clinician(s) gets the message.

Handle an addendum like an *urgent* diagnosis if new information changes the original diagnosis. Communicate directly, person-to-person (phone is best) with the clinician who needs to know; then, document that the communication took place—in the addended report or the medical record—including date, time, persons involved, and communication mode [19].

An addendum may supply additional information or interpretation that does not change the diagnosis: stain outcome, ancillary testing results, further reflections after reviewing archival material, consultative opinion, etc. Regardless, direct communication and its documentation is still advised, though it may be less personal and immediate than a phone call; e-mail and FAX, depending on institutional practices, may suffice.

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# Chapter 13
# Error Prevention in Transcription and Report Distribution

**Shannon J. McCall**

## Introduction

It has been established that laboratory services in general consume about 10 % of the overall healthcare budget but influence up to 70 % of health care decisions [1]. With regard to oncologic surgical pathology, a patient's entire treatment plan (surgery, radiation, and chemotherapy) is built on the pathologic diagnosis, therefore ensuring the overall quality of these diagnostic reports is critical. Surgical pathology reports, representing the final product of surgical pathology processes, are detailed with thorough gross and microscopic descriptions. Many diagnoses also contain comments meant to aid the clinician in interpreting the report. Historically, surgical pathology reports have been manually transcribed following dictation. More recently, voice recognition technology has been employed with or without the use of templates for common specimens. Required cancer reporting protocols are often combined with both manual transcription and voice recognition technology approaches.

The job of rendering a surgical pathology report on a specimen is not complete unless the verified diagnostic information is successfully transmitted in its intended format to the requestor. An evolution has occurred from manual pathology report distribution into the patient's official paper chart to inclusion of the report in the patient's comprehensive electronic health record (EHR). Data that cross an electronic interface between a laboratory information system (LIS) and an EHR are subject to loss of fidelity or formatting alterations which may render a final product different from what the pathologist originally intended. Inclusion of diagrams and/or photomicrographs with surgical pathology reports is possible in some systems, but can add a layer of complexity to successful electronic report distribution. Finally, some thought must be applied to the distribution of information within an individual pa-

S. J. McCall (✉)
Department of Pathology, Duke University, 327C Davison Building,
201 Trent Drive Box 3712, Durham 27712, NC, USA
e-mail: shannon.mccall@duke.edu



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thology report for maximum interpretability. This chapter discusses errors that can arise in the transcription and distribution of diagnostic data in pathology reports. Strategies for assessment and prevention of these errors in real practice situations are provided.

## Error Prevention in Transcription

### *Examining Transcription Errors*

The typical descriptive surgical pathology report begins with measurements and other visual observations from gross dissection. Also frequently included is a block summary which serves as a key for interpreting the submitted histologic sections. Dictated portions of the report, including gross descriptions, microscopic descriptions, and diagnoses are often manually transcribed into the LIS. The actual typographical error rate of manual transcription is difficult to ascertain because there are generally multiple opportunities for proofreading by different people (transcription supervisors, pathologists' assistants, and residents) with error correction before report verification. A metric that is somewhat more available is the typographical error rate observed in verified pathology reports. Several groups have conducted manual retrospective reviews of verified reports with the purpose of identifying all typographical errors—regardless of severity or clinical significance. Observed error rates in this context range from 6 to 12.3 % [2, 3]. Out of 4446 cases, Zardawi et al. reported a 3 % typographical error rate and a 3 % "other clerical error" rate for a total of 6 % in a large teaching hospital [3]. An examination of 1756 verified surgical pathology reports (generated on cases containing intraoperative consultations) at our institution demonstrated a typographical error rate of 11.7 % when all typographical and formatting errors were included (unpublished data). Malami and Iliyasu reported a typographical error rate of 12.3 % after examining 2877 cases from their teaching hospital [2]. Thus, unsolicited retrospective review of surgical pathology reports will identify typographical errors at a rate of up to one error per nine surgical pathology reports.

Fortunately, in the vast majority of cases such typographical and clerical errors are minor, have little to no impact on the interpretive meaning of a pathology report, and do not result in harm to the patient. Infrequently however, these errors may have a significant clinical impact. A study of 272 consecutive surgical pathology-related malpractice insurance claims over a 6 year period demonstrated one malpractice claim directly related to a surgical pathology transcription error. In the relevant case, the word "no" was omitted before the words "malignant cells" [4]. In another study, Hocking and colleagues randomly audited 250 reports from their hospital and graded identified reports as satisfactory, borderline, or unsatisfactory from a clinical care perspective. They identified an 8.8 % borderline rate in these reports. This borderline group included borderline errors of misinterpretation as well as borderline

report defects (such as omissions in cancer reporting or use of incorrect classification schemes). A subset of this group represented borderline typographical errors identified in microscopic descriptions which potentially altered interpretive meaning. However, the authors are careful to note—the proper meaning could generally be gleaned from the remainder of the report. Of note, 2% of their cases ($n=5$) were graded as unsatisfactory from a clinical care perspective; none of these were cases of typographical errors.

These types of careful, detailed retrospective audits of surgical pathology reports are labor intensive and can be expensive to perform. A different metric, and one that is more commonly included as part of routine quality assurance in surgical pathology, is the rate of report amendment/correction following verification, for report defects. This metric is easily calculated with the assistance of the anatomic pathology LIS. Amendment rates in surgical pathology are considerably lower than the typographical error rate identified in manual retrospective audits of all verified pathology reports. A College of American Pathologists Q-probes study examining surgical pathology report defects asked participants to review all surgical pathology reports that underwent changes to correct defects. The median defect rate in this study of 73 institutions was 5.7 corrected defects per 1000 reports, or 0.57%. In this study, 1.2 defects per 1000 reports were classified as a dictation or typographical error [5]. This is consistent with other published data showing about 18% of amended reports represent typographical errors [6]. Utilizing the report defect taxonomy developed by Meier et al., other reporting defects, defects in specimens, errors of misinterpretation, and errors of misidentification are also included in the amended report rate [7]. Therefore, a considerable gap exists between the typographical error rate observed in unselected retrospective audits and the typographical error rate obtained by examining only corrected reports. Quite simply, many surgical pathology typographical errors are never identified and so are never corrected.

Raab and colleagues reported the results of an earlier College of American Pathologists Q-Probe in which 74 participating institutions, mostly from the USA and Canada, reviewed 5268 previously verified surgical pathology reports as part of their regular practice processes (multidisciplinary conferences, externally reviewed cases, regular QA processes, and physician requests for second review). In this context, the surgical pathology overall discrepancy rate was 6.8%. In this study, the report defects were examined by organ system. None of the organ systems demonstrated a significantly different discrepancy rate. However, within the five most common subgroups (gastrointestinal and other, female genital, breast, lung, and male genital), there were differences between the types of discrepancies identified. The majority of discrepancies in male genital reports were misinterpretations (95.8%), with 4.2% of discrepancies being due to typographical errors. By contrast, 31.8% of the discrepancies identified in lung reports were due to typographical errors, with 63.6% classified as misinterpretations and 4.6% misidentification errors. These results suggest there may be inherent differences in the difficulty of manual transcription between organ systems reflecting complexity of terminology or transcriptionist level of familiarity with the vocabulary.

Anecdotally, the typographical error rate seen in surgical pathology reports at our institution represents the work of 25 pathologists whose typographical error rates vary but individually held fairly steady over a time period of 5 months (unpublished data). Our surgical pathology practice is subspecialized; therefore, it is uncertain whether differences in typographical error rates seen among individuals in our practice represent inherent differences in pathologists' proofreading and detail orientation, or whether they represent organ system-specific characteristics as suggested by the multi-institutional Q-Probe study above. Data are lacking as to whether individual typographical error rates correlate with other quality assurance metrics such as turnaround time, report defects including incomplete cancer reporting, or misinterpretation errors.

When specifically targeting typographical errors, it is clear that study design is important. As has been previously observed, the closer one looks for error, the more likely one will find it [6, 8, 9]. The data also seem to indicate that the vast majority of typographical errors have minimal if any clinical impact and so only very infrequently lead to adverse outcomes. In an era of limited resources and cost-containment, a strong argument can be made that programs targeting errors in medicine should focus on errors associated with adverse patient outcomes, rather than all errors [10]. However, one recent development that could change this paradigm is patient access to EHR data. At our institution, patients have access to the full text of their surgical pathology reports through an online patient portal, also called a personal health record (PHR). Typographical errors which would have previously been overlooked by surgical and clinical colleagues during routine practice are now subject to the scrutiny of individual patients and their families. Surgical pathology reports containing typographical error(s) when found within a PHR could lead to a perception of lower quality by patients, altering patient satisfaction. The potential also exists for patients to attempt to rectify identified errors through provider communication. A recent review of the literature on the subject of PHR access suggests both areas (effect on patient satisfaction and effect on physician workload) are understudied [11].

## *Methods of Transcription Error Prevention*

Beginning in the surgical pathology laboratory, prosectors should work, as much as possible, in an area free from extraneous background noises and stressors. In a review of patient safety and error reduction in surgical pathology, Nakhleh recommends that interrupting phone calls and other distractions be separated from tissue sectioning (and presumably the associated dictation process) because these functions require focus [12]. Rather than emphasizing speed, prosectors should carefully enunciate into recording devices, spelling long or difficult words as necessary.

In the manual transcription area, a quiet physical environment is essential. Transcriptionists should be seated at workstations with headphones, free from distraction by interrupting phone calls. Documents provided with the dictation file should

be proofread and double checked, especially for demographic and specimen information including laterality. Medical dictionaries and additional support materials should be available. Transcriptionists should not be hesitant to request assistance from a prosector if there is a problem with a dictation.

Proofreading at all steps is essential. In the case of manual transcription, the transcriptionist is the first person to see the content of the report text. Every effort should be made to have transcriptionists proofread their reports, or a representative sample of their reports, to insure continuous quality improvement. A second opportunity for proofreading of the demographic, clinical, and gross description portions of the report occurs before analysis of the slides. The prosector (pathologist, pathologists' assistant, staff member, or resident) should be required to proofread the transcribed product of their dictation. Again, this provides valuable feedback to the prosector about the dictation process. In academic medical centers, residents who are given a chance to "preview" slides and dictate or type their own surgical pathology diagnoses have another chance to review and correct transcription errors. Of course, before report verification, the attending pathologist responsible for the report should review the report in its entirety.

If auditing unselected verified reports for typographical errors is not part of the routine QA practice in your department, consider running such an audit on a subset of cases periodically. Reports at our institution found to contain typographical errors during such audits are forwarded to the verifying pathologist for review. The verifying pathologist may, at their discretion, amend the report to correct the typographical error. Attending pathologists may choose to share these reports with pathologist's assistants and residents as a periodic additional educational and quality assurance opportunity. If typographical errors are routinely audited in your practice, consider examining the data to identify correlations between typographical error rate and organ system, pathologist, or report type, and intervene as appropriate.

If transcription errors in clinical history are problematic, consider whether your practice could utilize standardized pathology requisition forms tailored to specific clinics. In this case, check boxes next to common symptoms associated with a particular medical specialty can be utilized. This limits the amount of additional vocabulary, abbreviations, and acronyms that the transcriptionists must learn to produce error-free reports. Similarly, use gross dissection and diagnostic templates whenever possible. Transcriptionists can pull up a template and use the case dictation only to fill in the blanks; this can reduce typographical errors.

Finally, although uncommon, critical errors in resulting in misinterpretation of benign versus malignant are potentially avoided by using best practices for diagnostically critical dictations. Specifically, one should avoid the use of the word "no" as in "no tumor cells present" and "no evidence of malignancy." Opt instead for terms that are less likely to be incorrectly transcribed, such as "negative for tumor" or "negative for malignancy."

## *Voice Recognition Software*

Voice recognition software has been in existence for more than two decades; however, systems used before 1994 were not "continuous speech" voice recognition systems. These early systems required the speaker to insert unnatural pauses between words while speaking; causing a slower and more frustrating dictation process. They were not widely used. During the late 1990s, however, hardware and software advancements enabled reasonable-cost, continuous speech systems to come to market [13].

There are obviously numerous potential uses for voice recognition in healthcare—examples are clinic notes, consultation notes, procedure notes, radiology reports, and pathology reports. Radiologists were relatively early experimenters with voice recognition technology; however, early studies of voice recognition in radiology disclosed frustration on the part of the attending radiologists. In an often-cited study of 2004 voice recognition utilization, Pezzullo and colleagues at Brown University describe paying for the benefit of shorter report turnaround time and decreased transcription personnel costs with increased error rates and increased physician time per dictation because of the need for real-time error correction [14]. The typographical error rate of manually transcribed reports in this study was 10 % prior to verification, whereas 89 % of the VR reports contained typographical errors prior to verification. Thus, physicians were spending more time correcting report errors prior to sign-out. The wage difference between physicians and transcriptionists resulted in a significant increase in cost per report. There is also a suggestion in this study that the radiologists may alter their dictation style (switching to fewer words per case) in an effort to compensate for the added correction time.

Frustration with voice recognition continued for several years in radiology as evidenced by a 2008 study of MRI reporting comparing voice recognition and human transcription. Strahan and Schneider-Kolsky echoed the previous findings that voice recognition resulted in a faster turnaround time overall but lowered productivity (reports generated per physician per hour) and had higher typographical error rates [15]. Similar findings were seen in an early study of voice recognition in generating surgical pathology reports. In a 2001 study where 206 routine surgical pathology reports were generated simultaneously using voice recognition and human transcription, the voice recognition accuracy was 93.6 % versus 99.6 % for human transcription [16]. Again, this decreased accuracy translated into an increased editing burden for the pathologist which was deemed unacceptable.

Practice pattern differences between radiology and pathology may be the gateway to successful and cost-effective uses of voice recognition technology in pathology. Henricks and colleagues at the Cleveland Clinic experimented with targeted deployment of voice recognition in the gross room from 2000 to 2001. In their study, utilization of the voice recognition system was limited to (1) pathologists' assistants and surgical pathology technicians performing (2) gross descriptions of low to moderate complexity of specimens including "gross only" diagnostic reports. In this context, an improved reporting turnaround time was also accompanied by a favorable cost: benefit analysis with a reasonable payback period of 1.9 years [17].

Kang and colleagues at the University of Pittsburgh first integrated voice recognition technology into their surgical pathology workflow in a limited way in 2001. The majority of their utilization has been by pathologists' assistants dictating gross descriptions of biopsy specimens; however, dermatopathologists, dental pathologists, and transplant pathologists have also used the system for final diagnostic reporting. They reported their multiple years of experience in 2010. Over the studied time period, gross description turnaround time decreased significantly—with an additional 89% of gross descriptions being completed within 1 day of accessioning. Interestingly, this group reported a decrease in transcription errors (defined as errors needing correction before report verification by pathologist). The authors infer that the observed decreased error rate results from the use of standardized templates, which limit the amount of entered text available for error [18].

In 2011, Singh and Pal reported their experience in a multiphase rollout of voice recognition technology for gross descriptions, then full reports. Like other groups, an improved turnaround time was experienced after the implementation of voice recognition technology. Interestingly, this group examined the amendment rate of verified reports for typographical errors. Compared to traditionally transcribed (in their case, often handwritten and subsequently transcribed) cases, the voice recognition cases had a lower amendment rate [19].

In summary, the data already have shown success and financial viability for limited uses of voice recognition in pathology beginning with the gross descriptions of small, common specimens, usually based on templates. The outcomes of voice recognition implementation are less clear as the complexity of the dictations increases and as the training level of the user increases. The main barrier to widespread implementation of voice recognition technology in surgical pathology has been the increased burden on pathologists to error-correct their own reports, costing valuable productivity time. The results of the Kang and Singh studies above suggest decreased error rates that may better offset this barrier. The recent reports of lower error rates may be attributable to improvements in voice recognition technology over time, suggesting the time may be right for a reexamination of voice recognition implementation costs in mainstream surgical pathology diagnostic reporting.

## Error Prevention in Report Distribution

Errors that occur in report distribution are part of the postanalytic phase of the surgical pathology test cycle, which includes the overall completeness and accuracy of the report, the communication of data and critical values, and end-user satisfaction with the report [12, 20]. Assuming the pathologist generates a complete, accurate pathology report within an internal LIS, there can still be errors or failures in the transmission of the report data from the pathologist to the intended recipient. There are two main points to consider in this section—errors in technical distribution of finalized pathology reports and more subtle errors of information distribution, i.e., how the diagnostic information is conveyed within the specific report. These errors will be examined, with suggestions for prevention, audit, and intervention.

## *Technical Report Distribution*

The technical aspects of pathology report distribution have evolved over the years. Previously, typeset pathology reports were photocopied and manually distributed to physician mailboxes and patient charts. Mail or courier services would deliver reports between institutions. Subsequently, fax machines began to supplant mailboxes and mail couriers. At the present time, the majority of inpatient anatomic pathology reports are distributed to recipients via an electronic interface into a patient's EHR, an internet portal, or a physician's e-mail "inbox." Methods of automatic report transmission are significantly faster than manual paper-based reporting [21].

Errors in technical report distribution can be divided into two types—that is, the complete failure of a completed report to appear where it is expected (autofax, printer, EHR, and e-mail inbox), and loss of fidelity or "degradation" in the content of the report. With degradation, the finalized report appears but there is loss of partial text content, loss of intended formatting, or loss of readability of tables, charts, or embedded images that decrease the overall interpretability of the report. In one study, report defects were shown to account for 29–48 % of surgical pathology report amendments [7]; a subset of these report defects consists of reports in which there was a failure of report transmission or degradation causing communication errors in the transmitted report. Thus, the integrity of pathology reports transmitted electronically to another location or another informatics system must be ensured.

The Clinical Laboratory Improvement Amendments of 1988 include a requirement that laboratories have an adequate manual or electronic system in use that can ensure patient data are sent accurately from their point of origin to the recipient in a timely fashion [22]. Compliance with this federal law in the surgical pathology laboratory can be demonstrated by comparing the original pathology report (in the native LIS) to the electronically transmitted result as viewed by the recipient. This process should be conducted as a formal audit with a sampling of a variety of anatomic pathology report types. Such verification should be performed prior to "going live" with a new electronic interface and periodically thereafter. Specifically, the audit should verify accurate data transmission from the laboratory to the first downstream system in which the user might be expected to access the data. Video displays should be reviewed to ensure effective communication of material. In the case of transmission to multiple types of video displays (traditional computer monitors, tablet personal computing devices, and mobile smartphones), a best practice would be to audit all of these output devices for loss of information fidelity, but also for readability and formatting. Records should be kept of the validation results. A simple method of record keeping is to print or save downstream screen captures. Many modern EHR systems may offer a patient portal or personalized health record which enables individual patients to access the vast majority of their medical records through an Internet-based system. In such cases, it is important to include the patient portal in the transmission audit as well.

Validation that a report has "crossed" the interface at all is binary. Evaluation of data degradation or loss of fidelity is more complex, relying on the specific interface protocol in use. Content must be compared exactly between systems to ensure

no loss of data has occurred. These processes are tedious but are required to assure that the diagnostic information is being transmitted accurately and completely [23]. It is important to note that the commonly used HL7 (Health Level 7, Ann Arbor, Michigan) interface does not support specialized font characteristics such as bold, italics, size, or color; therefore, many pathology groups have adopted the use of all uppercase characters to transmit important diagnostic information in a way that successfully crosses the interface.

A common degradation problem occurs when older LISs use fixed-width fonts and fixed-length lines of text. In the past, this enabled the pathologist to reliably create tables of information within the LIS using spacing and alignment properties. These tables would appear intact when the paper pathology report was printed directly from the LIS and distributed via photocopy. However, across the electronic interface, the information contained in such tables may be displayed in a proportional-width font, rendering the table of diagnostic information unreadable. Attention must also be paid to issues of text-wrapping and carriage returns. Carriage return symbols added in the middle of diagnostic information to affect the aesthetics of a report in the native LIS will transfer through the interface, which may not have the same character length lines. The result can be a report that frustratingly displays a single word on a line in the middle of a diagnostic string of text.

An important part of the audit which should not be overlooked is verification that addenda and amendments to previously verified pathology reports also cross the interface accurately. Records should be maintained showing validation of initial result transmission then validation of accurate result transmission after a change has been made to the pathology report. Special attention should be paid to the appearance of addenda and corrected reports in the patient portal to prevent unnecessary confusion or alarm in the patient. As the technology continues to advance, some systems allow sophisticated charts, figures, and digital images to be included as part of the pathology report. Accurate transmission of this content must be documented including proper image proportions and image color if necessary.

## *Information Distribution: Error Prevention in Report Content and Formatting*

A pathologist's strength is transforming observations and data into useful information through effective communication [24]. Given that the written surgical pathology report is the primary method of communication, care must be taken not only to transmit a complete, accurate report to the end-user, but also to distribute information within the report in the most effective way. The intentional formatting and word selection in our reports must not be overlooked as part of the postanalytic phase of testing.

In a fascinating study by Powsner et al., surgeons at various levels of training were given representative surgical pathology reports and asked to take an open-book examination with regard to specific pieces of data contained in the reports.

Overall, the surgeons misunderstood the pathologists' reports 30 % of the time [25]. This study, published in July 2000, was particularly timely and necessary on two fronts. First, the authors realized that large changes were occurring in methods of technical report distribution (EHRs and Internet-based portals). The authors also realized that the net effect of these changes would be a broader audience for surgical pathology reports (mid-level providers, students, and patients). The study tested and challenged some widely held pathologist assumptions as to report communication, and these lessons should be examined more fully.

Not surprisingly in the Powsner study, the number of report misunderstandings decreased with increasing years of medical training and experience. That is, the attending surgeons demonstrated fewer misunderstandings than the house staff, who in turn demonstrated fewer misunderstandings than the medical students. However, the number of misunderstandings even at the attending level was high (overall, 18 % misunderstanding rate of traditionally formatted pathology reports by attending surgeons). Analysis of some of the common misunderstandings will help to prevent these postanalytic errors in communication.

A common pathologist convention is to only mention in the diagnosis field the tissues that were identified in the specimen. Pathologists, in an effort to be concise or expedient, will sometimes intentionally exclude a "negative." The assumption is that "if X were present in the sample, it would have been listed in the diagnosis." However, this intended communication is not always understood by the surgeon, as demonstrated by the study. In a parathyroid resection surgical pathology report for which the diagnosis contained only a description of the parathyroid, 21 % of surgeons were unsure if the specimen contained any thyroid tissue. This result may cause some to rethink whether or not certain "pertinent negatives" should be listed in the diagnostic field. An even more common misunderstanding identified in the Powsner study was around specimen adequacy (surgeons were unsure if a specimen was adequate 59 % of the time, even if a firm diagnosis was rendered and no mention of specimen inadequacy was made).

Pathologists, when drafting reports, also make assumptions that nonpathologists have a general understanding of surgical pathology laboratory operations that should translate into complete understanding of the pathology report. However, when given a surgical pathology report on a transurethral prostate specimen, 38 % of surgeons were unsure if all the tissue was reviewed microscopically even though this information was clearly contained within the report [25].

In his comprehensive review of the literature and experience around formatting of pathology reports, Valenstein espouses the use of headlines when appropriate to emphasize important findings, the use of a consistent report layout, optimal "chunking" of information for the intended audience, and clutter reduction [26]. "Headlines" may not be appropriate for all surgical pathology reports, but the principle of answering the most important diagnostic question quickly and clearly is understood. For example, a re-excision of a skin malignancy should probably say "NEGATIVE FOR RESIDUAL MELANOMA" before any other comments about solar elastosis or scar.

Valenstein also discusses the lack of layout continuity between surgical pathology laboratories, including lack of consensus regarding whether or not the final diagnosis should be presented first or last in a surgical pathology report. Many practices have adopted the change to "diagnosis first" without data supporting a downstream improvement in interpretation. In another facet of the previously mentioned study by Powsner et al., misinterpretations by surgeons were analyzed using three differently formatted versions of the same pathology report. The data demonstrated that changing from a traditional pathology report format to either of two "improved" formats caused a 17 or 54 % increase in recall errors by the surgeons [25]. It is likely that the change itself, rather than the new format, created confusion in interpretation [24, 26]; however, more research is needed to elucidate this point; perhaps retesting the "improved" format interpretability after a period of some months. The existing data argue for careful and infrequent changes to reporting formats, utilizing advance notice of the changes and clinician training if necessary. It is also important to monitor our colleagues in radiology and cardiology—are CT scan reports and echocardiogram reports changing to a "diagnosis first" format? If not, why not?

As with oral communications, written communication is most successful when the target audience is envisioned upfront. At the current time, the audience for anatomic pathology reports includes patients, tumor registry staff, physician office staff, researchers, internists, specialists, surgeons, other pathologists, and public health officials [27]. Expanding on Miller's historic research into grouping or "chunking" bits of data for increased recall in working memory [28], Valenstein's research and experience suggest that there may be different options for data "chunking" that are most appropriate for diverse readers of pathology reports. Even the choice of words on the first headline ("cancer" versus "carcinoma" versus "adenocarcinoma, well-differentiated") can be best selected with the reader in mind. Continued research is necessary to determine the optimal balance for effective downstream interpretation of our reports by all readers.

It has been said that anatomic pathology converts cells and tissues into information [7]. The overall goal of surgical pathology reports is to extract and record the information from the specimens [29]. Medical education and residency training prepare us for the laboratory practices associated with this conversion (tissue fixation, sampling, slide preparation, and histologic interpretation). However, careful attention to detail and validation of our communication processes as outlined in this chapter are necessary to ensure that diagnostic information is accurately and completely transmitted to the clinician.

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# Chapter 14
# Error Management: Legal and Regulatory Responsibilities

**Timothy Craig Allen**

## Regulatory and Accrediting Agencies

Numerous local, state, and federal standards, regulations, and laws regulate laboratory environments and activities that affect safety and influence surgical pathology error prevention and reduction. Government bodies create and enforce laws and regulations, and nongovernmental bodies such as medical societies enforce standards [1]. Standards often contain legal and accreditation requirements and generally reflect the standard of care. State and local laws may differ from federal law, and may be more stringent [1]. As the surgical pathology laboratory uses chemicals, particularly for processing and staining, it is subject to numerous safety and environmental laws, regulations, and standards.

Although there are several governmental entities that influence surgical pathology both directly and indirectly, the primary governmental entity involved is the Centers for Medicare and Medicaid Services (CMS). The Center for Medicare and Medicaid Services regulates all nonresearch laboratory testing performed on human beings in the USA through the Clinical Laboratory Improvement Amendments, often referred to as CLIA [2]. The Division of Laboratory Services, within the Survey and Certification Group, under the Center for Clinical Standards and Quality is charged with implementing the CLIA Program [2]. For purposes of surgical pathology error reduction and prevention, the primary nongovernmental entities concerned are the College of American Pathologists (CAP) because of its widespread laboratory accreditation process, and to a lesser extent, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) due to its accreditation of hospitals. Both the CAP and the JCAHO have increasingly emphasized surgical pathology error reduction [3].

T. C. Allen (✉)
Department of Pathology, The University of Texas Medical Branch,
301 University Boulevard, Galveston, TX 77555, USA
e-mail: tcallen@utmb.edu, timallenmdjd@gmail.com



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In 1967, the US Congress enacted the Clinical Laboratory Improvement Act, regulating hospital-based laboratories that engage in interstate commerce; and in 1988, it passed the CLIA, which established quality standards for all laboratory-based tests [4]. Three Department of Health and Human Services agencies administer CLIA: the CMS, which manages the CLIA program; the Centers for Disease Control and Prevention (CDC), which is in charge of a Public Advisory Committee that advises the CDC on proposed regulatory changes; and the Food and Drug Administration (FDA), which is responsible for, among other things, complexity categorization of in vitro diagnostic devices and tests [4]. The CMS approves accrediting organizations, including JCAHO and CAP [4–7], CLIA may enforce its regulations including limiting a CLIA certificate, suspension or revocation of a CLIA certificate, civil suits, and criminal suits [4].

CLIA resulted from public and congressional concerns regarding the quality of clinical laboratory testing [8]. It developed standards to improve quality and ensure test result accuracy. CLIA regulations, part of the Code of Federal Regulations, set laboratory requirements for specimen testing [8]. The Health Care Financing Administration (HCFA) is responsible for CLIA implementation, including fee collection, regulation enforcement, and laboratory registration [8]. CLIA requires laboratory inspections every 2 years. Laboratories may choose inspection by JCAHO or CAP; however, these private accrediting agencies must have inspection standards as least as strict as CLIA's own regulations [7, 8].

To meet increasingly stringent accrediting agency requirements regarding surgical pathology error, surgical pathology laboratories have instituted or strengthened a number of error reduction programs, including redundant sign-out, second reviews of initial diagnoses of malignancy, review of cases with pathologic–pathologic or pathologic–clinical discrepancies, review of cases presented in conferences, intradepartmental consultation, and extradepartmental consultation [9, 10]. Intrainstitutional second reviews of initial diagnoses of malignancy are more frequently being mandated on the assumption that mandatory second reviews reduce false-positive and false-negative diagnoses [11, 12]. Evidence supporting mandatory second reviews is unclear; however, a combination of focused second review and liberal use of immunostains has been suggested to be an efficient method of minimizing false-positive and false-negative diagnoses in surgical pathology and cytopathology [11, 13–17]. Synoptic reporting as well as voice-recognition software-based dictation templates are also gaining wider acceptance not only for their ability to enhance communication but also for their related capacity for error reduction [18, 19]. Error reduction is strongly influenced by the efficiency of communication, and many regulatory and accreditation agencies require communication policies. CAP has stated that there should be a policy regarding the communication of urgent or critical diagnoses, and significant, unexpected diagnoses in anatomic pathology, separate, and distinct from communication policies regarding clinical laboratory testing [20].

## Surgical Pathology Error and Medical Malpractice

Improving patient care quality is the driving force behind pathologists' attempts to reduce anatomic pathology error; however, in tandem with patient care quality is medical malpractice risk. Indeed, as rendering a correct diagnosis is the most effective measure of avoiding medical malpractice lawsuits, reducing surgical pathology error is a central feature of reducing medical malpractice risk for pathologists [21]. Medical malpractice risk reduction from reduced anatomic pathology error has long been a focus for pathologists, the need to escalate surgical pathology error reduction methods to improve diagnostic accuracy and reduce medical malpractice risk has lately become more imperative because of increased medical understanding of disease with resultant therapeutic advances that have enhanced the value of early, accurate, and specific diagnoses.

Misdiagnosis, delayed diagnosis, and failure to diagnose are typical allegations in medical malpractice lawsuits, which are torts [22–24]. A tort is a legal term referring to a civil (i.e., not criminal) action that alleges an injury or damage done willfully, recklessly, or negligently for which a civil suit can be brought. Medical malpractice actions almost always fall under a claim of negligence, which can be defined as "[c]onduct which falls below the standard established by law for the protection of others against unreasonable risk of harm; it is a departure from the conduct expectable of a reasonably prudent person under like circumstances" [25].

A successful medical malpractice action requires that the four elements of negligence be met. A physician must be shown to have a duty of care to the patient; the physician must be shown to have breached the applicable standard of care in performing the duty; the breach must be a proximate cause of the patient's injury; and the injury must be compensable. If any one of the four elements cannot be shown, a medical malpractice lawsuit will fail. For example, if a biopsy is misdiagnosed, but the patient is not harmed, then a malpractice claim will fail. Also as an example, if a biopsy is misdiagnosed, but the misdiagnosis is not the proximate cause of the patient's injury (e.g., the patient falls out of bed, or is given the wrong strength of medication, or suffers a transfusion reaction—all unrelated to the misdiagnosed biopsy), then a medical malpractice action would fail [22].

Whether a physician has breached a duty to a patient is determined based on the applicable standard of care. A physician's standard of care requires a physician to use the degree of skill normally possessed and used by physicians in a similar practice and under similar circumstances. In order to determine what is the applicable standard of care in a medical malpractice case, and whether a physician has or has not met that standard of care, and whether the physician's action was the proximate cause of the patient's injury, both the plaintiff and defendant employ expert witnesses. The court and jury rely heavily on the expert witnesses' opinions regarding these issues; indeed, courts typically give more consideration to medical malpractice expert opinions than expert opinions in nonmedical negligence cases [26]. Although the expert witnesses have a duty of candor toward the court, expert witness shopping by the parties unfortunately often leads to the standard of care

being interpreted oppositely by the experts, resulting in a “battle of the experts” that frequently leaves the jury confused [22].

Traditionally, for many diseases, including cancers, limited imaging methods and treatment options have meant that patients received supportive care or basic chemotherapeutic care. In those cases, early diagnosis and specific diagnosis were not crucial as often neither affected prognosis nor treatment. As such, delay in diagnosis, misdiagnosis, or failure to diagnose often did not result in medical malpractice claims; the patient was not harmed by the misdiagnosis or delay, and the standard of care did not require increased diagnostic specificity and did not necessitate early diagnosis.

However, medical progress, for which new molecular therapies for cancer is but one example, has resulted in a need in many surgical pathology cases for earlier diagnosis and more specific diagnosis than has traditionally been required of pathologists [22, 27]. As these earlier diagnoses and more specific diagnoses have become or are quickly becoming the standard of care, it is essential that anatomic pathologists continue to limit diagnostic error in order to avoid claims of misdiagnosis, failure to diagnose, or delay in diagnosis [22]. The diagnosis of amyloidosis is one example of a changing standard of care.

The standard of care for lung cancer diagnosis is an example of an evolving standard of care caused by recent medical advances in diagnosis and treatment, for which more specific diagnoses are now required. Only a few years ago a pathologist met the standard of care by diagnosing a primary lung cancer as small cell carcinoma or non-small cell carcinoma, because whether the non-small cell carcinoma was adenocarcinoma, large cell carcinoma, or squamous cell carcinoma was not relevant for treatment purposes. Now, with molecular biomarkers and tyrosine kinase inhibitor therapies providing improved survival in late-stage lung adenocarcinoma patents, the standard of care requires a more specific biopsy diagnosis of adenocarcinoma or squamous cell carcinoma [28, 29]. Further, the increased understanding of lung cancer obtained from immunostains and molecular testing has made the diagnosis of large cell carcinoma all but extinct; and it is now an inappropriate diagnosis to render on a biopsy; its use, if at all, is reserved for lung cancer resection specimens [30]. These increasingly specific diagnoses, often requiring immunostains and molecular markers to support the histologic interpretation, inject variables that increase the risk of misdiagnosis or delay in diagnosis. Furthermore, the pathologist now has the responsibility for directing smaller and smaller lung biopsy tissue samples for more and more complex testing, adding to the risk that a diagnosis will be claimed delayed or inaccurate. The lung cancer biomarker guidelines [31] address these issues in order to promote quality patient care; their guidance regarding managing small biopsies to optimize testing also assists pathologists in reducing the medical malpractice risk in this realm.

Amyloidosis diagnosis presents a non-neoplastic example of standard of care evolution from a single broader diagnosis to multiple more specific diagnoses, with associated increased necessity for early diagnosis, thus expanding the medical malpractice risk of claims of delay in diagnosis, misdiagnosis, and failure to diagnose. In the past several years, new treatments for the various systemic amyloidoses have

been developed [32]. These treatments, such as stem cell rescue, liver transplantation, and stem cell transplantation, require early, accurate, and specific diagnosis of the systemic amyloidosis involved for optimal prognostic outcomes [32]. Before these dramatic medical and surgical advances in amyloidosis occurred, when the specific types of systemic amyloidosis were not well characterized, treatment for patients with amyloidosis was limited to supportive care. As such, a general diagnosis of amyloidosis was sufficient and met the standard of care. Further, before current stem cell transplant and other therapies, amyloidosis was almost invariably fatal. Missed diagnoses leading to diagnostic delay did not rise to malpractice because the patient's prognosis would not have been altered had the diagnosis been made earlier [22]. Now, with our advanced understanding of the types of amyloidosis and the resultant influence on specific therapy, delay in diagnosis, misdiagnosis, or failure to diagnose carry very significant detrimental consequences for patient prognosis. Therefore, the standard of care for amyloidosis diagnosis has quickly changed to require timely and specific diagnoses [22].

As our understanding of the molecular characteristics of both neoplastic and non-neoplastic diseases expands, personalized therapy develops, and diagnoses rendered by pathologists increasingly impact patient treatment options and survival, pathologists should expect that standards of care will adjust to require more specific diagnoses, with much more limited tolerance for delay.

Because our improved understanding of disease changes the prognostic and therapeutic impact of surgical pathologists' diagnoses, with the resultant changes in standard of care, the legal system is adapting to take into account the standard of cares' increasing requirement for early, accurate, and specific diagnoses. That adaptation can be identified in the increasing adoption in negligence law of the "loss of chance" doctrine. The "loss of chance" doctrine addresses a characteristic of medical malpractice negligence law that some believe is ill-suited for use in the increasingly complex and sophisticated world of modern medicine, and takes into account the level of medical nuances that simply were not present when traditional medical malpractice law was developed.

Traditional medical malpractice negligence law, which includes medical malpractice, structures plaintiff's recovery for damages with the view of restoring the plaintiff "to the position he would be in but for the defendant's negligence" [33]. But to recover damages, plaintiff must prove proximate causation, as noted earlier. To prove causation, plaintiff must show that the physician's actions "more likely than not" caused the injury [33, 34]. Specifically, it entails that "[i]f the plaintiff had a 51% chance of survival, and the misdiagnosis reduced that chance to zero, the estate is awarded full wrongful death damages, but if the patient had only a 49% chance of survival, and the misdiagnosis reduced it to zero, the plaintiff receives nothing. Thus, whenever the chance of survival is less than even, the 'all or nothing' rule gives a 'blanket release from liability for doctors and hospitals…regardless of how flagrant the negligence.'" [34]. This harsh, all or nothing approach has led to criticism of the "more likely than not" standard and to calls for reform predominantly in the guise of adoption of the "loss of chance" doctrine. "The 'loss of chance' doctrine, which is also known as the 'lost opportunity' doctrine, views a

person's prospect for surviving a serious medical condition as something of value, even if the possibility of recovery was less than even (i.e., less than a 50% chance) prior to the physician's allegedly tortuous conduct." [34]. Adoption by courts has so far been sporadic and far from uniform. When the "loss of chance" doctrine has been used by courts, it has mostly been for medical malpractice lawsuits, where "reliable expert evidence is more likely available than in other domains. In addition, the court expressly has left open the question of whether the doctrine is available in cases where ultimate harm (such as death) has not yet occurred" [34].

That the "loss of chance" doctrine is becoming more accepted in courts is not surprising. With traditional medical malpractice cases, involving nonspecific or limited therapeutic options, or where prognosis was not improved if diagnosis was delayed, the plaintiff's ability to show that misdiagnosis, failure to diagnose, or delay in diagnosis was the "proximate cause" of a plaintiff's injury is often limited. For those cases, the "loss of chance" doctrine provides no greater benefit than traditional medical malpractice negligence doctrine because for both the plaintiff's burden in showing "proximate cause" is similar. Traditional lung cancer diagnosis, referred earlier, is such a situation. Today, however, with new diagnostic tools and molecular-based lung cancer treatments, resulting in increased survival in some subsets of lung cancer patients, the "loss of chance" doctrine could potentially help plaintiffs obtain recovery where diagnostic delay or missed diagnosis cannot be proven to "more likely than not" been the proximate cause of injury [22].

Although gaining acceptance, many courts still consider the "loss of chance" doctrine controversial [33–35]. Relaxation of the causation standard to less than the normal "preponderance of the evidence" threshold (which demands a "more likely than not" or greater than 50% probability) has been considered particularly troubling in that it allows plaintiffs to recover damages "despite an inability to prove causation by a preponderance of the evidence. This is achieved by allowing the presentation of expert testimony to demonstrate that the plaintiff was either deprived of a 'substantial possibility' of survival or recovery or simply incurred an 'increased risk' of suffering the ultimate injury as a result of the defendant's negligence." [22, 36].

Advocates believe "the loss of chance doctrine makes up for all of the traditional all-or-nothing approach's shortcomings [by allowing] a jury to award recovery to any plaintiff who can prove a real loss resulting from a physician's negligence" [36]. Proponents consider the doctrine's ability to "provide a tailor-made recovery for a prevailing plaintiff that is proportional to the actual harm incurred" as a significant benefit, holding physicians better "accountable in their treatment of seriously ill and injured patients" than traditional causation doctrine does [36]. Opponents counter that the "loss of chance" doctrine is "the most pernicious example of a new tort action resulting in expanded liability"; "a cause of action unique to medical malpractice litigation [which] permits a patient-turned-plaintiff to recover damages from a doctor-turned-defendant without even needing to establish that the doctor was probably (i.e., more likely than not) responsible for the patient's alleged injury" [37]. Moreover, damages' calculation, difficult enough in traditional medical malpractice cases, is even more difficult under the "loss of chance doctrine." [38].

Indeed, calculation of damages has been called "a 'rabbit-out-of-the-hat' approach" in "loss of chance" lawsuits [22, 39].

"Loss of chance" doctrine is likely to continue to gain favor in courts because those courts that have so far adopted the doctrine have used it carefully, avoiding its use in medical malpractice actions for which traditional causation suffices and continuing to require valid statistical evidence and rigorous expert testimony [22].

Increasingly, plaintiffs' attorneys consider timely and specific surgical pathology diagnoses such as those now rendered for lung cancer and amyloidosis to be "routine" and the "standard of care" [22]. Expect that trend to continue. "As one medical malpractice attorney group makes clear, 'Not every patient presents to a physician with "classic" signs and symptoms. If they did, we would not need skilled physicians. At [our law office] we do not accept the "the symptoms were atypical" defense when a preventable injury has occurred.'" [22, 40]. For surgical pathologists, documentation of intradepartmental and extradepartmental consultations, clinician communications, and specific concerns as part of the surgical pathology or cytopathology report can potentially provide significant benefit in defending a medical malpractice lawsuit predicated on misdiagnosis, delay in diagnosis, or lack of diagnosis.

## Future Possibilities

Medical error is the eighth leading cause of death in the USA [41]. Attempts at medical error reduction, including surgical pathology error reduction, will undoubtedly continue. Surgical pathology error reduction will very likely continue to be informed by medical error reduction understanding generally. Legal and regulatory challenges and opportunities for reducing surgical pathology error will continue, and likely guidelines will become increasingly employed for the purpose of addressing accreditation and regulatory demands [42].

Checklists, a relatively recent addition to the health quality armamentarium, have been shown to provide not only cost savings but also to decrease medical error [43]. They are likely to play an increasingly important role in reducing surgical pathology error; however, hospitals and pathologists may remain discouraged from applying them in the laboratory because of fear of their discovery as part of a medical malpractice lawsuit. It has been argued that policy makers should strongly consider extending evidentiary privilege protections to include checklists, so that checklists can be used effectively to reduce error. As posterror reports, protected from discovery by state and federal law, merit evidentiary privilege protections, pre-error prevention efforts should also be afforded similar protections [43]. Yet, such protection is not easily obtained in today's patient safety arena, where safety and error information is typically deemed merely administrative information, and subject to discoverability [44].

There is also a growing acceptance of hospitals as having expanded fiduciary duties in tandem with expanding tort obligations [45]. The recognition of increased

institutional responsibility will lead to a hospital-based demand for medical error information, including surgical pathology error information, as hospitals attempt to meet their duty of "protective intervention," as well as their duties to report adverse events to state entities and others [45].

Apology for medical error, a few years ago considered a popular mechanism for reducing medical malpractice risk [46, 47], has recently received heavy criticism. "Apologies—statements of regret, remorse and responsibility—do little to achieve the policy goal of making patients safer in the healthcare setting." [48]. "Apologies, by chilling the open disclosure of sensitive information and accompanying frank discussion, run counter to the goals of improving patient safety. Unlike other forms of disclosure of the events surrounding an injury, apologies also establish responsibility. In many circumstances, individual assignment of 'shame and blame' unfairly open up the involved individuals and organizations to liability and loss." [48]. There is a strong argument that the physician's duty to the patient "requires something more than convincing them not to seek compensation through litigation for injuries caused by negligent errors…[, taking] advantage of their weakened state." [49]. Yet, even before apology became popular, its death knell had been rung. Put succinctly, "requiring the last person who touched the patient to disclose without more than merely a persona of humiliation, shame, and blame, simply represents an iteration of the ineffective, individually-oriented shame and blame approach." [50]. In place of apology, physicians and hospitals would better serve patients, and improve healthcare quality and patient safety, by accounting to the patient. "Accounts… [involving excuses and justifications,] can bridge the gap between adverse events and patient expectations." [48].

One proposed change that might allow for more surgical pathology error transparency is the institution of a no-fault system of compensation for medical injuries, regardless of, and without determination of, whether medical malpractice occurred. Various no-fault systems have been proposed, including patient's compensation insurance, which models itself closely to worker's compensation insurance [51]. However, for any model to succeed, much more detailed information on errors and their causation must be produced, notwithstanding physicians' wariness in reporting errors that might leave them open to accusations of negligence in today's punitive world of medical error reporting [52]. Physicians' fear of blame unduly inhibits attention to systemic improvements that would decrease harmful medical errors [53].

## Conclusion

It has been almost a decade and a half since the Institute of Medicine's report on medical quality, To Err is Human, caused a groundswell of attention to medical errors. Society has waited expectantly for improvements, but has now become impatient with medicine's relatively feeble attempts to minimize medical errors. The medical error issue has had an unexpectedly long life and continues to evolve and broaden [54]. The number of errors occurring continues to remain surprisingly high

[55]. Many believe the lack of progress is due to physicians' professional dominance minimizing the role of educated consumers and competitive markets, allowing physicians and hospitals to continue to economically benefit while remaining insulated from efficiency demands [56]. Society has looked past physicians to reduce medical error. Mandated error reporting is increasingly being demanded [57]. Calls for greater federal oversight and intensity of federal action are increasingly insistent [58]. And using financial incentives to reward health care quality and patient safety is already being employed [59, 60].

In the end, advancement of medical error reduction, including surgical pathology error reduction, will require reduced physician antipathy toward other stakeholders, particularly attorneys [61]. Physicians typically have little understanding of the legal system, regardless of medical experience years; nonetheless, the decades-old breakdown in interprofessional relations between physicians and attorneys must change [62]. It is becoming increasingly apparent that educating medical students, residents, and practicing physicians about the law is necessary [63]. Antipathy must give way to novel cooperative engagements between all stakeholders, so that medial error, including surgical pathology error, may be candidly evaluated and ultimately minimized. And although shame and blame has slowly been giving way to risk management methods, risk management activities have not been particularly effective in reducing patient injury; indeed, participation in these activities might actually increase the risk of medical error and patient injury [64]. Further, because health care reform is expected to extend health insurance coverage to an additional 32 million people in the USA, while at the same time the pathologist workforce is expected to have a deficit of almost 20,000 full time pathologists [65, 66], without effective error reduction procedure in place soon, the risk of surgical pathology error can logically be expected to dramatically increase.

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