Lung Cancer Action Network
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February 2, 2015

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

By Online Submission

RE: Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories: Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs) -- (FDA-2011-D-0360)

The lung cancer advocacy organizations that comprise the Lung Cancer Action Network are concerned about the FDA's proposed "Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)" released in the 2014-10-03 Draft Guidance. This framework could limit lung cancer patients' access to molecular testing essential for guiding treatment and identifying potentially life-saving therapies.

We want the laboratories where these clinical testing services are performed to be able to exercise the flexibility, innovation and medical judgment necessary for good outcomes in thousands of lung cancer patients. The FDA's proposed framework does not allow this to happen. To the extent there are concerns with the current oversight of these laboratories and their testing services, we strongly urge the agency charged with their oversight--the Centers for Medicare & Medicaid Services--to fulfill its legal statutory obligations and engage in notice and comment rule-making to modernize the Clinical Laboratory Improvement Amendments (CLIA)[1] regulations. This position is supported by a broad array of stakeholders in the medical community.[2,3,4,5,6].

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[1] Clinical Laboratory Improvement Amendments at http://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/index.html

[2] AMA Statement for the Record to FDA re: Framework for Regulatory Oversight of Laboratory Developed Tests (LDTS), January 8, 2015. http://www.ama-assn.org/ama/pub/advocacy/topics/personalized-medicine.page

[3] Clement PD, Tribe LH for American Clinical Laboratories Association. Laboratory testing services, as the practice of medicine, cannot be regulated as medical devices. http://www.acla.com/wp-content/uploads/2015/01/Tribe-Clement-White-Paper-1-6-15.pdf

[4] A Molecular Diagnostic Perfect Storm: The Convergence of Regulatory & Reimbursement Forces that Threaten Patient Access to Innovations in Genomic Medicine. http://www.amp.org/publications_resources/position_statements_letters/documents/PerfectStorm-FINAL-CD.pdf

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Lung cancer is the greatest cancer killer, responsible for a quarter of all cancer deaths[7]. Only 15% of patients are diagnosed before the disease has already spread beyond the primary tumor. The majority of patients die within a year. The historic five-year survival rate for metastatic lung cancer is 4%.[8]

However, advances in personalized medicine over the past five years are changing dismal survival statistics. Patients who were diagnosed with genomic variations such as EGFR- and ALK-positive non-small cell lung cancer (NSCLC) and were treated with appropriate targeted therapies are living months or even years longer.[9] All lung cancer patients should have access to the most current validated methods of testing for these genomic variations.

Two FDA-approved test kits currently exist for detecting genomic variations in lung cancer – one for ALK translocations, and one for EGFR mutations. However, knowledge of ALK, EGFR, and other oncogenes, as well as ways of detecting them, is evolving faster than federal regulatory agencies can respond. As medical research has learned more about ALK and EGFR, laboratory clinicians have developed additional tests to detect them. Under the FDA's proposed framework, these additional tests and others used to diagnose lung cancer genomic variations are labeled laboratory developed tests (LDTs). We believe the term laboratory developed testing procedures (LDPs) is more accurate.

Like the FDA, we want LDPs to be as validated, accurate, and clinically relevant as possible. However, we don't want a new regulatory process to block any lung cancer patient's access to LDPs whose analytical and clinical validity has been documented and demonstrated by qualified medical professionals in clinical laboratories, especially when treating physicians have determined the tests would be useful in guiding treatment decisions. Demonstration of clinical validity can be made part of modernized CLIA regulations, and should continue to allow for

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[5] American Society of Cytopathology. Position Statement Regarding FDA oversight of Laboratory Developed Tests (LDTs). http://www.cytopathology.org/wp-content/uploads/2013/05/ASC-Position-Regarding-FDA-oversight-of-LDTs1.pdf

[6] Joint stakeholders letter to FDA dated 2014-11-18. https://www.amp.org/publications_resources/documents/Sign%20On%20Letter%20FDA%20Rulemaking.pdf

[7] Centers for Disease Control and Prevention. National Center for Health Statistics. CDC WONDER On-line Database, compiled from Compressed Mortality File 1999-2012 Series 20 No. 2R, 2014.

[8] U.S. National Institutes of Health. National Cancer Institute. SEER Cancer Statistics Review, 1975-2011 .

[9] Kris M, Johnson BE, Berry LD, Kwiatkowski DJ, Iafrate AJ, Wistuba II, Varella-Garcia, M, et al. Using Multiplexed Assays of Oncogenic Drivers in Lung Cancers to Select Targeted Drugs. *JAMA*. May 21, 2014; 311(19): 1998–2006. doi: 10.1001/jama.2014.3741. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4163053/

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adoption of testing based on medical literature, rather than requiring independent clinical trials or government review for every laboratory assay.

The proposed regulations state that once a companion test for a genomic variation obtains FDA approval, the parameters of that test are frozen. Any modification to the approved test or any change in specimen type, such as fine needle aspirates acquired in minimally invasive procedures, requires new FDA approval before it can be offered to patients. This is problematic for metastatic lung cancer patients, who often have limited tumor tissue available for testing and urgently need targeted therapies to survive. The FDA approval process can take years. Many metastatic lung cancer patients would die waiting for critical diagnostic LDPs to be approved.

The proposed regulations require laboratories to submit all cancer-related LDPs for registration and listing; some laboratories (such as those at academic cancer centers) have hundreds of LDPs. In addition, LDPs for which a cleared or approved companion diagnostic exists (like EGFR and ALK) must be submitted for financially prohibitive and lengthy premarket review; once the FDA has begun enforcing its proposed regulations, these LDPs must complete premarket review before they can be used to treat patients. If this proposal were finalized, many labs, including those in major cancer centers, might not have the deep pockets or other resources to seek FDA approval for their LDPs. Improved testing options might not be offered or pursued when an FDA-approved test exists-- even where the FDA-approved kit is inferior to the existing LDPs. Many labs would have to pull LDPs from their list of patient services, and some labs might even have to close. This would impede not only access to potentially life-saving diagnostics, but impede innovation as well. Lung cancer patients can't afford to wait.

As an example of how these proposed regulations could harm patients, consider the FDA-approved molecular companion test for ALK-positive NSCLC, the break-apart FISH test, which is approved for testing on formalin-fixed paraffin-embedded (FFPE) NSCLC tumor tissue.

- Many patients who cannot safely provide sufficient tumor tissue have tested ALK-positive based on cells obtained from cytology specimens such as pleural fluid.[10,11] However, testing on cytology specimens is not allowed

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[10] Rosenblum F, Hutchinson LM, Garver J, , Cosar E, Kurian EM. Cytology specimens offer an effective alternative to formalin-fixed tissue as demonstrated by novel automated detection for ALK break-apart FISH testing and immunohistochemistry in lung adenocarcinoma. *Cancer Cytopathol*. 2014 Nov;122(11):810-21. doi: 10.1002/cncy.21467. Epub 2014 Aug 5. http://www.ncbi.nlm.nih.gov/pubmed/25099128 .

[11] Vanderlaan PA, Yamaguchi N Folch E, Boucher DH, Kent MS, Gangadharan SP, et al. Success and failure rates of tumor genotyping techniques in routine pathological samples with non-small-cell lung cancer. Lung Cancer. 2014 Apr;84(1):39-44. doi: 10.1016/j.lungcan.2014.01.013. Epub 2014 Jan 28. http://www.ncbi.nlm.nih.gov/pubmed/24513263

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with the FDA-approved ALK test kit. Many patients might need to undergo risky biopsies or surgery to obtain tumor tissue.

- Completing molecular tests for both EGFR and ALK (as recommended in National Comprehensive Cancer Network[12] and national professional association[13] guidelines) may leave insufficient tissue to test for other mutations like ROS1. The treating physician and laboratory clinician may, in their medical judgment, determine that using next-generation sequencing (NGS) will capture more mutation data from the available sample than molecular tests, and would support better clinical decision making for the patient. Some patients who test negative for ALK using FISH test positive using alternate, non-FDA approved assays and respond well to treatment with crizotinib.[14,15,16] However, under the proposed framework, these non-FDA approved assays would only be available if they first completed the FDA's premarket review, even though they have already been validated in certified clinical laboratories. As a result, some patients might not have access to potentially life-altering testing and therapy

Selection and analysis of lung cancer genomic LDPs usually depend on the judgment and skills of medical professionals in labs already certified by CLIA, state health agencies and accredited by organizations like the College of American Pathologists. Getting the best diagnostic and treatment outcomes from available lung cancer specimens relies of the practice of medicine, particularly the judgment and skill of pathologists, molecular pathologists and other molecular laboratory professionals. The use and safety of LDPs can't be regulated in the same manner as self-contained medical devices such as stents, or commercial test kits that come with pre-defined instructions.

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[12] NCCN NSCLC guidelines for Non-Small Cell Lung Cancer, v3.2015. NSCL-16, note hh. http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

[13] CAP, IASLC and AMP Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors. http://jmd.amjpathol.org/article/S1525-1578(13)00041-X/pdf

[14] Weickhardt AJ1, Aisner DL, Franklin WA, Varella-Garcia M, Doebele RC, Camidge DR. Diagnostic assays for identification of anaplastic lymphoma kinase-positive non-small cell lung cancer. *Cancer*. 2013 Apr 15;119(8):1467-77. doi: 10.1002/cncr.27913. Epub 2012 Dec 20. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3935240/

[15] Ren S, Hirsch FR, Varella-Garcia M, Aisner DL, Boyle T, Zhou C, et al. Atypical Negative ALK Break-Apart FISH Harboring a Crizotinib-Responsive ALK Rearrangement in Non–Small-Cell Lung Cancer. *J Thorac Oncol*. 2014 Mar; 9(3): e21–e23. doi:10.1097/JTO.0000000000000013. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4117236/

[16] Peled N, Palmer G, Hirsch FR, Wynes MW, Ilouze M, Varella-Garcia M, et al. Next-generation sequencing identifies and immunohistochemistry confirms a novel crizotinib-sensitive ALK rearrangement in a patient with metastatic non-small-cell lung cancer. *J Thorac Oncol*. 2012 Sep;7(9):e14-6. doi: 10.1097/JTO.0b013e3182614ab5. http://www.ncbi.nlm.nih.gov/pubmed/22895149 .

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Molecular and genomic profiling offer hope that patients can get the right drug at the right time. Lung cancer patients have waited decades for access to such breakthroughs in treatment. We must not throttle hope with cumbersome regulations that slow the pace of innovative treatments. Please consider the impact of the proposed FDA framework on the lives of lung cancer patients who may have no options for targeted therapy if LDPs are not accessible in a timely manner. Please withdraw the proposed FDA framework for regulation of LDTs.

Members of the Lung Cancer Action Network (LungCAN)

About LungCAN

The Lung Cancer Action Network is an association comprising U.S.-based 501(C)(3) advocacy nonprofit organizations united to serve as a vehicle, filter, and incubator for the exchange of ideas and information. LungCAN facilitates and enhances opportunities for collaboration with the focus on lung cancer. For more information about LungCAN, visit lungcan.org.