Memorial Sloan Kettering Cancer Center

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Attention: CLIAC Secretariat
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To CLIAC Members:

For remote pathology, laboratory, and molecular review and results reporting, I urge CLIAC to recommend that the U.S. Department of Health and Human Services (HHS) extend current enforcement discretion beyond the end of the COVID-19 Public Health Emergency (PHE).

When performed from a site other than the primary laboratory site, leveraging transformed operational workflows, existing network connectivity, and digital technologies like digital slides/images and digital laboratory/molecular diagnostic platforms, remote reviewing and reporting is safe, secure, and effective.

Background:

The abrupt shift to remote working arrangements during the pandemic impacted many professions, including pathology and the laboratory. The transformation to remote working arrangements challenged pre-pandemic assumptions of the necessity for physicality to perform work. Before the COVID-19 pandemic, the Clinical Laboratory Improvement Amendments of 1988 (CLIA) regulation mandated on-site physicality for review and reporting. To perform remote review and reporting from remote sites other than the primary clinical laboratory site required separate CLIA certificates or submission of multiple Centers for Medicare & Medicaid Services (CMS) 116 forms for all its accountable remote sites. With the multiple safe, secure, and effective modalities to perform remote review and reporting, the administrative hurdles of CLIA proved antiquated, impractical, and onerous. Furthermore, given the urgency of the pandemic, the CLIA regulation for on-site physicality endangered a vulnerable aging majority of the pathology and laboratory workforce. (ref 1)

Likewise, before the COVID-19 PHE, rigid FDA regulation of digital pathology devices contributed to the greatly delayed deployment and lower adoption rate in the United States than in nations operating under different and much less restrictive regulatory domains (i.e., Canada, the European Union, and Japan). The FDA regulatory framework required end-to-end evaluation of digital pathology slide scanning systems until the COVID-19 PHE, which meant that each component of the overall image pipeline gets tied to a monolithic configurational approval. The consequence was the prevention of device substitution, even when new components with superior performance became available.

Both regulations from CLIA and FDA stymied adoption and delayed deployment in the U.S., hurting efforts to ramp up implementation for remote work to adjust to the pandemic.

Months before the pandemic, the mindset toward the necessity of on-site physicality started to shift. CLIAC recognized that access to a LIS in a secure environment is the same whether the access is via a monitor inside of a CLIA-certified facility or the access is via a monitor located elsewhere. CLIAC recommended that the CLIA program "consider that, when laboratory professionals provide patient care through selection, interpretation, and reporting of patient results by accessing data remotely in a secure environment, they get deemed as performing those services at the primary site housing the CLIA Certificate." (ref 2)

In March 2020, early in the pandemic and as part of a COVID-19 PHE protective effort, the Center for Clinical Standards and Quality within CMS issued guidance to State Survey Agency Directors for the CLIA program to "exercise enforcement discretion to ensure pathologists may review pathology slides remotely" at a temporary testing site such as a pathologist's home. (ref 3) Shortly after in April 2020 and following the CMS COVID-19 PHE protective effort, the Food and Drug Administration (FDA) issued an enforcement discretion policy to expand the scope intended for remote

reviewing and reporting of digital pathology devices, by permitting modification (like device substitution) to the FDA-cleared indications, functionality, hardware and software and the marketing of non-510(k)-cleared digital pathology devices. (ref 3)

Though intended for the duration of the public health emergency, both the CLIA and the FDA enforcement discretions afforded clinical laboratories the autonomy and flexibility to respond to the crisis by assembling digital pathology systems, using carefully selected:

1. Consumer off-the-shelf (COTS) displays
2. Research use only (RUO) slide scanners
3. Any other interoperable components required for digital pathology sign-out

A valuable byproduct of this forced experiment was a significant body of real-world experiential feedback and evidence regarding the safe, secure, and effective review and reporting of digital pathology slides/images along with laboratory/molecular analytical and results from output data from remote sites other than the primary clinical laboratory site for reporting. There was also concurrent accumulation of a wealth of operational knowledge concerning how effectively to use such modular approach with device substitution of digital pathology slide solutions.

By October 2020, about 6% of pathologists used digital pathology devices for remote diagnosis (i.e., telepathology), which allowed them to facilitate continuity of care while protecting pathologists and laboratory staff's health. (ref 5) This practice model was under many state directives, which stipulated that remote sign-out work is feasible and should get carried out remotely, when possible, to curb the horizontal transmission of SARS-CoV-2.

Real-world experiential feedback and evidence show that having a display used in an FDA-cleared system is unnecessary. Non-medical-grade (i.e., non-FDA-cleared), high-quality monitors (including COTS displays) that a clinical laboratory deems safe can be used to perform pathologic diagnoses. (ref 6, 7, 8) In some instances, COTS displays outperformed medical-grade displays significantly. (ref 8) For example, during the peak of the COVID-19 surge, Memorial Sloan Kettering Cancer Center (MSKCC) in New York City performed digital pathology primary diagnosis (sign-out) safely and efficaciously in a remote setting at scale using a wide variety of displays. Digital pathology displays ranged from consumer-grade laptop computers to higher specification desktop computers with high definition dual displays, none of which were medical-grade. (ref 9)

Clinical laboratories and individual pathologists have the expertise to determine if a display has enough resolution and is safe to make accurate diagnoses and determine which commercial grade products to use in medical practice, regardless of whether the monitor is an FDA-cleared device. In current practice, pathologists have already made such local decisions regarding the optical quality of microscopes and microscope lenses and the suitability of histologic preparations for making diagnoses.

Besides digital pathology technologies, pathologists and laboratory professionals could access a laboratory information system (LIS) remotely and securely to review molecular testing data, histograms, or gene sequencing results and analysis and render an interpretation. Any professional pathology service, whether digital pathology, laboratory or molecular, is configurable so that remote review and reporting are indistinguishable from on-site review and reporting.

Accreditation provides a regulatory pathway for CLIA to evolve and accommodate digital technologies for remote review and reporting. CMS and their respective accreditation bodies (i.e., College of American Pathologists (CAP), The Joint Commission, and NY State) regulate clinical laboratories and handle digital pathology displays as an integrated digital pathology practice component through CLIA. These accreditation bodies can verify or validate the entirety of digital pathology systems and laboratory/molecular platforms used for clinical diagnosis. Not required are devices used within these systems that are FDA-cleared and legal accountability at the case level remains with the pathologist.

My thoughts on moving forward:

I am the Director of Pathology Informatics at Memorial Sloan Kettering Cancer Center (MSKCC) and an Associate Attending and member of the Warren Alpert Center for Computational Pathology at MSKCC. I am also a board-certified in Anatomic and Clinical Pathology and Clinical Informatics and practice surgical pathology specializing in genitourinary tumors. In addition, my efforts are in digital and computational pathology. I work towards a better understanding of technology's cognitive and social impacts on clinical practice, particularly "operationalization" or the translation of digital pathology and computational pathology innovations to practice. Though I am also the 2021 Past-President of the Association for Pathology Informatics (API), I speak for myself and not for either MSKCC or API.

Enacted in 1988, the regulations of CLIA could not have anticipated the emergence of today's digital technologies, their effectiveness, and the need to adjust policies and guidance on their use for remote review and reporting. I am aligned with CLIA's purpose to establish quality standards for laboratory tests performed on human specimens for diagnosis, prevention, treatment of disease, or health assessment. Likewise, I align with the FDA's priorities in risk management and efforts to establish a more agile and adaptive regulatory framework that can keep pace with accelerating medical innovation.

I urge extending the current enforcement discretion beyond the end of the COVID-19 PHE so that primary clinical laboratory site do not need to obtain separate CLIA certificates or submit multiple CMS 116 forms for all of its accountable remote sites. At the very least, such enforcement discretion should continue until CMS has an opportunity to enhance CLIA regulations in formalizing a policy and guidance moving forward with digital technologies for remote review and reporting.

Achieving this extension of current enforcement discretion may not require significant changes. For example, CMS can expand on CLIA regulations by specifying extra guidance for remote review of images like digital slides and laboratory and molecular data, with pathology reporting by pathologists, PhDs, genetic counselors, and other laboratory professionals.

One consideration is taking a "risk-based" distinction between the layers of review and reporting and then formulating regulatory requirements/governance around the layer. Risk layers include:

1. Remote report release = Low risk

2. Remote review = Low to intermediate-risk

3. Remote review and reporting/rendering of primary diagnosis with report release = Higher risk

Risk layers 1 and 2 may require little to no additional requirements, specifications, or guidance. Risk layer 3 can be fanned out into other accountability requirements by stakeholders. Stakeholder examples and requirements include:

- CLIA-C – Specify regulatory guidance for enforcement discretion; examples include:
    - Defining further a laboratory site in the context of incorporated digital technologies and remote sites
    - Specify further requirements of licensure, liability, and CMS billing in the setting of remote review and reporting
    - Disentangle credentialing location (where one gets licensed), with the place of practice (where one reviews and reports) and where state borders and licensure come into play if place of practice is different
- Inspector/auditor – Follow a standardized checklists for state-level lab inspections (designed based on regulatory guidance by CLIA-C)
- Pathologist – Undergo training plus competency assessment (courses organized by lab/medical director)
- Accreditation "deemed entities" – Provide and audit proficiency testing (i.e., CAP program for remote diagnostics)
- Laboratory and the director – Construct remote digital modalities for secure remote review and reporting, within regulatory guidance by CLIA-C, with validation, standard operation procedures (SOPs), responsibility for infrastructure, ongoing maintenance, staff competency, and quality improvement

Personally, I recommend that digital pathology displays need not be FDA-cleared and endorse the permanent regulatory flexibility on devices like COTS displays for both on-site and remote. Required instead are high-quality digital pathology display products that meet minimum enough specifications to produce an accurate pathology diagnosis deemed by the pathologist, laboratory and director, inspector/auditor, and accreditation “deemed entities”. There is already enough evidence that digital pathology displays, with enough resolution, provide accurate diagnoses.

Finally, remote review and reporting should be permissible for regulatory guidance if the remote digital modality is clinically validated, flexibly constructed with sufficient specifications for image storage, retrieval protocols, and availability clinical information for accurate pathology diagnosis. Clinical validation should be comparable non-inferiorly to the on-site clinically validated solution within a CLIA lab.

If there is hesitancy, one last option is doing a "pilot" period where CMS extends the enforcement discretion for digital pathology under specific provisions that would then collect state-level audit data for informed decision-making.

I appreciate CLIAC considering my thoughts on regulation of remote digital review and reporting in pathology under CLIA.

Sincerely,

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