Fact Sheet for Health Care Providers: Interpreting ***LightMix® Zika rRT-PCR Test*** Results

Updated: November 21, 2016

Dear Health Care Provider:

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to authorize the use of the ***LightMix®*** Zika ***rRT-PCR Test*** for the *in vitro* qualitative detection of Zika virus with specified instruments. This assay tests for Zika virus RNA in human serum and/or plasma. Testing should be conducted only on specimens from individuals meeting Centers for Disease Control and Prevention (CDC) Zika clinical and/or epidemiological criteria for testing and be performed by laboratories in the United States that are certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), 42 U.S.C. §263a, to perform high complexity tests, or by similarly qualified non-U.S. laboratories (http://www.cdc.gov/zika/hc-providers/index.html). This test should be performed according to CDC's algorithm for Zika testing (see http://www.cdc.gov/zika/laboratories/lab-guidance.html).

The information in this Fact Sheet is to inform you of the significant known and potential risks and benefits of the emergency use of the ***LightMix® Zika rRT-PCR Test***. For more information on this EUA, please see FDA's website at (http://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm).

Why is this test needed at this time?
Public health officials have determined that Zika virus poses a potential public health emergency. Current information on Zika virus infection for healthcare providers, including case definitions and information about signs and symptoms, is available at www.cdc.gov/zika/hc-providers/index.html. All information and guidance, including those on Zika virus laboratory testing, may change as more data are gathered on this virus. Please check CDC's Zika virus website regularly for the most current information (www.cdc.gov/zika/index.html).

The US Secretary of Health and Human Services (HHS) has declared that circumstances exist to justify the emergency use of *in vitro* diagnostic tests for the detection of Zika virus and/or diagnosis of Zika virus infection. This EUA will terminate when the HHS Secretary's declaration terminates, unless FDA revokes it sooner.

At this time, there are no FDA approved/cleared tests available that can detect Zika virus in clinical specimens in the U.S. Therefore, Roche Diagnostics, together with TIB MOLBIOL GmbH, has developed the ***LightMix® Zika rRT-PCR Test*** to detect evidence of Zika virus infection.

When should the *LightMix® Zika rRT-PCR Test* be performed?
If Zika virus infection is suspected based on CDC's published clinical and/or epidemiological criteria, the ***LightMix® Zika rRT-PCR Test*** may be ordered and should be performed according to the CDC-issued guidance (http://www.cdc.gov/zika/laboratories/lab-guidance.html). The algorithms included within the guidance illustrate the appropriate Zika testing approach based on the presence of signs and symptoms, pregnancy status, and the time between onset of symptoms or suspected exposure and specimen collection.

As disease manifestations of dengue and chikungunya virus infections can resemble those of Zika virus infection, additional testing for these viruses should be considered to aid in differentiating dengue and chikungunya virus infections from Zika virus infections or identifying possible co-infections. Please contact your state or local health department to facilitate testing.

Zika virus RNA is typically detectable in serum during the acute phase of infection (generally up to 7 days post-symptom onset). Zika virus RNA has been detected in serum up to 13 days post-symptom onset in non-pregnant patients, and up to 62 days post-symptom onset in pregnant patients. In addition, Zika virus RNA has been detected up to 53 days after the last known possible exposure in an asymptomatic pregnant woman (references 3-4).

As of November 21, 2016, serum is the primary diagnostic specimen for Zika virus RNA and serologic testing, and should be the priority specimen for collection and testing. Specimens should be collected with appropriate infection control precautions and according to the manufacturer's instructions for the specimen collection device, handling, and storage. Additional guidance for collection of body fluid specimens for Zika diagnostic testing may be found at: http://www.cdc.gov/zika/laboratories/test-specimens-bodyfluids.html.

If your patient has been symptomatic but is beyond the recommended window for ***LightMix® Zika rRT-PCR Test*** testing, serologic testing for antibodies to Zika virus may be helpful.

What does it mean if the specimen tests positive for Zika virus RNA?
A positive test result for Zika virus from the ***LightMix® Zika rRT-PCR Test*** indicates that RNA from Zika virus was detected in the patient's specimen. A positive test result in any authorized specimen collected from a patient is indicative of Zika virus infection. Laboratory test results should always be considered in the context of clinical observations, epidemiologic data and travel history in making a final diagnosis and patient management decisions. For guidelines on Zika virus, please refer to http://www.cdc.gov/zika/hc-providers/index.html.

The ***LightMix® Zika rRT-PCR Test*** has been designed to minimize the likelihood of false positive test results. Cross-reactivity of any of the components of this test resulting in false positive results is not expected. However, in the event of a false positive result, risks to patients could include any or all of the following: impaired ability to detect and receive appropriate medical care for the true source of symptoms; in the case of pregnant women, an unnecessary increase in the monitoring of a woman's pregnancy; or other unintended adverse effects.

In the US and its territories, Zika virus infection and disease (non-congenital and congenital) are nationally notifiable conditions and should be reported to the local or state health department. For guidance on Zika virus, please refer to http://www.cdc.gov/zika/hc-providers/index.html.

While there is an established association between Zika virus infection during pregnancy and microcephaly, detection of Zika virus RNA in specimens collected from a pregnant woman does not provide definitive information about the health of her fetus and does not indicate imminent harm to her fetus. If a pregnant woman is diagnosed with Zika virus infection based on detection of Zika virus RNA, issues such as timing of infection during the course of pregnancy, presence of symptoms and other factors may help determine the risk to her fetus.

What does it mean if the specimen tests negative for Zika virus RNA?
A negative test for Zika virus RNA in the specimen means that RNA from Zika virus is not present in the specimen above the test's limit of detection. However, a negative result does not rule out infection with the virus and should not be used as the sole basis for treatment or other patient management decisions.

A negative ***LightMix® Zika rRT-PCR Test*** result does not exclude the possibility of Zika virus infection. In serum, negative rRT-PCR test results are known to occur in Zika virus infection, particularly if testing is conducted outside the acute phase of infection (generally up to 7 days post symptom-onset) or in asymptomatic people. When other diagnostic testing is negative, the possibility of a false negative result should be considered in the context of a patient's recent exposures and the presence of clinical signs and symptoms consistent with Zika virus infection. Such patients should have antibody testing performed on their serum sample, as per the CDC testing algorithm (found at http://www.cdc.gov/zika/laboratories/lab-guidance.html).

Absence of laboratory evidence of Zika virus infection cannot definitively rule out Zika virus infection in persons with epidemiological risk factors. All results should be considered in the context of clinical signs and symptoms, exposure risk and time since symptom onset, or in the absence of symptoms, time since exposure.

Guidance for healthcare providers, including those caring for pregnant women and women of reproductive age with possible Zika virus exposure, is available on the CDC website: www.cdc.gov/zika/hc-providers/index.html.

Reporting Adverse Events
You should report adverse events, including problems with test performance or results, to MedWatch at www.fda.gov/medwatch, by submitting a MedWatch Form 3500 (available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM349464.pdf) or by calling 1-800-FDA-1088.

All patients should receive the Fact Sheet for Patients: Understanding Results from the *LightMix® Zika rRT-PCR Test*.

Contact Information for Instrument Manufacturers:
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Contact Information for Technical Assistance for the LightMix® Zika rRT-PCR Test:
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Any significant new findings that negatively impact the performance of the test and that are observed during the course of the emergency use of the ***LightMix® Zika rRT-PCR Test*** will be made available at lifescience.roche.com.

References

1) Rasmussen, S.A., Jamieson, D.J., Honein, M.A., Petersen, L.R. Zika Virus and Birth Defects – Reviewing the Evidence for Causality. New England Journal of Medicine, April 12, 2016. DOI: 10.1056/NEJMsr1604338.
2) CDC Website - http://www.cdc.gov/zika/
3) Driggers, R.W., et al. Zika virus Infection with Prolonged Maternal Viremia and Fetal Brian Abnormalities. New England Journal of Medicine, June 2, 2016; 374:2142-2151. DOI: 10.1056/NEJMoa1601824
4) Meaney-Delman et al. Prolonged Detection of Zika Virus RNA in Pregnant Women. Obstetrics and Gynecology, July 29, 2016 [epub ahead of print]. DOI:10.1097/AOG.0000000000001625