Anthem

Clinical UM Guideline

Subject: Zika Virus Testing
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Description

This document addresses the current stance on testing for Zika virus (ZIKV), a mosquito-borne flavivirus and member of the Flaviviridae family, which includes RNA real time reverse transcription-polymerase chain reaction (RT-PCR), immunoglobulin M (IgM) and the plaque reduction neutralization test (PRNT).

Clinical Indications

Medically Necessary:

Zika virus testing is considered **medically necessary** for individuals in accordance with the recommendations of the U.S. Centers for Disease Control and Prevention (CDC).

When the CDC recommendations are updated, the updated guidance regarding testing for Zika virus disease is considered **medically necessary** as of the effective date of the updated recommendations.

The following tests for Zika virus disease are considered **medically necessary,** in accordance with the latest CDC recommendations:

- Zika RNA Real-Time RT-PCR (for serum, urine, combined serum and urine, cerebrospinal fluid, amniotic fluid and saliva);
- Zika Virus IgM and Neutralizing Antibody Titers (PRNT) (for serum testing).

Not Medically Necessary:

Zika virus testing is considered **not medically necessary** for individuals, when not in accordance with the most recent recommendations of the U.S. Centers for Disease Control and Prevention (CDC).

Notes:
*Probable Zika virus exposure is considered when an individual:

A. Resides in an area with ongoing Zika (ZIKV) transmission; **or**
B. Travel to a country or region with known ZIKV transmission; **or**
C. Has direct epidemiologic linkage to a person with laboratory evidence of recent ZIKV infection (for example, sexual contact, in utero or perinatal transmission, blood transfusion, organ transplantation); **or**
D. Association in time and place with a confirmed or probable case.

***Clinical Criteria (signs and symptoms of Zika infection):
A person with **one or more** of the following:

- Acute onset of fever (measured or reported);
- Maculopapular rash;
- Arthralgia;
- Conjunctivitis;
- Complication of pregnancy:
  - fetal loss in a mother with compatible illness and/or epidemiologic risk factors; **or**
  - in utero findings of microcephaly and/or intracranial calcifications with maternal risk factors;
- Guillain-Barré syndrome not known to be associated with another diagnosed etiology.

**No data is available to determine how long Zika virus is present in semen. (http://www.cdc.gov/zika/transmission/sexual-transmission.html)

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be Medically Necessary when criteria are met:

CPT	
86794	Antibody; Zika virus, IgM
87662	Infectious agent detection by nucleic acid (DNA or RNA); Zika virus, amplified probe technique

ICD-10 Diagnosis	
	All diagnoses

When services are Not Medically Necessary:
For the procedure codes listed above when criteria are not met or for situations designated in the Clinical Indications section as not medically necessary.

Discussion/General Information

Zika virus (ZIKV), a mosquito-borne, single-stranded, RNA flavivirus and member of the Flaviviridae family, was originally isolated in 1947 from a sentinel primate in Uganda. According to the U.S. Centers for Disease Control and Prevention (CDC), local mosquito-

borne transmission of ZIKV in U.S. territories has been reported in the Commonwealth of Puerto Rico, the U.S. Virgin Islands, and American Samoa. Although most cases in residents of U.S. states were travel-associated, local transmission has been reported. Following the introduction and spread of ZIKV in the Americas in 2015, the number of travel-associated cases in U.S. states increased, with 5168 confirmed or probable cases of non-congenital ZIKV reported in 2016. The first autochthonous, mosquito-borne cases in the continental U.S. occurred in Florida in June 2016; local transmission peaked in August and then sharply declined. Although cases were reported from 49 states and the District of Columbia, approximately half (48%) were reported from three states (Florida 21%; New York 19%; and California 8%) (Hall, 2018). ZIKV is closely related to dengue, West Nile, Japanese encephalitis, and yellow fever viruses. Among flaviviruses, ZIKV and dengue virus share similar symptoms of infection, transmission cycles, and geographic distribution. Diagnostic testing for ZIKV infection can be accomplished using both molecular and serologic methods.

According to the initial U.S. CDC Morbidity and Mortality Weekly Report (MMWR), which was issued on May 10, 2016 and updated May 13, 2016, the following guidance was initially provided: *(See updated CDC recommendations below).*

> Criteria for ZIKV testing included persons who experienced two or more of the following symptoms: rash, fever, arthralgia or conjunctivitis during or within 2 weeks of return from an area with ZIKV activity, or who had an epidemiologic link to a ZIKV–infected traveler (sexual partner, household member, etc.). RT-PCR was routinely performed on urine, serum, or saliva specimens collected within 21 days of symptom onset. Clinicians were informed that only the serum RT-PCR and antibody tests were to be used for diagnostic purposes. Urine and saliva RT-PCR tests were only used for surveillance purposes. Serologic testing was performed on all serum specimens included in this analysis. The probable case definition criteria for ZIKV disease, based on serology, required ZIKV–specific immunoglobulin M (IgM) antibodies and no dengue virus–specific IgM antibodies detected in serum or cerebrospinal fluid.
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> Specimens reported as positive had cycle threshold (Ct) values ≤ 38 for at least one of the replicates in both the primary and secondary RT-PCR assays. Specimens reported as equivocal had a Ct value ≤ 38 in the primary assay, but not the secondary assay. For the purpose of this analysis, equivocal specimens were considered as negative. Specimens reported as negative had Ct values > 38 in the primary assay and were not tested further. ZIKV and dengue virus IgM antibody testing was performed at BPHL (Florida Department of Health Bureau of Public Health Laboratories) using a laboratory-developed IgM antibody capture enzyme-linked immunosorbent assay (MAC-ELISA) based on a CDC flavivirus MAC-ELISA protocol. In March 2016, BPHL transitioned to the Food and Drug Administration's Emergency Use Authorization (EUA) ZIKV MAC-ELISA developed by CDC. ZIKV antigen and positive control material were provided by CDC. A positive/negative (P/N) ratio was calculated from results of the MAC-ELISA for each specimen tested and was interpreted as the following: P/N ratios < 2 were reported as negative, P/N ratios 2 - < 3 were reported as equivocal, and P/N ratios ≥ 3 were reported as presumptive positive, as defined in the EUA (Bingham; MMWR, May 13, 2016).

Additional information was provided by the CDC MMWR issued on June 3, 2016, as follows:

> For persons with suspected ZIKV disease, a positive RT-PCR result confirms ZIKV infection, but a negative result does not exclude infection. In these cases, antibody testing can identify additional recent ZIKV infections. If IgM test results are positive, equivocal, or inconclusive, performing a plaque reduction neutralization test (PRNT) is needed to confirm the diagnosis. However, recent evidence suggests that a 4-fold higher titer by PRNT might not discriminate between anti-ZIKV antibodies and cross-reacting antibodies in all persons who have been previously infected with, or vaccinated against, a related flavivirus. Thus, a more conservative approach to interpreting PRNT results is now recommended to reduce the possibility of missing the diagnosis of either ZIKV or dengue virus infection.

On the basis of the available data, the CDC recommended that ZIKV RT-PCR be performed on urine collected < 14 days after onset of symptoms in individuals with suspected ZIKV disease. ZIKV RT-PCR testing of urine should be performed in conjunction with serum testing if using specimens collected < 7 days after symptom onset. A positive result in either specimen type provides evidence of ZIKV infection (Bingham MMWR; Erratum, May 13, 2016).

On July 28, 2017 the CDC MMWR issued updated interim guidance for U.S. health care providers caring for pregnant women with possible ZIKV exposure that revised the routine testing procedures for *asymptomatic* women who may have traveled to a region where ZIKV is circulating. This interim guidance was released in response to the declining prevalence of ZIKV in the continental U.S. and emerging evidence indicating prolonged detection of ZIKV immunoglobulin (IgM) antibodies. According to the CDC interim guidance:

> As the prevalence of ZIKV declines, the likelihood of false-positive test results increases. Further, emerging data indicate that ZIKV IgM antibodies can persist beyond 12 weeks after infection, and, therefore, cannot always reliably distinguish between an infection that occurred *during* the current pregnancy and one that occurred *before* the current pregnancy.
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> The CDC affirms that the new guidance should NOT be seen as a sign that ZIKV infections are any less dangerous for pregnant women. Instead, these recommendations reflect the limitations of the most commonly used blood test for the virus.

The most recent CDC key recommendations (December 9, 2019) are as follows:

1. All pregnant women in the U.S. and U.S. territories should be asked about possible ZIKV exposure *before and during* the current pregnancy, at every prenatal care visit. The CDC recommends that pregnant women not travel to any area with risk for ZIKV transmission. It is also recommended that pregnant women with a sex partner who has traveled to, or lives in, an area with risk for ZIKV transmission use condoms or abstain from sex for the duration of the pregnancy.
2. Pregnant women with recent possible ZIKV exposure and symptoms of ZIKV disease should be tested to diagnose the cause of their symptoms. The updated recommendations include concurrent ZIKV nucleic acid testing (NAT)* of serum and urine and serologic IgM testing as soon as possible up to 12 weeks after symptom onset.
3. Asymptomatic pregnant women with ongoing possible ZIKV exposure should be offered ZIKV NAT testing three times during pregnancy. IgM testing is no longer routinely recommended because IgM can persist for months after infection; therefore, IgM results cannot reliably determine whether an infection occurred during the current pregnancy. The optimal timing and frequency of testing of asymptomatic pregnant women with NAT alone may be informed by jurisdictional trends in ZIKV transmission, the expected length of ZIKV nucleic acid detection in serum, and the duration of exposure during pregnancy. Although not routinely recommended, after pre-test counseling and individualized risk assessment, physicians and patients, through a shared decision-making model, may collaboratively elect to have IgM testing performed concurrent with NAT testing. For pregnant women who have received a diagnosis of laboratory-confirmed ZIKV infection (by either NAT or serology [positive/equivocal ZIKV or dengue virus IgM and ZIKV PRNT ≥ 10 and dengue virus PRNT < 10 results]) any time before or

during the current pregnancy, additional ZIKV testing is not recommended. For pregnant women without a prior laboratory-confirmed diagnosis of ZIKV, NAT testing should be offered at the initiation of prenatal care, and if ZIKV RNA is not detected on clinical specimens, two additional tests should be offered during the course of the pregnancy coinciding with prenatal visits.

4. Asymptomatic pregnant women who have recent possible ZIKV exposure (i.e., through travel or sexual exposure) but without ongoing possible exposure may be considered for testing but are not routinely recommended to have ZIKV testing. Testing may be considered on a case-by-case basis using a shared patient-provider decision-making model, in line with jurisdictional recommendations. If testing of asymptomatic pregnant women is performed, the same algorithm as for symptomatic pregnant women should be followed using the timeframe from the last possible exposure to ZIKV. Jurisdictions may take into account local epidemiologic considerations (e.g., seasonality, geography, and mosquito surveillance and control factors) in making recommendations for ZIKV testing for this group of pregnant women; therefore, testing recommendations for this group of pregnant women may differ by jurisdiction. Please contact your state, tribal, local, or territorial health department for jurisdiction-specific guidance.
5. Pregnant women who have recent possible ZIKV exposure and who have a fetus with prenatal ultrasound findings consistent with congenital ZIKV syndrome should be tested. NAT and IgM testing should be performed on maternal serum and urine following the algorithm for symptomatic pregnant women. If amniocentesis is being performed as part of clinical care, NAT testing of amniocentesis specimens should also be performed. Testing of placental and fetal tissues may also be considered.
6. **Non-pregnant symptomatic individuals with possible exposure to ZIKV should receive testing of serum and urine by ZIKV RNA, NAT and ZIKV and/or dengue virus IgM testing of serum. NAT testing is dependent on the timing of specimen collection. NAT testing should be performed on specimens collected < 14 days after symptom onset. ZIKV and dengue virus IgM serology testing should be performed on NAT negative samples collected < 14 days after onset of symptoms or on samples collected ≥ 14 days after onset of symptoms. NAT testing is not recommended on specimens collected ≥ 14 days after symptom onset.
   **This information was updated in another guidance document for Dengue and ZIKV diagnostic testing for patients with a clinically compatible illness and risk for infection with *both* viruses as follows:
   - For symptomatic non-pregnant persons, dengue and ZIKV NAATs*** should be performed on serum collected ≤7 days after symptom onset. Dengue and ZIKV IgM antibody testing should be performed on NAAT-negative serum specimens or serum collected >7 days after onset of symptoms.
   - For symptomatic pregnant women, serum and urine specimens should be collected as soon as possible within 12 weeks of symptom onset for concurrent dengue and ZIKV NAATs and IgM antibody testing. Positive IgM antibody test results with negative NAAT results should be confirmed by neutralizing antibody tests (PRNT) when clinically or epidemiologically indicated, including for all pregnant women. Data on the epidemiology of viruses known to be circulating at the location of exposure and clinical findings should be considered when deciding which tests to perform and for interpreting results (CDC, Sharp 2019).
     ***Nucleic acid amplification test, or NAAT, is a generic term referring to all molecular tests used to detect viral genomic material. For additional information about tests for ZIKV, see: https://www.cdc.gov/zika/laboratories/types-of-tests.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fzika%2Fhc-providers%2Ftypes-of-tests.html. Accessed on May 10, 2023.
7. The comprehensive approach to testing placental and fetal tissues has been updated. Testing placental and fetal tissue specimens can be performed for diagnostic purposes in certain scenarios (e.g., women without a diagnosis of laboratory-confirmed ZIKV infection and who have a fetus or infant with possible ZIKV-associated birth defects). However, testing of placental tissues for ZIKV infection is not routinely recommended for asymptomatic pregnant women who have recent possible ZIKV exposure but without ongoing possible exposure and who have a live born infant without evidence of possible ZIKV–associated birth defects.
8. ZIKV IgM testing as part of preconception counseling to establish baseline IgM results for nonpregnant women with ongoing possible ZIKV exposure is not warranted because ZIKV IgM testing is no longer routinely recommended for asymptomatic pregnant women with ongoing possible ZIKV exposure (CDC, June 2019).

Regarding sexual transmission and prevention, the CDC provides the following guidance (May 21, 2019):

- ZIKV can be passed through sex from a person with ZIKV to his or her partners.
- Sex includes vaginal, anal, and oral sex and the sharing of sex toys.
- ZIKV can be passed through sex even in a committed relationship.
- The timeframes that men and women can pass ZIKV through sex are different because ZIKV virus can stay in semen longer than in other body fluids.
- There is no available test to know if you have ZIKV in your semen or how likely you are to pass ZIKV through sex. ZIKV can stay in your semen and may be passed to your partner (and the fetus) for months after infection, even if you have no symptoms.

***NAT** is a ZIKV RNA nucleic acid test (cobas Zika, Roche Molecular Systems, Inc., Pleasanton, CA) which was authorized by the FDA under an investigational new drug application (IND) (March 30, 2016). RT-PCR is an example of an NAT test. For symptomatic pregnant women with possible exposure to ZIKV, NAT should be performed concurrently with IgM serology. For further information, see: https://www.cdc.gov/zika/hc-providers/types-of-tests.html. Accessed on May 10, 2023.

On August 19, 2016 the CDC published interim guidance for the evaluation and management of infants with possible congenital ZIKV infection. The new recommendations stated:

> Recommended infant laboratory evaluation includes both molecular (real-time reverse transcription–polymerase chain reaction [rRT-PCR]) and serologic (immunoglobulin M [IgM]) testing. Initial samples should be collected directly from the infant in the first 2 days of life, if possible; testing of cord blood is not recommended. A positive infant serum or urine rRT-PCR test result confirms congenital ZIKV infection. Positive ZIKV IgM testing, with a negative rRT-PCR result, indicates probable congenital ZIKV infection.

On September 29, 2016 the CDC updated its guideline recommendations for infants and children as follows:

- Infants and children can acquire ZIKV congenitally and postnatally. Guidance is available on testing, clinical management and prevention of ZIKV for children under the age of 18;
- Testing of infants with possible congenital ZIKV infection should be guided by:
  - Whether the infant has abnormalities consistent with congenital ZIKV syndrome (e.g., microcephaly, intracranial calcifications, or other brain or eye abnormalities);
  - The mother's ZIKV testing results.
- Congenital ZIKV infection can be diagnosed by RT-PCR and through serologic testing.
- Postnatal ZIKV disease should be suspected in an infant or child < 18 years old who:
  - Has traveled to or lived in an area with active ZIKV transmission in the last 2 weeks;

    - Has two or more symptoms of ZIKV: fever, rash, conjunctivitis, or arthralgia;
    - Has another possible exposure to ZIKV (sexual contact with a person who lives in or traveled to an area with ZIKV or an association in time and place with a confirmed or probable case).
- Perinatal ZIKV disease should also be suspected in an infant in the first 2 weeks of life if:
    - The mother traveled to or resided in an affected area within 2 weeks of delivery;
    - The infant has two or more of the following manifestations: fever, rash, conjunctivitis, or arthralgia.
- For diagnosing postnatal ZIKV infection, RT-PCR is recommended during the first two weeks after symptom onset, serologic testing is recommended 2-12 weeks after symptom onset (CDC, September 29, 2016. Additional information available at: http://www.cdc.gov/zika/hc-providers/index.html. Accessed on May 10, 2023)

On August 30-31, 2017 the CDC, in collaboration with the American Academy of Pediatrics (AAP) and the American College of Obstetricians and Gynecologists (ACOG), convened the Forum on the Diagnosis, Evaluation, and Management of ZIKV infection among infants, "With the goal of obtaining individual expert opinion to inform development of updated guidance for diagnosing, evaluating, and managing infants with possible congenital ZIKV and to identify strategies to enhance communication and coordination of care of mothers and infants affected by ZIKV." Additional detailed information is available at: https://www.cdc.gov/mmwr/volumes/66/wr/mm6641a1.htm#suggestedcitation. Accessed on May 10, 2023.

According to the October 7, 2016 MMWR on Zika testing, the following is provided:

> Persons with possible ZIKV exposure who have symptoms of ZIKV disease should receive testing in accordance with CDC interim guidance: "Algorithm for U.S. Testing of Symptomatic Individuals." CDC does not recommend ZIKV testing of nonpregnant persons with possible ZIKV exposure who do not have symptoms of ZIKV disease, including persons who are planning to attempt conception, or to assess the risk for sexual transmission of ZIKV. ZIKV testing for this purpose remains of uncertain value, because current understanding of the duration and pattern of shedding of ZIKV in reproductive tissues is limited. Information on the performance of serologic ZIKV testing remains limited, with falsely positive tests resulting in avoidable stress and expense and falsely negative tests providing false reassurance and possibly leading to inadvertent fetal exposure to ZIKV (Petersen; MMWR, October 7, 2016).

According to the World Health Organization (WHO), laboratory confirmation of ZIKV is considered the following:

1. Presence of ZIKV RNA or antigen in serum or other samples (e.g. saliva, tissues, urine, whole blood); or
2. IgM antibody against ZIKV positive and $PRNT_{90}$ for ZIKV with titre ≥ 20 and ZIKV $PRNT_{90}$ titre ratio ≥ 4 compared to other flaviviruses; and exclusion of other flaviviruses (WHO, 2019).

Regarding interpretation of ZIKV test results, the CDC provides the following:

> For persons with suspected ZIKV disease, a positive RT-PCR result confirms ZIKV infection, and no antibody testing is indicated. However, because of the decline in the level of viremia over time and possible inaccuracy in reporting of dates of illness onset, a negative RT-PCR result *does not exclude ZIKV* infection. Therefore, serum IgM antibody testing for ZIKV and dengue virus infections should be performed if RT-PCR is negative. For serum specimens collected < 7 days after onset of symptoms, the combination of a negative RT-PCR result and negative IgM antibody testing suggests that there was no recent infection. However, a negative IgM antibody test, in the absence of RT-PCR testing, might reflect specimen collection before development of detectable antibodies and does not rule out infection with the viruses for which testing was performed. For specimens collected from 7 days to 12 weeks after onset of symptoms, a negative IgM antibody result to both ZIKV and dengue viruses rules out recent infection with either virus.
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> If either the ZIKV or dengue virus IgM antibody testing yields positive, equivocal, or inconclusive results, PRNTs against ZIKV and dengue viruses (or other flaviviruses endemic to the region where exposure occurred) should be performed. A PRNT using a 90% cutoff value with a titer ≥ 10 (the typical starting serum dilution used to establish the presence of virus-specific neutralizing antibodies) against ZIKV, together with negative PRNTs (< 10) against other flaviviruses is confirmatory for recent infection with ZIKV. A PRNT titer ≥ 10 for both ZIKV and dengue virus (or another flavivirus) provides evidence of a recent infection with a flavivirus but precludes identification of the specific infecting virus. A negative PRNT against ZIKV in a specimen that is collected > 7 days after illness onset rules out ZIKV infection. For specimens collected < 7 days after onset of symptoms, the combination of a negative RT-PCR and a PRNT titer < 10 suggests that there was no infection with ZIKV. However, in the absence of RT-PCR testing, a PRNT titer < 10 might reflect specimen collection before development of detectable neutralizing antibodies and does not rule out infection with the viruses for which testing was conducted. Without confirmatory PRNTs, it is not possible to determine whether a presumptive positive IgM antibody result against ZIKV reflects recent flavivirus infection or a false-positive result.

Regarding the adverse effects of ZIKV on the unborn fetus of infected pregnant women, Rasmussen and colleagues reviewed the available evidence in 2016 and concluded that, "Sufficient evidence has accumulated that infers a causal relationship between prenatal ZIKV and microcephaly and other severe brain anomalies" (Rasmussen, 2016). Other investigators studied the 2013-2014 ZIKV outbreak in French Polynesia where the risk of microcephaly due to ZIKV in the first trimester of pregnancy was 0.95% (95% confidence interval [CI]; 0.34 to 1.91), on the basis of 8 microcephaly cases identified retrospectively in a population of approximately 270,000 people with an estimated rate of ZIKV of 66%. Additional data was analyzed from Bahia, Yap Island, the Federated States of Micronesia and French Polynesia and assessed for the association of ZIKV risk with microcephaly cases, reported in the Brazilian Live Births Information System between July 2015 and February 2016. The investigators reported a strong association between the risk of microcephaly and ZIKV risk in the first trimester and a negligible association in the second and third trimesters. The estimated baseline risk for microcephaly was low, approximately 2 per 10,000 births, but the estimated risk due to ZIKV in the first trimester ranged from 0.88% (95% CI; 0.80 to 0.97) when an 80% overall ZIKV rate was assumed and 100% over-reporting of microcephaly cases, to 13.2% (95% CI; 12.0 to 14.4) when a 10% ZIKV rate was assumed and no over-reporting. The authors noted the uncertainties and limitations with all current estimates of microcephaly risk associated with ZIKV. Additional recent studies have revealed associations between symptomatic ZIKV during all trimesters and adverse pregnancy outcomes with potential peak risk during gestational weeks 14 to 17. Microcephaly is only one possible adverse outcome among a spectrum of conditions that may be part of congenital Zika syndrome. More data are needed to refine gestational age-specific risk estimates for microcephaly and other outcomes related to ZIKV, especially in relation to symptomatic and asymptomatic infection (Johansson, 2016). Recently ZIKV has also been associated with cases of Guillain-Barré syndrome in the infected individual.

The following is excerpted from the instructions for use of the Trioplex Real-time RT-PCR Assay (Trioplex rRT-PCR) which was developed by the CDC and has been authorized by the FDA under the Emergency Use Authorization (EUA) as follows:

> The Trioplex Real-time RT-PCR assay is intended for the qualitative detection and differentiation of RNA from ZIKV, dengue virus, and chikungunya virus in human sera or cerebrospinal fluid (collected alongside a patient-matched serum specimen), and for the qualitative detection of ZIKV RNA in urine and amniotic fluid (each collected alongside a patient-matched serum specimen). The assay is intended for use with specimens collected from individuals meeting CDC ZIKV clinical criteria (e.g., clinical signs and symptoms associated with ZIKV infection) and/or CDC ZIKV epidemiological criteria (e.g., history of residence in or travel to a geographic region with active ZIKV transmission at the time of travel, or other epidemiologic criteria for which ZIKV testing may be indicated as part of a public health investigation). Testing is limited to qualified laboratories designated by the CDC. Assay results are for the identification of Zika, dengue, and chikungunya viral RNA. Viral RNA is generally detectable in serum during the acute phase of infection (approximately 7 days following onset of symptoms, if present). Positive results are indicative of current infection. Laboratories are required to report all results to the appropriate public health authorities. Within the U.S. and its territories results must be reported to CDC. Negative Trioplex rRT-PCR results do not rule out dengue, chikungunya and/or ZIKV and should not be used as the sole basis for patient management decisions. Negative results must be combined with clinical observations, patient history, and epidemiological information (CDC; May 17, 2016).

The Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for the CDC Zika IgM Antibody Capture Enzyme-Linked Immunosorbent Assay (Zika MAC-ELISA) for antibody testing as follows:

> An enzyme-linked immunosorbent assay (ELISA) can be used to detect anti-ZIKV IgM antibodies in serum or cerebrospinal fluid; however, the ZIKV IgM ELISA can provide false-positive results because of cross-reacting IgM antibodies against related flaviviruses or nonspecific reactivity. This assay has been introduced and is being used in qualified public health and Department of Defense laboratories in the United States. The Zika MAC-ELISA is used for the qualitative detection of ZIKV IgM antibodies in serum or cerebrospinal fluid collected from persons meeting the clinical and epidemiologic criteria for suspected ZIKV disease. Results are reported as positive (termed “presumptive positive” to denote the need to perform a confirmatory PRNT), equivocal, negative, or inconclusive (i.e., results uninterpretable because of high background optical density). To resolve false-positive results that might be caused by cross-reactivity or nonspecific reactivity, presumptive positive results should be confirmed with PRNT against ZIKV, dengue, and other flaviviruses to which the person might have been exposed. In addition, equivocal and inconclusive results that are not resolved by retesting also should have PRNT performed to rule out a false-positive result…If serologic testing indicates recent flavivirus infection that could be caused by either ZIKV or dengue virus, individuals should be clinically managed for both infections because they might have been infected with either virus (FDA; February 26, 2016).

On May 23, 2019, the FDA authorized marketing of the ZIKV Detect™ 2.0 IgM Capture ELISA (InBios International, Inc., Seattle, WA) to detect ZIKV IgM antibodies in human blood. The ZIKV Detect 2.0 IgM Capture ELISA is the first diagnostic test for ZIKV that the FDA has allowed to be marketed in the U.S. Prior to this time, no test for ZIKV had been approved or cleared by the FDA. This FDA approval was based on data review through the De Novo premarket review pathway which then serves as a resource for future FDA approvals.

Multiple additional tests have been authorized by the FDA under an EUA for ZIKV testing at FDA approved laboratories, including the cobas® Zika test, (Roche Molecular Systems Inc., Pleasanton, CA) for screening individual blood donations. On August 15, 2018 according to the FDA, the Procleix® Zika virus assay was approved for blood screening on the Procleix Panther® system (Grifols Diagnostic Solutions, Inc., Barcelona, Spain). This assay is approved for detecting ZIKV in donated individual or pooled plasma specimens, making it useful for blood banks. It is also approved to test plasma or serum samples to screen other living or dead organ donors and human cells, tissues and cellular and tissue-based products. Detailed information for each authorized test is available at: http://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm#zika. Accessed on May 10, 2023.

On June 27, 2016 the FDA announced that Inovio Pharmaceuticals, Inc. (Plymouth, PA) and GeneOne Life Science, Inc. (Seoul, South Korea; VGXI, Inc., TX) have been given approval to commence a Phase 1 clinical trial to evaluate their ZIKV vaccine GLS-5700. This 40-subject trial is an open label, dose-ranging study which will evaluate the vaccine’s safety, tolerability and immunogenicity. The GLS-5700 assay is administered intradermally with the CELLECTRA®, Inovio’s proprietary DNA delivery device. A preliminary report of interim analysis at 14 weeks, (following the third dose of vaccine), was published in 2017 indicating no serious adverse events. Local reactions at the vaccination site, (for example, injection-site pain, redness, swelling, and itching), occurred in approximately 50% of the participants. After the third dose of vaccine, binding antibodies, (as measured on enzyme-linked immunosorbent assay), were detected in all the participants, with geometric mean titers of 1642 and 2871 in recipients of 1 mg and 2 mg of vaccine, respectively, and neutralizing antibodies developed in 62% of the samples on Vero-cell assay. On neuronal-cell assay, there was a 90% inhibition of ZIKV infection in 70% of the serum samples and 50% inhibition in 95% of the samples reported. Although promising, the authors acknowledged that further study is warranted to determine the safety and efficacy of this vaccine (Tebas, 2017). As of August 1, 2019 this study (NCT02809443) was listed as completed.

An updated version of the study results was published in 2021 (Tebas, 2021). In addition to the previous findings, results were presented indicating protection of mice from a lethal dose of ZIKV by human postvaccination serum. IFNAR knockout mice (bred with deletion of genes encoding interferon-α and interferon-β receptors) have a defective immune system, and when infected with ZIKV normally die within 6-7 days. When these mice were first injected with human serum collected at week 14 (after the third dose of the vaccine) before being infected with ZIKV, 92% of the mice survived the infection. No mice receiving baseline (prevaccination) serum survived. These results suggest that the antibody response generated in humans by the vaccine was protective in this infection model. Despite the promising results, further studies involving larger randomized trials in a region where ZIKV is endemic will be required to address the efficacy of this ZIKV vaccine in humans.

The above assay tests and additional tests and laboratories have been authorized by the FDA under the EUA to perform NAAT for the qualitative detection of RNA for the ZIKV in human specimens, (such as serum, urine, amniotic fluid, cerebrospinal fluid). These laboratories are certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) to perform high complexity tests, or are certified by similarly qualified non-U.S. laboratories, subject to, “The duration of the declaration that circumstances exist justifying authorization of the emergency use of in-vitro diagnostic tests for the detection of, or diagnosis of, ZIKV” (FDA, 2017).

On May 2, 2018, the FDA issued revised guidance for establishments that make donor eligibility determinations for donors of human cells, tissues, and cellular and tissue-based products: Donor Screening Recommendations to Reduce the Risk of Transmission of Zika Virus by Human Cells, Tissues, and Cellular and Tissue-Based Products; Guidance for Industry. This update supports the continuation of recommendations to screen living donors for risks of infection with ZIKV based on geographic areas with risk. On July 6, 2018, the FDA announced the availability of a revised final guidance: Revised Recommendations for Reducing the Risk of Zika Virus Transmission by Blood and Blood Components. This revised guidance replaces the August 2016 guidance, which

recommended universal nucleic acid testing for ZIKV of individual units of blood donated in the U.S. states and territories. The revised guidance explains that, in order to comply with applicable testing regulations, blood establishments must continue to test all donated whole blood and blood components for ZIKV using a nucleic acid test. The revised guidance explains the basis for the FDA's determination that pooled testing of donations using a screening test licensed for such use by the FDA is a sufficient method for complying with these regulations and effectively reducing the risk of ZIKV transmission, unless there is an increased risk of local mosquito-borne transmission of ZIKV in a specific geographic area that would trigger individual donation testing in that location. Alternatively, blood establishments may use an FDA-approved pathogen-reduction device for plasma and certain platelet products (Federal Register notice, 2018).

Definitions

According to the CDC National Notifiable Diseases Surveillance System (NNDSS), the following is provided as a summary of criteria and classifications for ZIKV and ZIKV disease (June 2016):

Clinical Criteria
A person with one or more of the following:

- Acute onset of fever (measured or reported);
- Maculopapular rash;
- Arthralgia;
- Conjunctivitis;
- Complication of pregnancy:
    - fetal loss in a mother with compatible illness and/or epidemiologic risk factors; OR
    - in utero findings of microcephaly and/or intracranial calcifications with maternal risk factors
- Guillain-Barré syndrome not known to be associated with another diagnosed etiology.

Epidemiologic Linkage

- Travel to a country or region with known ZIKV transmission; OR
- Sexual contact with a laboratory confirmed case of ZIKV infection; OR
- Receipt of blood or blood products within 30 days of symptom onset; OR
- Organ transplant recipient within 30 days of symptom onset; OR
- Association in time and place with a confirmed or probable case.

Case Classification

Probable ZIKV Disease meets clinical criteria AND:

- Resides in, or has recently traveled to, an area with ongoing ZIKV transmission, OR;
- Has direct epidemiologic linkage to a person with laboratory evidence of recent ZIKV infection (for example, sexual contact, in utero or perinatal transmission, blood transfusion, organ transplantation); OR
- Association in time and place with a confirmed or probable case.

AND meets the following laboratory criteria:

- Positive ZIKV-specific IgM antibodies in serum or cerebrospinal fluid (CSF); AND
- Negative dengue virus-specific immunoglobulin M (IgM) antibodies; AND
- No neutralizing antibody testing performed; OR
- Less than four-fold difference in neutralizing antibody titers between ZIKV and dengue or other flaviviruses endemic to the region where exposure occurred.

Confirmed ZIKV Infection meets clinical criteria AND has laboratory evidence of recent ZIKV infection by:

- Detection of ZIKV by culture, viral antigen or viral ribonucleic acid (RNA) in serum, CSF, tissue, or other specimen (for example, amniotic fluid, urine, semen, saliva); OR
- ZIKV IgM antibodies in serum or CSF with ZIKV neutralizing antibody titers 4-fold or greater than neutralizing antibody titers against dengue or other flaviviruses endemic to the region where exposure occurred.

Emergency Use Authorization (EUA): A temporary approval issued by the FDA which, for the ZIKV testing, is based on data submitted by CDC to FDA, and on the U.S. Secretary of Health and Human Services' (HHS) declaration that circumstances exist to justify the emergency use of in vitro diagnostic tests for the detection of ZIKV and/or diagnosis of ZIKV infection. "This EUA will terminate when the HHS Secretary's declaration terminates, unless FDA revokes it sooner" (FDA, 2016).

Immunoglobulin M (IgM): A test for quantitative immunoglobulins (or antibodies) which is used to confirm an infectious process, including a diagnosis of ZIKV.

Plaque Reduction Neutralization test (PRNT): A highly specialized test of serum used to confirm a diagnosis of ZIKV when prior IgM testing has yielded positive or inconclusive results.

Real Time Reverse Transcription-Polymerase Chain Reaction (RT-PCR or rRT-PCR) testing: A molecular test for the presence of viral RNA which is used in the diagnostic workup of suspected ZIKV and other infectious conditions. A positive RT-PCR result for ZIKV is considered conclusive.

References

Peer Reviewed Publications:

1. Dang J, Tiwari SK, Lichinchi G, et al. Zika Virus depletes neural progenitors in human cerebral organoids through activation of the innate immune receptor TLR3. Cell Stem Cell. 2016; 19(2):258-265.
2. Driggers RW, Ho CY, Korhonen EM, et al. Zika virus infection with prolonged maternal viremia and fetal brain abnormalities. N Engl J Med. 2016; 374(22):2142-2151.
3. Faria NR, Azevedo RS, Kraemer MU, et al. Zika virus in the Americas: Early epidemiological and genetic findings. Science. 2016; 352(6283):345-349.
4. Fitzgerald B, Boyle C, Honein MA. Birth defects potentially related to Zika virus infection during pregnancy in the United States. JAMA. 2018; 319(12):1195-1196.
5. Garcez PP, Loiola EC, Madeiro da Costa R, et al. Zika virus impairs growth in human neurospheres and brain organoids.

Science. 2016; 352(6287):816-818.
6. Granger D, Hilgart H, Misner L, et al. Serologic testing for Zika virus: Comparison of three Zika virus IGM-screening enzyme-linked immunosorbent assays and initial laboratory experiences. J Clin Microbiol. 2017; 55(7):2127-2136.
7. Johansson MA, Mier-y-Teran-Romero L, Reefhuis J, et al. Zika and the risk of microcephaly. N Engl J Med. 2016; 375(1):1-4.
8. Mead PS, Duggal NK, Hook SA, et al. Zika virus shedding in semen of symptomatic infected men. N Engl J Med. 2018; 378(15):1377-1385.
9. Mckenzie BA, Wilson AE, Zohdy S. Aedes albopictus is a competent vector of Zika virus: A meta-analysis. PLoS. 2019; 14(5):1-16.
10. Mlakar J, Korva M, Tul N, et al. Zika virus associated with microcephaly. N Engl J Med. 2016; 374(10):951-958.
11. (No authors provided). Zika virus infection: global update on epidemiology and potentially associated clinical manifestations. Wkly Epidemiol Rec. 2016; 91(7):73-81.
12. Paz-Bailey G, Rosenberg ES, Doyle K, et al. Persistence of Zika virus in body fluids-final report. N Engl J Med. 2018; 379:1234-1243.
13. Rasmussen SA, Jamieson DJ, Honein MA, et al. Zika virus and birth defects: reviewing the evidence for causality. N Engl J Med. 2016; 374(20):1981-1987.
14. Ravichandran S1, Hahn M1, Belaunzarán-Zamudio PF2, et al. Differential human antibody repertoires following Zika infection and the implications for serodiagnostics and disease outcome. Nat Commun. 2019; 10(1):1943.
15. Rolfe AJ, Bosco DB, Wang J, et al. Bioinformatic analysis reveals the expression of unique transcriptomic signatures in Zika virus infected human neural stem cells. Cell Biosci. 2016; 6:42.
16. Saá P, Proctor M, Foster G, et al. Investigational testing for Zika virus among U.S. blood donors. N Engl J Med. 2018; 378(19):1778-1788.
17. Saiee F, Badawi A. Maternal infection with Zika virus and prevalence of congenital disorders in infants: systematic review and meta-analysis. Can J Public Health. 2019; 110(5):638-648.
18. Santiago GA, Vázquez J, Courtney S, et al. Performance of the Trioplex real-time RT-PCR assay for detection of Zika, dengue, and chikungunya viruses. Nat Commun. 2018; 9:1391.
19. Tang H, Hammack C, Ogden SC, et al. Zika virus infects human cortical neural progenitors and attenuates their growth. Cell Stem Cell. 2016; 18(5):587-590.
20. Tebas P, Roberts CC, Muthumani K, et al. Safety and immunogenicity of an anti-Zika virus DNA vaccine - Preliminary Report. N Engl J Med. 2017; Oct. 4 [Epub ahead of print]. Available at: https://www.nejm.org/doi/suppl/10.1056/NEJMoa1708120/suppl_file/nejmoa1708120_preliminary.pdf. Accessed on May 10, 2023.
21. Tebas P, Roberts CC, Muthumani K, et al. Safety and immunogenicity of an anti-Zika virus DNA vaccine. N Engl J Med. 2021; 385(12):e35.

Government Agency, Medical Society, and Other Authoritative Publications:

1. Adebanjo T, Godfred-Cato S, Viens L, et al. Update: interim guidance for the diagnosis, evaluation, and management of infants with possible congenital zika virus infection — United States, October 2017. MMWR Morb Mortal Wkly Rep. 2017; 66:1089-1099. Available at: https://www.cdc.gov/mmwr/volumes/66/wr/mm6641a1.htm#suggestedcitation. Accessed on May 10, 2023.
2. Bingham AM, Cone M, Mock V, et al. Comparison of test results for Zika virus RNA in urine, serum, and saliva specimens from persons with travel-associated Zika virus disease -- Florida, 2016. MMWR Morb Mortal Wkly Rep. 2016; 65. Available at: http://www.cdc.gov/mmwr/volumes/65/wr/mm6518e2.htm. Accessed on May 10, 2023.
3. Centers for Disease Control (CDC). Dedicated web site for information about Zika Virus including approved laboratories designated for performing Zika testing by the CDC. Updated November 20, 2019. Available at: https://www.cdc.gov/zika/index.html. Accessed on June 9, 2022.
4. Centers for Disease Control (CDC). National Notifiable Diseases System (NNDSS). Zika Virus Disease and Zika Virus Infection 2016 Case Definition, Approved June 2016. Available at: https://ndc.services.cdc.gov/case-definitions/zika-virus-disease-and-zika-virus-infection-2016-06-01/. Page last reviewed: April 16, 2021. Accessed on May 10, 2023.
5. Centers for Disease Control (CDC). Sexual Transmission and Prevention. Last updated May 21, 2019. Available at: https://www.cdc.gov/zika/prevention/sexual-transmission-prevention.html. Accessed on May 10, 2023.
6. Centers for Disease Control (CDC). Testing Guidance. New zika and dengue testing guidance (Updated December 9, 2019). Available at: https://www.cdc.gov/zika/hc-providers/testing-guidance.html. Accessed on May 10, 2023.
7. Goodman AB, Dziuban EJ, Powell K, et al. Characteristics of Children Aged <18 Years with Zika Virus Disease Acquired Postnatally — U.S. States, January 2015–July 2016. MMWR Morb Mortal Wkly Rep. 2016; 65:1082-1085. Available at: https://www.cdc.gov/mmwr/volumes/65/wr/mm6539e2.htm?s_cid=mm6539e2_w#suggestedcitation. Accessed on May 10, 2023.
8. Hall V, Walker WL, Lindsey NP, et al. Update: Noncongenital Zika Virus Disease Cases — 50 U.S. States and the District of Columbia, 2016. MMWR Morb Mortal Wkly Rep. 2018; 67:265-269. Available at: https://www.cdc.gov/mmwr/volumes/67/wr/mm6709a1.htm?s_cid=mm6709a1_w#suggestedcitation. Accessed on May 10, 2023.
9. GeneOne Life Science, Inc., Inovio Pharmaceuticals. Study of GLS-5700 in healthy volunteers. NLM Identifier: NCT02809443. Last updated August 1, 2018. Available at: https://clinicaltrials.gov/ct2/show/NCT02809443. Accessed on May 10, 2023.
10. Oduyebo T, Igbinosa I, Petersen EE, et al. U.S. Morbidity and Mortality Weekly Report (MMWR). Update: Interim Guidance for Health Care Providers Caring for Pregnant Women with Possible Zika Virus Exposure — United States, July 2016. Morb Mortal Wkly Rep. 2016; 65:739-744. Available at: http://www.cdc.gov/mmwr/volumes/65/wr/mm6529e1.htm?s_cid=mm6529e1_e#suggestedcitation. Accessed on May 10, 2023.
11. Oduyebo T, Polen KD, Walke HT, et al. Update: Interim Guidance for Health Care Providers Caring for Pregnant Women with Possible Zika Virus Exposure — United States (Including U.S. Territories), July 2017. MMWR Morb Mortal Wkly Rep. 2017; 66:781-793. Available at: http://dx.doi.org/10.15585/mmwr.mm6629e1. Accessed on May 10, 2023.
12. Pan American Health Organization and World Health Organization. Zika virus (ZIKV) Surveillance in the Americas: Laboratory detection and diagnosis. Algorithms and recommendations. 2016.
13. Petersen EE, Meaney-Delman D, Neblett-Fanfair R, et al. Update: Interim Guidance for Preconception Counseling and Prevention of Sexual Transmission of Zika Virus for Persons with Possible Zika Virus Exposure — United States, September 2016. MMWR Morb Mortal Wkly Rep. 2016; 65:1077-1081. Available at: https://www.cdc.gov/mmwr/volumes/65/wr/mm6539e1.htm?s_cid=mm6539e1_w#suggestedcitation. Accessed on May 10, 2023.
14. Rabe IB, Staples JE, Villanueva J, et al. Interim Guidance for Interpretation of Zika Virus Antibody Test Results. U.S. Morbidity and Mortality Weekly Report (MMWR). Morb Mortal Wkly Rep. 2016; 65. Available at: http://www.cdc.gov/mmwr/volumes/65/wr/mm6521e1.htm. Accessed on May 10, 2023.
15. Sharp TM, Fischer M, Muñoz-Jordán JL, et al. Dengue and Zika virus diagnostic testing for patients with a clinically compatible illness and risk for infection with both viruses. MMWR Recomm Rep. 2019; 68(RR-1):1–10. Available at: https://www.cdc.gov/mmwr/volumes/68/rr/rr6801a1.htm?s_cid=rr6801a1_w. Accessed on May 10, 2023.

16. Staples JE, Dziuban EJ, Fischer M, et al. Interim guidelines for the evaluation and testing of infants with possible congenital zika virus infection — United States, 2016. MMWR Morb Mortal Wkly Rep. 2016; 65:63-67.
17. U.S. Food and Drug Administration (FDA). Emergency Use Authorizations (EUA) for an updated list of all diagnostic tests, serologic assays, vaccines under development and additional chronological information from the FDA. 2017. Available at: https://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMIssues/ucm485199.htm. Accessed on May 10, 2023.
18. U.S. Food and Drug Administration (FDA) Dept of Health and Human Services (HHS). Revised recommendations for reducing the risk of zika virus transmission by blood and blood components; guidance for industry. July 9, 2018. Available at: https://www.federalregister.gov/documents/2018/07/09/2018-14537/revised-recommendations-for-reducing-the-risk-of-zika-virus-transmission-by-blood-and-blood. Accessed on May 10, 2023.
19. U.S. Morbidity and Mortality Weekly Report (MMWR). Interim guidance for Zika virus testing of urine. MMWR updated May 10, 2016. Morb Mortal Wkly Rep. 2016; 65:484. Available at: http://www.cdc.gov/mmwr/volumes/65/wr/mm6518e1.htm. Accessed on May 10, 2023.
20. U.S. Morbidity and Mortality Weekly Report (MMWR). Erratum: MMWR. Morb Mortal Wkly Rep. 2016; 65(18):484. Available at: http://www.cdc.gov/mmwr/volumes/65/wr/mm6518a10.htm. Accessed on May 10, 2023.
21. U.S. Morbidity and Mortality Weekly Report (MMWR). Transmission of Zika virus through sexual contact with travelers to areas of ongoing transmission — continental United States, 2016. Morb Mortal Wkly Rep. 2016; 65:215-216.
22. World Health Organization (WHO). Zika Virus Outbreak Toolbox. Updated September 2019. Available at: https://www.who.int/emergencies/outbreak-toolkit/disease-outbreak-toolboxes/zika-outbreak-toolbox. Accessed on June 9, 2022.

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ADVIA Centaur Zika IgM

Aptima® Zika Virus Assay, Hologic Inc.

Baebies Seeker™ Analyzer, Baebies, Inc.

DPP® Zika IgM System
GLS-5700, Vaccine
IgM

LightMix® Zika rRT-PCR Test, Roche Molecular Systems Inc.
NAT (cobas Zika nucleic acid test), Roche Molecular Systems, Inc.
PRNT, Testing
PROCLEIX, Hologic Inc., Grifols

RealStar® Zika Virus RT-PCR Kit, Altona Diagnostics
rRT/PCR, Assay

Sentosa® SA ZIKV RT-PCR, Vela Diagnostics USA, Inc.
Trioplex, rRT/PCR Test

VERSANT® Zika RNA 1.0 Assay (kPCR), Siemens Healthcare Diagnostics, Inc.

ZIKV Detect™ IgM Capture ELISA, InBios International, Inc.
Zika MAC-ELISA, CDC
Zika Virus Real-Time RT-PCR, Viracor-IBT Laboratories, Inc.
Zika Virus RNA Qualitative Real-Time RT-PCR Test, Focus Diagnostics
Zika Virus Detection by RT-PCR, ARUP Laboratories

ZIKV Detect™ 2.0 IgM Capture ELISA

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

History

Status	Date	Action
Reviewed	08/10/2023	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated Discussion/General Information, References and Index sections.
Reviewed	08/11/2022	MPTAC review. Updated Discussion/General Information, Definitions and References sections.
Reviewed	08/12/2021	MPTAC review. Updated Discussion/General Information and References sections.
Reviewed	08/13/2020	MPTAC review. Updated Background and References sections. Reformatted Coding section.
Reviewed	08/22/2019	MPTAC review. The Discussion and References sections were updated.
Reviewed	09/13/2018	MPTAC review. The Discussion and References sections were updated.
Revised	11/02/2017	MPTAC review. The document header wording was updated from “Current Effective Date” to “Publish Date.” The criteria for ZIKV testing were revised to clarify and align with updated CDC guidance regarding testing. The Discussion, References and Index sections were updated. Updated Coding section with 01/01/2018 CPT changes, removed NOC codes 86790, 87798.
	03/28/2017	Added the new VERSANT Zika RNA 1.0 assay test kit to the Index section.
New	12/15/2016	MPTAC review. Initial document development. Moved content of LAB.00032 Zika Virus Testing to new clinical utilization management guideline document with the same title.

Alternatively, commercial or FEP plans or lines of business which determine there is not a need to adopt the guideline to review services generally across all providers delivering services to Plan's or line of business's members may instead use the clinical guideline for provider education and/or to review the medical necessity of services for any provider who has been notified that his/her/its claims will be reviewed for medical necessity due to billing practices or claims that are not consistent with other providers, in terms of frequency or in some other manner.