

**Questions and Answers for laboratory directors and scientists
reporting results of GC/CT NAAT tests**

There have been inquiries following the distribution of the CDC Dear Colleague letter on August 18, 2010. The following questions and answers have been formulated by CDC to share with all interested parties, and were developed in consultation with APHL, FDA, and CMS.

Q. What were the specific concerns addressed by the CDC Dear Colleague letter?

The August 18, 2010 letter from Dr. Fenton, Director of CDC's National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention, to laboratory directors addressed CDC concerns that arose from knowledge that some laboratories are routinely retesting positive specimens that are close to the positive cutoff (i.e., low positive) on commercially available chlamydia and gonorrhea nucleic acid amplification tests (NAATs) and reporting them as negative if the repeat test is found to be negative. The intent of the advisory was to clarify how laboratories should report test results, rather than laboratories' testing procedures. This concern relates only to those laboratories that are not following manufacturer instructions and have not validated their changes to the instructions.

The letter requested that Laboratory Directors review their procedures and affirm appropriate diagnostic results by following manufacturers' instructions or using verified modifications to the product insert. The letter was not intended to circumvent Laboratory Directors' professional judgment when repeat testing is performed as a result of suspicion that a run was not valid, or when discrepant test results are reported as "indeterminate", "equivocal", "inconclusive", or a similar reporting terminology that indicates doubt about interpretation.

Q. How should laboratories report discrepant results from routinely retested specimens?

In the event of discrepancy in results when specimens are retested, both results should be reported to the clinician who ordered the test, along with an overall interpretation of "indeterminate" or "equivocal". This would allow a clinical decision to be made to either treat the index case and to inform partner(s); or to obtain a second specimen for testing, depending on such factors as individual risk and local population prevalence. This approach is a minor clarification of the most recent guidance provided by CDC in the 2002 document "*Screening Tests to Detect Chlamydia trachomatis and Neisseria gonorrhoeae Infections*"¹ namely:

"...All positive screening tests should be considered presumptive evidence of infection....When additional testing has been performed, the laboratory should report the results of both the screening test and the additional tests, as well as the overall interpretation[sic 'of "indeterminate" or "equivocal"']. The laboratory has the responsibility to educate clinicians regarding the importance of all laboratory results, including both screening and additional test results. In particular, clinicians need to be aware of the limitations of the additional tests, including the possibility that they yield false-negative results when the screening test is positive. Because serious side effects from therapies for C. trachomatis and N. gonorrhoeae are uncommon, clinicians might recommend treatment after a positive screening test for a

person at risk for infection, pending additional testing or even when a positive screening test is not verified by additional testing.”

Q. Does the CDC believe that the performance characteristics of NAATs for GC/CT are sub-optimal?

No, this specific concern relates to how the test results are interpreted and reported and not the quality and accuracy of the FDA-cleared, commercially available diagnostic tests. CDC believes that NAATs are the most sensitive and specific tests available for the detection of *C. trachomatis* and *N. gonorrhoeae* infections and has actively promoted the use of these tests in screening for these infections – particularly in young, sexually active women to prevent the sequelae caused by these organisms – namely pelvic inflammatory disease (which is frequently asymptomatic) and tubal infertility.

Q. Why isn't CDC more concerned about the potential for false positive results with these tests?

Routinely retesting low-positive specimens may reduce false positives, but reporting them as 'negative' if the retest result is negative will increase false negatives. Clearly, 'false positive' results can cause undue patient anxiety and disruption to close relationships. However, false negative tests will result in failure to treat infections that could progress to serious health problems such as asymptomatic PID and infertility and allow further spread of these infections. Only by accurately following the manufacturer's instructions in FDA-cleared assays or by using documented performance data or other verified diagnostic algorithm, can the appropriate balance of test accuracy and predictive value be best achieved. NAATs provide qualitative results and their respective signal values cannot be used to judge organism load. Therefore, positive test results close to the positive cutoff of the assay cannot be assumed to be a low-grade infection that will spontaneously clear any more frequently than any other positive result.

Q. Why is CDC recommending that health-care providers be notified of test results that could have been misinterpreted during the past 2 years?

The recommendation applies only to laboratories that modified manufactures' instructions for retesting specimens and did not complete a verification study for the modified procedure. The recommendation to go back two years is based on two studies. In one, approximately 18% of asymptomatic women with untreated chlamydial infection remained infected two years later.² The other demonstrated that treatment can prevent PID; 7 of 74 women with untreated chlamydial infection (9.5%) developed symptomatic PID in the year following detection of the infection.³ In a recently documented two year lookback study after repeat *C. trachomatis* testing was done and discordant results were reported as negative, 5 of 49 persons notified and subsequently retested were positive for *C. trachomatis* (recognizing some may have acquired new infections).⁴ Therefore, it is imperative for laboratorians to inform clinicians, who can

reach patients, offer them an opportunity to be retested and for those who may be unknowingly infected with chlamydia, give them treatment that can ultimately cure the infection and prevent serious related health consequences.

Q. When will CDC update the 2002 screening guidelines with more specific information on chlamydia and gonorrhea testing procedures?

In January 2009, a consultation was held to discuss recommendations for updated guidance. New CDC Laboratory Guidelines for the Laboratory Diagnosis of Sexually Transmitted Diseases are currently being drafted, and we plan to publish these guidelines in early 2011.

If you have any questions or comments, please contact Tom Peterman, MD, MSc, Acting Chief, Epidemiology and Surveillance Branch, Division of STD Prevention, CDC via E-mail (tap1@cdc.gov) or telephone (404-639-6102).

References:

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