AMERICAN SOCIETY OF Cytopathology

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Position Statement Regarding FDA oversight of Laboratory Developed Tests (LDTs)

The American Society of Cytopathology (ASC) has a primary interest in meeting the needs of patients through high quality medical practice standards and ensuring access of necessary medical care to all who are in need. Laboratory Developed Tests (LDTs) are critical to the overall practice of medicine and are an integrated component of the current standard of patient care. The FDA's recent announcement of a proposed framework to regulate LDTs, which currently fall under the laboratory testing oversight by CMS through CLIA '88 standards, raises significant concerns regarding every laboratory's ability to provide timely and important technologically advanced medical testing to patients. The ASC is concerned with the inevitable increased costs associated with FDA oversight and perhaps more importantly, the stifling of the timely development and implementation of innovative advancements that provides quality care and hope for patients across the country (see bulleted details below):

- One of the advantages of cytopathology laboratory testing is the diverse methodologies for cytologic specimen preparations (e.g., direct smears, liquid based preparations, and cell blocks). Numerous ancillary laboratory tests (including immunohistochemistry, FISH, ISH and PCR based molecular testing) utilizing these preparations are LDTs and represent the standard of care at many institutions. Advances in the minimally invasive nature of acquisition of these types of patient samples obviates the need for open biopsies, which incur cost and patient morbidity and increase turnaround time for appropriate therapeutic decision-making (1, 5, 10, 14).
- The ASC supports and endorses the maintenance of the current medical practice standard of performing ancillary tests, including LDTs, on cytologic specimens in order to continue providing high quality, timely, and cost effective health care for patients. However, few, if any FDA approved companion diagnostics include cytopathology specimens as an approved specimen type, thus requiring the development of LDTs in order to offer state of the art testing on what is often the only specimen available for an individual patient (1, 5, 10).
- Salient examples and significances of important LDT's currently performed on cytologic samples include:
    - ALK rearrangement, EGFR mutation and ROS1 FISH testing on cytologic samples of non-small cell lung carcinoma (NSCLC) to guide candidacy for companion diagnostic therapy. Specifically, the ALK Break-Apart FISH probe set has only been FDA approved for paraffin-embedded specimens, not for cytologic specimens. Currently, there are no FDA approved tests available for ROS1 testing. Yet, without the testing, opportunities to treat patients with NSCLC driven by these genetic mutations with targeted therapy (e.g., erlotinib and geftinib for EGFR targeted therapy and crizotinib for NSCLCs with ALK or ROS1 rearrangements) will be missed (4, 7, 9, 11, 12, 14, 15).
    - *ERBB2* (*HER2*) FISH is used on gastric adenocarcinoma specimens to determine if these patients are candidates for trastuzumab. Again, no FDA approved test for this context

exists. Without the laboratory tests, it is likely that patients will be negatively affected both financially as well as medically (2, 3, 13).

- *BRAF* mutational analysis is used for advanced melanoma. Currently, FDA approved methods for detection of BRAF mutation are not approved for implementation on cytopathology materials (6, 8). Patients with advanced stage melanoma harboring the V600E mutation in *BRAF* are candidates to receive vemurafenib therapy.

- Precision medicine and molecular diagnostic testing continue to evolve. The ASC supports the need for continuing studies to define clinical validity and utility supporting the use of LDTs to meet this demand. The ASC also support that effective utilization management strategies be used to ensure unnecessary testing is not performed.
- Pathologists play a critical role in interpreting existing data regarding clinical utility and facilitate the integration of sophisticated tests results with clinical assessment to help clinicians make informed decisions. Adding FDA oversight of LDTs would add redundant oversight, cost and confusion. It would place substantial additional burden on clinical labs and clinical providers, thus limiting critical test offerings and access for patients.
- Given the current turn around for FDA approvals, the FDA likely would not be able to keep pace with the important medical advances or process improvements that characterize high quality laboratory testing, and which are necessary to meet patient care needs. This would apply to innovative improvements on currently existing FDA approved molecular tests and innovative developments of novel relevant assays.
- Regulatory oversight for LDTs through the current regulatory framework (CLIA 88 with CMS jurisdiction) is sufficiently robust to ensure high quality laboratory testing and appropriate medical care access for patients while maintaining patient safety. Any concerns regarding a potential need for enhanced oversight should be addressed through the existing framework.

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