COLA'S 1st Quarter 2022

inSIGHTS

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LETTER FROM THE CHAIR

1ST QUARTER 2022

This edition of inSights comes with a special announcement: COLA has been granted deemed status by CMS to accredit laboratories for the specialty of Pathology, including the sub-specialties of Histopathology, Oral Pathology and Cytology. This was announced in the federal register on March 4, 2022, and as we expand our scope, we stand ready to deliver our expertise and guidance to a larger number of clinical laboratories than ever before.

COLA's clear and accessible pathology criteria reflect the current CLIA requirements for all Pathology sub-specialties and incorporate recent advances in the science and technology of Pathology testing. COLA's Pathology accreditation will deliver the same consistent services and emphasis on customer service as the rest of our ISO 9001:2015 certified clinical laboratory accreditation program has done for over thirty years.

In our commitment to quality, COLA has hired industry leaders to manage and guide our pathology program. Our new Chief Medical Officer, David Chhieng, MD, is a world renowned surgical and cytopathologist, and is board certified in Anatomic and Clinical Pathology, Cytopathology, and Clinical Informatics. He has over 20 years of laboratory accreditation experience, especially in the area of Histopathology and Cytopathology. Dr. Chhieng is also a prolific author with over 180 peer-reviewed articles and a dozen of books and book chapters. Kathy Wilson, HT(ASCP)QLS, is our new Director of Pathology Accreditation. She is an ASCP certified Histotech and has her ASCP Qualification in Safety. Joining COLA in December of 2021, she has over 40 years of experience and a diverse background in both hospital and independent laboratories, to include clinical, technical, safety, operations and business management, laboratory builds, and regulatory inspection processes. We hope that you find their articles in this edition of inSights educational and enlightening. We are excited to have them on our team, with other subject matter experts, and we are looking forward to growing with our laboratories as we incorporate Pathology into the many services we offer to improve laboratory quality and patient safety.

William E. Kobler, MD
Chair, COLA Board of Directors

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PROFICIENCY TESTING FOR PREDICTIVE MARKERS IN ANATOMIC PATHOLOGY

By David Chhieng, MD, MBA, MSHI, MSEM, MLS, MDR

Dr. David Chhieng is the Chief Medical Officer of COLA Inc. Before he joined COLA, he was a professor, the director of Anatomic Pathology and Pathology Informatics, and vice chair of clinical operation, of the department of Pathology at the University of Washington in Seattle WA. Prior to that, he was the director of Cytopathology at the Yale University and the Icahn School of Medicine at Mount Sinai. He obtained his medical degree from the University of Hong Kong, his master degrees in business administration and health informatics management from the University of Alabama at Birmingham, master degree in engineering management from the University of New Haven, and master degrees in legal studies and dispute resolution from the Pepperdine University. He completed his Pathology residency training at the Albany Medical Center and his fellowship training in Surgical Pathology and Cytopathology at the Memorial Sloan Kettering Cancer Center and New York University, respectively. He is board certified in Anatomic and Clinical Pathology, Cytopathology, and Clinical Informatics. Dr. Chhieng has published 170+ peer-reviewed articles on the topics of Cytopathology as well as Surgical Pathology. He also co-authored several books and a number of book chapters. He has been a practicing surgical and Cytopathologist for 20+ years and in a directorship position for 10+ years.

Predictive markers are biologic variables that objectively evaluate the probability of benefit from a specific clinical intervention, or the differential outcomes of two or more interventions, including toxicity. They are different from prognostic markers which inform about the course of a cancer (e.g. disease recurrence, disease progression, death) independent of treatment received. A biomarker can be both prognostic and predictive. Additionally, it can be unfavorable prognostically but predict favorable response to certain therapy, or vice versa. Furthermore, it is possible that a predictive marker can predict favorably for one therapy and unfavorably for another therapy. In the era of precision medicine, predictive marker testing is essential for cancer management when determining the appropriate choice of therapy. A companion diagnostic refers to a predictive marker assay, which is developed in parallel to a new drug. (Jorgensen, 2021) The most notable example is the HercepTest (Dako/Agilent, Santa Clara CA) which was simultaneously granted approval by the Food and Drug Administration (FDA) along with trastuzumab (Herceptin) for treating breast cancer through a new coordinated procedure in 1998. An accurate and reliable companion diagnostics assay is essential for most targeted anti-cancer drugs to achieve their optimal benefits.

Clinical laboratories offering predictive marker testing should minimize any laboratory errors,

which can result in wrong or suboptimal treatment decisions, and in turn serious patient harm such as unnecessary toxicity or delays in treatment. Therefore, it is important for clinical laboratories offering predictive marker assays to ensure accurate and reliable results by implementing a quality assurance (QA) system and complying with the Clinical Laboratory Improvement Amendments (CLIA) and with relevant national standards for testing from their accrediting organization such as COLA, the College of American Pathologists (CAP) or The Joint Commission.

One of the most frequently used techniques for evaluating predictive markers in tissue is immunohistochemistry (IHC) and, to a lesser extent, in-situ hybridization (ISH). Therefore, it is not surprising clinicians' and patients' expectations of accuracy and reliability for IHC and ISH testing is exceedingly high, which reflects on the increased adoption of the principles and concepts of quality assurance (QA) traditionally reserved for the measurement of analytes in blood and other body fluids. This can be challenging because anatomic pathology (AP) often feels to be more qualitative and subjective, and less quantitative and objective, therefore, AP should not be assessed the same way as clinical pathology.The author shares the sentiment that interpretation in AP is part art and part science, but believes that a minimum standard is beneficial to ensure reliability and accuracy.

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One important QA tool is the requirement that laboratories participate in proficiency testing (PT).

PT, also called interlaboratory comparison and external quality assessment (EQA), is a way to determine and monitor the performance of individual laboratories for specific tests or analytes by comparing results obtained by different laboratories. PT samples are sent to all participating laboratories by the PT providers on a scheduled basis. The results are reported to the PT providers, who then grade the results according to the CLIA criteria and send the scores back to the participating laboratories, thus allowing participating laboratories to see trends in their own testing performance and compare their results with other laboratories.

Under the CLIA, all US clinical laboratories are required to participate in a federally-approved PT program on any regulated analytes being tested under the laboratory license. Failure to participate in required PT, or repeated unsatisfactory PT performance, may result in ceasing of testing either voluntarily or involuntarily. Currently, none of the predictive markers being tested under anatomic pathology specialty are classified as "regulated" analytes according to the Center for Medicare and Medicaid Services (CMS). However, many US accrediting organizations, such as COLA Inc., require clinical laboratories to perform PT or some form of interlaboratory comparison if the laboratories offer predictive marker testing to their patients and clients. Putting aside the mandatory accreditation requirements, all laboratories should welcome the opportunity to participate in PT for the following reasons: to compare individual laboratory's performance against its peers; to identify potential problems before they become critical, and to fulfill the competency requirements for testing personnel.

The first guidelines for ER, PR, and Her2 testing were published in the late 2000's as a result of a joint efforts by American Society of Clinical Oncology (ASCO) and College of American Pathologists (CAP). (Wolf, Hammond, & Schwartz, 2007) (Hammond, Hayes, & Dowsett, 2010) Among many other elements, the guidelines mandate ongoing proficiency testing, at least twice a year, with satisfactory performance defined as 90% correct responses on graded challenges." (Hammond, Hayes, & Dowsett, 2010) (Wolf, Hammond, & Schwartz, 2007) For each PT challenge, participating laboratories are mailed unstained slides with 10% formalin-fixed, paraffin-embedded tissue, often in tissue microarray (TMA) format, to be stained with their routine, validated, in-house IHC and/or FISH protocols for each marker requested in the PT survey. Participating laboratories then submit their interpretations to the PT providers before the submission deadline. The laboratories are also required to provide details of the protocol used for each IHC/FISH test, including primary antibody clone or FISH probe, manufacturer, dilution, incubation time, epitope retrieval method, and detection system used. In addition, the laboratory may be asked to submit additional/supplemental information.

The majority of the PT rules that govern PT for regulated analytes apply to those of predictive markers. First, all PT samples are to be handled, prepared, processed, examined, tested and reported the same way as patient samples, unless otherwise instructed by the PT providers. This means having all testing personnel, who would normally handle patient testing, perform PT on a rotational basis. Second, repeat testing on PT samples is prohibited unless repeat testing is routinely performed on patient samples. In addition, group reviews are allowed for PT samples that require morphologic examinations, such as ER/PR/Her2 PT, if and only if, a group review is routinely performed on patient samples.

Third, participating laboratories are prohibited from communicating or discussing the results or information on PT samples with other laboratories before the results submission deadline. This also applies to sharing such information on social media. Additionally, it is important to have separate personnel perform and enter results for laboratories that belong to the same integrated health system because entering results by same individual for more than one laboratory would be considered interlaboratory communication. Fourth, PT referral, i.e. forwarding or sharing PT samples with any other laboratory, is not permitted. The latter also applies to situations where patient samples are routinely referred to another laboratory with different CLIA number, whether internal or external to the laboratory system, for confirmatory, distributive, and reflex testing. The Test Act of 2012, as an amendment to CLIA 88, allows the Secretary of Health and Human Services (HHS) the discretion to impose a mandatory two-year ban on a laboratory's owner/operator when the laboratory's CLIA certificate is revoked for PT referral. There is one exception regarding PT samples for ER/PR/Her2 predictive marker testing utilizing IHC slides in regard to PT referral. Both CAP and COLA allow laboratories participating in ER/PR/Her2 PT to send PT unstained slides to another laboratory for staining only, provided that this is part of the laboratory's routine testing protocol. Fifth, all PT test records, including QC results of the day of testing, instrument printouts, worksheets to document results, etc., should be retained for a minimum of 2 years (3 years for the State of California). Finally, the Laboratory Director or qualified designee and all personnel involved in the PT testing process must sign the attestation statement.

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The Laboratory Director or qualified designee should review and evaluate all returned PT results from the PT providers in a timely manner, preferably within 30 days of the receipt of the results. Result evaluation should include both graded and ungraded PT challenges. The latter can be attributed to many reasons, including submission of results after the submission deadline, failure to submit PT results, incorrect completion of the result form, lack of consensus, or education challenges. When PT results are unsatisfactory, or for any PT scores of less than 100%, laboratories are required to conduct a root cause analysis, develop appropriate corrective actions to prevent recurrence of the problem, and document the investigation as well as corrective plans.

Technical problems with ER/PR/Her2 IHC are often manifested as weak or absent staining, over-staining, and/or high background staining.

Troubleshooting should include each step of the IHC protocol such as adequate deparaffinization, rehydration, antigen retrieval, blocking, primary antibody, secondary antibody, chromogen, dehydration, cover-slipping, and interpretation. Similarly, technical problems with Her2 FISH can be manifested as weak or absent fluorescence signals, variation of fluorescence signal intensity across tissue sections, or high background fluorescence. Investigations should include adequate paraffinization, adequate protease digestion, hybridization, post-hybridization washing, and fluorescence microscopy, and interpretation.

Unsatisfactory PT performance can also be caused by non-technical problems such as failure to submit results on time or clerical errors made while submitting.

Accrediting organizations may require a laboratory to cease patient testing

for an analyte as a result of repeat PT failures regardless if the problem is technical or non-technical in nature. To be granted permission to resume patient testing, the laboratory will be required to demonstrate successful performance of two consecutive PT survey events for the analyte in question.

IN CONCLUSION,

Although there is currently no CMS-approved PT program for predictive markers assay using IHC and FISH, participation in such PT programs are required by accrediting organizations, including COLA, to ensure accuracy and reliability of such assays. Rules that govern PT for regulated analytes apply to those of predictive markers with the exception of permitting laboratories to send PT unstained slides to another laboratory for staining only.

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GENERAL SAFETY IN THE ANATOMIC PATHOLOGY LABORATORY

By Kathy Wilson, HT(ASCP)QLS CM

Ms. Wilson recently joined COLA's Executive Team. She is an ASCP certified histotechnician with the ASCP Qualification in Safety. She has over 45 years total experience in the laboratory to include the clinical laboratory, EMT, autopsy diener, histotechnician, inspection processes, and progressive leadership experience culminating in operations and project management Prior to joining COLA, Ms. Wilson was the Operations Manager for Anatomic Pathology and was a key member of the laboratory operations team, Safety Officer and Safety Committee Chair, for local and regional laboratories in Austin, Texas.

PERSPECTIVE FROM A SAFETY ENTHUSIAST

The laboratory can be a hazardous place to work. Hazards to staff in the pathology laboratory include physical, environmental, biological, chemical, radioactive, and ergonomic hazards, just to name a few. However, the mere presence of hazards does not automatically make the laboratory unsafe. Training on laboratory safety can go a long way towards mitigating these risks and keeping laboratory staff from harm.

All laboratorians are trained in safety procedures before starting a laboratory job. But do they really understand the day-to-day importance of safety in the laboratory while performing their job?

When I started in the laboratory, I was trained in safety procedures, followed them, and was compliant with all the rules and regulations. It was not until I became responsible for safety in the laboratory and for the safety of employees that I began to understand what safety truly meant. It doesn't mean reading policies and procedures, and being trained once. It is the ongoing everyday compliance with procedures and practices that keeps employees safe on the job. When safety is ingrained in one's daily practices at work, ultimately one will be more aware outside of the work environment as well.

Every individual in the laboratory has a responsibility to ensure they are performing their job assignments safely and responsibly and that they are observing all safety procedures and practices. When employees are non-compliant, they put themselves, their co-workers, and possibly their facility in jeopardy.

Unsafe practices ultimately compromise patient safety.

The **Occupational Safety and Health Act (OHSA)** requires employers to comply with safety and health standards and regulations promulgated by OSHA or by a state with an OSHA approved state plan. There are currently 22 states that have OSHA-approved plans that cover both private, state, and local government workers. Five additional states and one U.S. territory have OSHA approved State Plans that cover state and local government workers only. If the plan covers state and local government workers only, private sector workers and employers remain under federal OSHA jurisdiction. State Plans are required to have standard and enforcement programs and must be at least as effective as OSHA's though they may have additional or more stringent requirements.

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OSHA's publication Laboratory Safety Guidance is not a standard or regulation, but the publication contains recommendations as well as descriptions of mandatory safety and health standards for the laboratory. The publication contains details and requirements of safety plans and references applicable to the Code of Federal Regulation (CFR) standards.

OSHA laboratory standards include:

- Chemical hazards
- Chemical hygiene
- Hazard communication to include labeling and Safety Data Sheets
- Latex and latex allergy
- Specific chemical hazards to include air contaminants
- Formaldehyde standard which requires fume monitoring
- Biological hazards other than bloodborne pathogens
- Physical and other hazards to include ergonomic, radiation, and noise
- Personal protective equipment
- Eye and face protection
- Respiratory protection
- Hand protection
- Control of hazardous energy
- Electrical and fire safety
- Additional safety hazards – compressed gases, cryogens, and dry ice

Controls or measures used to protect laboratory workers include engineering controls, administrative controls, work practices, and personal protective equipment. These controls can include the use of chemical hoods and biological safety cabinets.

CONCLUSION

Laboratory personnel must receive safety training regarding laboratory standards and safety subjects that are applicable to their workplace Future COLA Insights articles will focus on the individual standards and provide more in-depth information about each of the standards. In the meantime, it is recommended that you review OSHA's Laboratory Safety Guidance. Laboratories must ensure they are in compliance with all federal, state, and local requirements as well as their accreditation agency requirements.

As we navigate these challenging times, laboratories, regardless of their size and number of employees, must ensure that safety remains a priority. Following established safety and pandemic guidelines in the workplace is crucial to keeping employees healthy and able to meet their responsibilities at work. Short staffing and other internal matters should not preclude laboratories from ensuring that safety remains at the forefront.

REFERENCES

OSHA Laboratory Safety Guidance
https://www.osha.gov/sites/default/files/publications/OSHA3404laboratory-safety-guidance.pdf

OSHA Fact Sheets for quick reference:
Bloodborne pathogens
https://www.osha.gov/sites/default/files/publications/bbfact04.pdf

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https://www.osha.gov/sites/default/files/publications/OSHAfactsheet-laboratory-safety-chemical-hygiene-plan.pdf

Chemical Fume Hoods
https://www.osha.gov/sites/default/files/publications/OSHAquickfacts-lab-safety-chemical-fume-hoods.pdf

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WHOLE SLIDE IMAGING SYSTEM IN ANATOMIC PATHOLOGY
REGULATORY AND VALIDATION REQUIREMENTS

By : David Chhieng, MD, MBA, MSHI, MSEM, MLS, MDR

Dr. David Chhieng is the Chief Medical Officer of COLA Inc. Before he joined COLA, he was a Professor, the Director of Anatomic Pathology and Pathology Informatics, and Vice Chair of Clinical Operation, of the Department of Pathology at the University of Washington in Seattle WA. Prior to that, he was the Director of Cytopathology at the Yale University and the Icahn School of Medicine at Mount Sinai. He obtained his Medical Degree from the University of Hong Kong, his master degrees in Business Administration and Health Informatics Management from the University of Alabama at Birmingham, master degree in Engineering Management from the University of New Haven, and master degrees in Legal Studies and Dispute Resolution from the Pepperdine University. He completed his Pathology residency training at the Albany Medical Center and his fellowship training in Surgical Pathology and Cytopathology at the Memorial Sloan Kettering Cancer Center and New York University, respectively. He is board certified in Anatomic and Clinical Pathology, Cytopathology, and Clinical Informatics. Dr. Chhieng has published 170+ peer-reviewed articles on the topics of Cytopathology as well as surgical Pathology. He also co-authored several books and a number of book chapters. He has been a practicing surgical and cytopathologist for 20+ years and in a directorship position for 10+ years.

Since its introduction in 1999, there has been an exponential growth in whole slide imaging (WSI) technology and its application in the field of Pathology. WSI refers to the digital conversion of entire tissue sections on a glass slide to a digital image. It allows pathologists to render an accurate pathologic diagnosis of tumors and other diseases on a digital display/monitor instead of using traditional light microscopy, therefore giving the pathologists the flexibility to work remotely, i.e., outside the physical confines of a laboratory setting. Until recently, the use of WSI in the clinical setting was often limited to intraprocedural consultation, second opinion, conference presentation, education, research, and quality assurance activities, with few institutions and laboratories integrating WSI processes into their primary Pathology sign-out workflow. With the onset of the COVID-19 (coronavirus disease 19) pandemic in 2020, there has been an increase in demand for the integration of WSI and remote services to include primary diagnosis and remote pathologist sign-out. These workflows address new safety concerns and practice measures. Most of the reviews address the technical aspects of WSI as well as the benefits, limitations, and various challenges related to the adoption of this technology in the clinical setting.

Therefore, this article attempts to provide a summarized review of current U.S. regulatory and validation requirements related to the application of WSI for primary diagnosis and Pathology sign-out in routine clinical setting.

CLIA 88 REQUIREMENTS CONCERNING REMOTE SIGN-OUT

One of the benefits of WSI provides pathologists with the ability to review tissue sections in digital form and sign-out cases remotely. The latter refers to a pathologist's ability to render diagnostic pathologic interpretations at a location that is not considered part of the clinical laboratory under CLIA. Until recently, The Centers for Medicare and Medicaid Services (CMS) prohibited remote sign-out of primary diagnoses or interpretations at a non-CLIA certified location unless conducted on an infrequent basis. Due to the declaration of the COVID-19 pandemic, in March of 2020, CMS granted clinical laboratories a temporary waiver from CLIA regulations requiring pathologists to conduct sign-out only at CLIA-certified locations. Under this temporary waiver, qualified personnel would be eligible to perform all sign-out activities at remote locations, such as a pathologist's home, under the auspices of a laboratory/facility with an active and valid CLIA certificate provided that:

1. the activities have been successfully validated to be performed remotely,
2. all required procedures and polices pertaining to remote sign-out activities have been approved by the facility's Laboratory Director and made available to personnel performing remote sign-out of cases, and
3. adequate security and privacy measures are in place for viewing and/or storing protected health information (PHI) at the remote locations.

This waiver applied not only to digital and glass slide evaluation but also to the review of clinical Pathology images and data such as electrophoresis diagrams, gel images, flow cytometry graphs, FISH, cytogenetic and molecular results, etc. In addition, there is no limit regarding the percentage or types of cases that can be signed out remotely. However, this waiver is temporary and may be rescinded when the COVID-related public health emergency is over.

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FDA REGULATIONS REGARDING WSI DEVICES

All medical devices that are labeled, promoted, and sold in the U.S. require clearance from the Food and Drug Administration (FDA) according to the perceived risk and regulatory requirements of suitable controls. Class III devices are deemed to be of the highest risk, lacking general controls, and must follow a premarket approval (PMA) pathway that requires a clinical investigation. On the other hand, Class II devices are cleared through the less resource-intensive 510(k) pathway because they are perceived to be of moderate risk, have existing general and special controls, and bear resemblance to another legally marketed device. Prior to 2016, WSI systems were classified as a Class III device, requiring PMA clinical trials for FDA approval. In 2016, after the successful de novo application of the first WSI systems for FDA approval, FDA downgraded any WSI devices applying for FDA approval to Class II, allowing for their clearance via the simpler 510(k) pathway. Currently, two WSI systems have been FDA approved/cleared for primary histopathological diagnosis—one from Philips after a successful de novo application as a Class III medical device and the other from Leica Biosystems which was cleared via the 510(k) pathways as a Class II device. The FDA approval does not extend to frozen sections, Cytology, or non-formalin fixed paraffin embedded hematopathology specimens.

According to the FDA, a WSI system, which is sometimes referred to as the pixel pipeline, is comprised of the scanner, the server, the image management software, the image viewer software, and the display. If any of the component(s) is (are) modified or replaced, for example, by using a different monitor other than the one approved or cleared by the FDA, then the system is no longer considered FDA approved or cleared. The use of a modified system as well as any unmodified FDA-cleared system for purposes other than those intended would be considered a laboratory-developed test (LDT).

The FDA regulations apply only to vendors and their products but not pathologists or the practice of Pathology.

Therefore, laboratories and pathologists can use any WSI systems/devices, regardless of their FDA-clearance/approval status, for both intended and non-intended uses e.g. primary diagnosis, frozen sections, teleconsultations, image analysis of predictive biomarkers, etc., as long as an adequate and successful validation has been performed, documented, and approved by the Laboratory Director as it would be used clinically, according to the requirements set forth by the laboratory's accrediting organization (AO) such as COLA.

VALIDATION OF WSI SYSTEM

Laboratories are required to validate all new testing platforms and/or instruments prior to clinical use to ensure the new method/instrument performs as expected for its intended use and environment. WSI is no exception; validation is required prior to its implementation in patient care, to ensure the WSI system performs as effectively or better than traditional light microscopy without any additional risks to patient safety.

Currently, there are published recommendations for validating WSI.

AOs do not dictate specific details about how the validation should be performed. Laboratories will need to design and implement their own validation plan approved by the Laboratory Director. Fortunately, consensus guidelines on the validation of WSI for diagnostic use, first published in 2013 and subsequently updated in 2021, can serve as the basis of the design of such a validation study. (Table 1) (Pantanowitz, Sinard, Henricks, & Fatheree, 2013) (Evans, Brown, Bui, & Chipala, 2021)

The fundamental elements of the guidelines include the following:

1. The validation set should comprise at least 60 cases that represent the spectrum and complexity of specimen types and diagnoses that would be encountered for the intended application.
2. The diagnostic concordance rate should be measured primarily based on intra-observer reproducibility between WSI and traditional microscopy, with a recommended threshold of 95%.
3. There should be a minimum of 2-week washout period between viewings.

It is important to recognize that the recommended number of cases for validation is not intended to be rigid and that adding more cases does not necessarily influence the validation results. Also, laboratories should decide whether a case should include all or representative parts and/or slides based on the balance between completeness and practicality with respect to available time and resources. Finally, laboratories should determine whether various WSI systems from different vendors being used across a multisite network are sufficiently different in terms of proprietary scanning technologies and/or viewing software to warrant a separate validation study for each system.

Laboratories should not treat the minimum concordance rate of 95% as a pass/fail mark but rather consider it as an indication to investigate and resolve any systematic issues that may have contributed to a concordance rate of less than 95%. One potential scenario may be that a disproportionate percentage of disconcordant cases can be traced back to certain types of diagnoses/cases or 1-2 particular pathologists; such findings can be explored further by reviewing additional cases of that type(s). It may be prudent to refrain from using WSI to evaluate similar cases if laboratories were unable to resolve any major discordances encountered during WSI validation.

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The Guideline recommends that laboratories should conduct separate validation if the new application is sufficiently different from the application for which the prior validation was intended. For example, a new study should be performed to validate the use of WSI for intraoperative consultation if the prior validation study was confined to the evaluation of digitized slides for routine surgical Pathology. The validation study should be conducted in a manner that mimics as closely as possible the actual clinical use and environment after "go live."

The validation team should include pathologist(s) who have been adequately trained

and will be involved in the actual usage of the WSI system after "go live." It would be up to the Medical Director to define the adequacy of user training and the number of pathologists participating in the validation study. The entire WSI system and imaging process, including the pathologists, should be validated as a whole.

Although there is no need to validate each component of WSI or individual steps of the process, a validated system in the hospital may differ from those being used in the remote site, such pathologist's home office. To account for any significant variabilities, laboratories should establish, verify, and document the minimum performance requirements of all remote sites. Last but not least, laboratories would need to repeat the validation study if there is ever a significant change to the WSI system and/or process.

QUALITY MANAGEMENT POST GO LIVE

All users, including the pathologists who render a diagnosis from WSI, should be adequately trained, familiar with, and able to access departmental protocols and policy for WSI. In addition, laboratories should establish protocols on how to manage cases for which the pathologist is unable to render a diagnosis due to suboptimal quality images; possible solutions include rescanning of slides or deferral to glass slides. Laboratories must continue to audit and evaluate digital diagnosis after adoption WSI as part of routine laboratory operations. For example, all quality issues, including cases for which pathologists can render a diagnosis despite suboptimal quality, should be reported and monitored to determine the root causes. Documentation and investigation of scanning issues, such as failure to scan, out of focus, and digital artifact, as well as diagnostic issues, such as frequency and reason for deferral to glass should be performed. Diagnostic performance using WSI should be evaluated periodically by comparing the reviewed interpretations based on glass slides and traditional microscopy with the original digital ones using a random sample of archived cases.

12 RECOMMENDATIONS OF THE MOST RECENT GUIDELINE FOR WSI

STRONG RECOMMENDATIONS

- The validation set should consist of at least 60 cases for one application, or use case (e.g., hematoxylin-eosin–stained sections of fixed tissue, frozen sections, hematology), that reflect the spectrum and complexity of specimen types and diagnoses likely to be encountered during routine practice. An additional 20 cases to cover additional applications such as IHC and/or special stains should be included if they are relevant to an intended use and were not included in the 60 cases mentioned above.
- The threshold for diagnostic concordance should be established between digital and glass slides for the same observer (i.e., intraobserver variability). The laboratory should investigate and resolve any issues resulting in less than 95% concordance.
- A washout period of at least 2 weeks should occur between viewing digital and glass slides.

GOOD RECOMMENDATIONS

- Laboratories implementing WSI for clinical uses should conduct their own validation studies.
- Validation should be appropriate for and applicable to the intended clinical use and clinical setting of the application. A separate validation should be performed If a new application for WS, which differs substantially from the previously validated use.
- The validation study should closely match the real-world clinical environment in which the technology will be used
- The validation study should encompass the entire WSI system but there is no need to separately validate each individual component of the system or the individual steps of process
- Laboratories should have procedures in place to address changes to the WSI system that could impact clinical results.
- Pathologists must be involved in the validation process
- The validation process should confirm all material present on a glass slide to be scanned is included in the digital image
- Documentation should be maintained for the method, measurements, and final approval of validation by the medical director.
- Pathologists should review cases/slides in a validation set in random order.

Modified from (Evans, Brown, Bui, & Chipala, 2021)

CONCLUSION

This article summarizes the current regulatory and validation recommendations governing the use of WSI in primary Pathology diagnoses sign-out. It is paramount that laboratories are familiar with these requirements when they are preparing for digitization and continues to prioritize the quality and safety regarding the use of WSI process in Pathology workflow.

REQUIREMENTS FOR **GROSSING PERSONNEL**

By Kathy Wilson, HT(ASCP)QLS CM

Ms. Wilson recently joined COLA's Executive Team. She is a ASCP certified Histotechnician with the ASCP Qualification in Safety. She has over 45 years total experience in the laboratory to include the clinical laboratory, EMT, autopsy diener, Histotechnician, inspection processes, and progressive leadership experience culminating in operations and project management Prior to joining COLA, Ms. Wilson was the Operations Manager for Anatomic Pathology and was a key member of the laboratory operations team, Safety Officer and Safety Committee Chair, for local and regional laboratories at Clinical Pathology Laboratories in Austin, Texas. Ms. Wilson started her career in Northern Michigan, moved to Fairbanks, Alaska, Kansas City, Missouri, and finally Austin, Texas. Safety, regulatory compliance, quality, and project management have always been key areas of interest. Ms. Wilson is a member of the National Society of Histotechnology and serves on the convention committee and program team.

The term "gross" probably registers as unpleasant to the average person. However, those who work in what is commonly referred to as the gross room or grossing section of the laboratory know that grossing has an entirely different meaning when it comes to Pathology. Grossing is the beginning of a series of technical processes in Pathology that are necessary for the pathologist to render an accurate patient diagnosis.

The **gross examination** or macroscopic examination is the visual inspection of a tissue specimen received by the laboratory. Specimens can be received fresh or preserved in a variety of fixatives, the most common being 10% neutral buffered formalin. The visual macroscopic examination of those specimens are then detailed in the **gross description.**

The gross description includes information such as the state of receipt (received fresh or in fixative), any gross abnormality or anomaly, and any additional descriptive findings uncovered after sectioning the specimen. It typically also includes the source and/or type of tissue received, color, size along all sides, weight, shape, and pigmented or discolored areas. The gross description also notes any orientation of the specimen marked with sutures, notches or cuts, or different tissue marking dyes.

In addition, some specimen types require documentation of cold ischemia time (time of removal from the body to time placed in formalin) and total time in formalin. If specimens are prepared and sent for special studies from the grossing bench, this would also be noted in the gross description.

Historically, grossing of tissue specimens was performed by a pathologist.

Current practices allow for delegation of the grossing of tissue specimens to pathologists' assistants and other grossing personnel in hospitals, laboratories, and small specialty laboratories to assist with the workload. Some facilities do not allow delegation of grossing to non-pathologist personnel due to facility procedure and preference, volume of workload, affordability, or guidelines that pertain to their locality.

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GROSSING PERSONNEL REQUIREMENTS

Who can gross tissue specimens has been a topic of discussion in recent years amongst Histology personnel, laboratories, and regulatory bodies. Personnel who were not qualified were being delegated to gross specimens classified as "processing-only" specimen types (e.g. specimens to be entirely submitted without need of sectioning or orientation, such as tiny biopsies, core biopsies, and curettings), requiring only a gross description and submission for tissue processing. However, per the CLIA regulations, this definition does not apply to any specimen type submitted to the laboratory for grossing.

Grossing of any and all tissue specimens is considered high-complexity testing.

Individuals performing grossing must meet the requirements of education and training for high-complexity testing personnel as defined in the Code of Federal Regulations 42 CFR 493.1489 and must be in compliance with all federal, state, and local guidelines, whichever is more stringent.

A Pathologists' Assistant (PA) is a highly trained professional, both academically and practically, who provides a variety of services under the direction and supervision of the pathologist. They perform the grossing duties for the majority of Pathology specimens received in the laboratory. Grossing technicians or others delegated to grossing must meet at least the minimum educational requirements and are generally trained "on the job" under the direct supervision of a pathologist. Personnel trained to gross could include histotechnicians and histotechnologists.

Grossing personnel must have documented training that includes either of the following:

1. *Completion of a clinical laboratory training program approved or accredited by the ABHES, the CAHEA, or other organization approved by HHS.*
2. *At least 3 months documented laboratory training in each specialty in which the individual performs high complexity testing.*

Reference CLIA 42 CFR 493.1489 and 42 CFR 493.1491 for additional details of requirements of education and training for high complexity testing personnel.

Personnel who are qualified and trained can visually inspect and describe tissue specimens that range from gross-only specimens, such as hardware, to tiny biopsies, whole organ resections, and amputations. Every specimen and every piece of tissue submitted to the laboratory is important. The tiniest piece of tissue can provide a vast amount of information for the pathologist to render a patient diagnosis.

It is the Laboratory Director's responsibility to ensure there are approved procedures and guidelines for grossing and job descriptions for grossing personnel. It is the Laboratory Director's responsibility to define the extent and scope of responsibilities that can be delegated to non-pathologist grossing personnel. The laboratory must assess and verify qualifications, training, and competency of each individual performing gross tissue processing. Competency of each individual must be assessed every six (6) months the first year and annually thereafter. The extent of supervision must be defined and may vary from indirect to consultative to direct depending on the level of complexity of the tissue specimen. All gross examinations and descriptions must be reviewed by the pathologist prior to rendering the final Pathology report.

CONCLUSION

The importance of grossing may not be known to all that work outside of the Histopathology laboratory. For those of us who work or have worked in the Pathology laboratory, it is educational, fascinating, and truly gives one a different perspective on the both the fragility and resilience of the human body.

REFERENCES

Laboratories Performing High Complexity Testing
eCFR :: 42 CFR Part 493 -- Laboratory Requirements

Code of Federal Regulations 42 CFR 493.1489 Standard; Testing Personnel Qualifications
https://www.ecfr.gov/current/title-42/chapter-IV/subchapter-G/part-493#:~:text=%C2%A7%20493.1489%20Standard%3B%20Testing%20personnel%20qualifications

Additional qualifications are published in the Code of Federal Regulations 42 CFR 493.1491 for those individuals that previously qualified or could have qualified prior to 1992.
https://www.ecfr.gov/current/title-42/chapter-IV/subchapter-G/part-493#:~:text=%C2%A7%20493.1491%20Technologist%20qualifications%20on%20or%20before%20February%2028%2C%201992

ABBREVIATION DEFINITIONS:

ABHES – Accrediting Bureau of Health Education Schools

CAHEA - Committee on Allied Health Education and Accreditation

CFR – Code of Federal Regulations

CLIA – Clinical Laboratory Improvement Amendments

HHS – Health and Human Services

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