Guidance for Clinical Laboratories Using FDA Authorized Diagnostic Assays for Ebola Virus Detection

Introduction

On October 25, 2014 the **BioFire Defense "FilmArray Biothreat-E test"** received Emergency Use Authorization (EUA) from the Food and Drug Administration (FDA) for the presumptive detection of Ebola Zaire virus in whole blood or undiluted urine specimens. Prio**r** to this, the only diagnostic tests available in the U.S. were the Department of Defense (DoD) EZ1 Real-time RT-PCR Assay (FDA EUA August 5, 2014) performed in select State and Local Public Health Laboratory Response Network (LRN) Reference Laboratories, and CDC developed assays and confirmatory methods. Two CDC developed assays, CDC Ebola Virus NP and VP40 Real-time RT-PCR Assays, received EUA on October 10, 2014. Several other companies are in different stages of completing their applications for EUA of a number of additional commercially available Ebola Virus Disease (EVD) assays.

Clinical laboratories considering implementation of commercially available EVD assays must remember the importance of connecting with Public Health authorities whenever EVD is suspected, the regulatory requirements for verification of assay performance before utilization for patient testing and to consider the risk/benefit of using this assay in their laboratory. This document is intended to provide laboratories with information to guide decisions on whether to implement any of the EVD *in-vitro* diagnostic assays available to clinical laboratories under EUA and includes a recommended algorithm for testing to support clinical and public health management of persons suspected to be infected with ebola virus. Clinical laboratories must consult with state or local Public Health partners both prior to testing and after testing to report results (both negative and positive) and determine next steps.

Considerations for Implementing Ebola Testing In Your Laboratory

- Use of EVD *in-vitro* diagnostic assays available under EUA requires Notification of Public Health. "*Notification of Public Health: Local, state and national public health agencies (for example, county and state health departments or the U.S. Centers for Disease Control and Prevention (CDC) should be notified of any patient suspected to have Ebola Virus Disease (EVD). Confirmatory testing at the state/local public health laboratory or at CDC is necessary for positive detection results and may be necessary for negative detection results. Laboratories should consult with local, state or national public health officials on any positive detection OR no detection EVD test result on the need for additional testing and appropriate transportation of specimens.*"
- In order to report patient results to clinicians and use results for patient management in compliance with the Centers for Medicare and Medicaid Services (CMS) Clinical Laboratory

Improvement Amendments (CLIA) regulations, clinical laboratories are required to verify performance characteristics for the assay in their facilities. Verification materials (e.g. inactivated RNA) are available for purchase from companies such as Biodefense and Emerging Infections (BEI) Resources. However, the company may experience inventory issues due to high demand. If verification of performance characteristics is not performed laboratories will not be in compliance with CLIA regulations.

- Prior to implementing any assay, laboratories should conduct a Biosafety Risk Assessment to identify sources of risk and implement safety measures to mitigate them. Laboratories should be fully compliant with all recommended biosafety and personal protective equipment (PPE) standards and guidelines.
- Carefully review the Ebola virus assay product to ensure a full understanding of the approved intended use of the assay, result interpretation criteria, warnings and limitations.
- Laboratories should also be aware that Ebola virus is regulated as a select agent under federal regulations 42 CRF Part 73. The select agent regulations would not apply until the specimen that has tested presumptively positive using molecular methods has been proven to contain live-infectious Ebola virus by virus isolation at CDC. Viral culture, including culture on any rapid culture systems, should NOT be attempted in a clinical laboratory, under any circumstances on any specimen from an Ebola virus suspect. Laboratories should exercise caution and ensure that all specimens associated with Ebola cases are appropriately monitored. Upon successful isolation of Ebola virus at CDC, all primary specimens and samples at non select agent regulated laboratories must be transferred to a registered select agent facility or destroyed within 7 days.
- The use of commercially available EVD assays under EUA is only authorized for use with specimens from individuals with signs and symptoms of Ebola virus infection in conjunction with epidemiologic risk factors. These tests should not be used on patients that do not exhibit symptoms.
- Although commercially available EVD assays may be authorized for specimen types other than blood, collection of blood specimens at the initiation of testing is recommended. Blood specimens are required for confirmatory testing. Therefore, the use of blood specimens throughout the testing algorithm will provide the most efficient turnaround time.
- Test results are for the PRESUMPTIVE identification of Ebola Zaire virus. Confirmatory testing in consultation with public health authorities is required. Negative results do NOT preclude Ebola Zaire infection and should not be used as the sole basis for patient management or isolation decisions.

Additional Resources

BioFire Defense FilmArray Biothreat-E test

- Emergency Use Authorization https://www.federalregister.gov/articles/2014/08/12/2014-19026/declaration-regarding-emergency-use-of-in-vitro-diagnostics-for-detection-of-ebola-virus
- Package Insert

http://www.fda.gov/downloads/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMLegalRegulatoryandPolicyFramework/UCM420424.pdf

Patient Evaluation

- Checklist for Evaluating Patients Under Investigation
  http://www.cdc.gov/vhf/ebola/pdf/checklist-patients-evaluated-us-evd.pdf
- Algorithm for Evaluation of the Returned Traveler
  http://www.cdc.gov/vhf/ebola/pdf/ebola-algorithm.pdf

Packaging and Shipping

- Interim Guidance for Specimen Collection, Transport, Testing and Submission
  http://www.cdc.gov/vhf/ebola/pdf/ebola-lab-guidance.pdf
  http://www.cdc.gov/vhf/ebola/hcp/interim-guidance-specimen-collection-submission-patients-suspected-infection-ebola.html
- Packaging and Shipping eLearning Course
  http://www.cdc.gov/labtraining/course_listing/packing_shipping.html

Personal Protective Equipment

- CDC Guidance on PPE
  http://www.cdc.gov/vhf/ebola/hcp/procedures-for-ppe.html

Risk Assessment

- Risk Assessment Template. While this template is designed for public health laboratories, clinical laboratories may find this tool useful in conducting risk assessment for their facilities.
  http://www.aphl.org/aphlprograms/preparedness-and-response/Documents/APHL-Template.pdf

Points of Contacts for Additional Questions

- CDC Emergency Operations Center: 770-488-7100
- State or Local Public Health Laboratory (find contact information at link below)
  http://www.aphl.org/AboutAPHL/memberlabs/Pages/default.aspx

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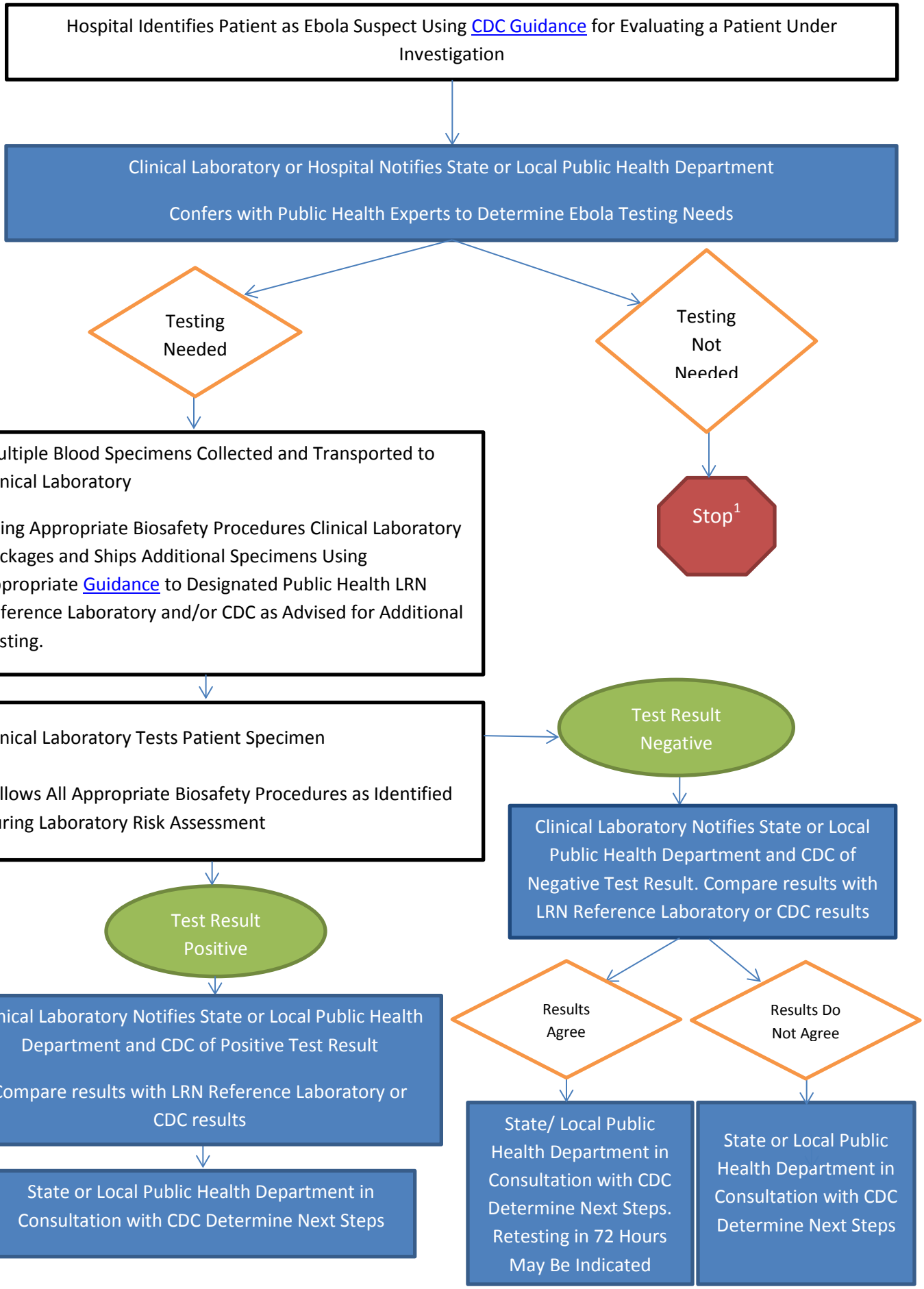

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[1]Information on Testing When Public Health Officials Determine It Is Not Indicated

Testing performed on individuals who do not meet the intended use criteria as defined in FDA labeling or without consultation with public health is not advisable and carries inherent risk.

- Testing outside the approved parameters of the EUA is considered to be a test modification and the laboratory performing the testing is responsible for establishing and assuring the safety and efficacy of the test in the patient population being tested (e.g. asymptomatic individuals).
- A positive result in a patient who is at low risk for EVD may be a false positive and can cause undue public health concern.
- Patients without symptoms but with risk factors for EVD who are tested outside the recommended parameters of the assay may be overly assured by a negative result and not comply with federal or state Movement and Monitoring requirements or seek medical care if symptoms develop.
- Individuals with a travel history to West Africa may be at risk for other infectious diseases including malaria and other viral hemorrhagic diseases (Lassa Fever, Marburg). All risk factors must be assessed and testing for other conditions should be considered.

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