NEW YORK
state department of
HEALTH

Nirav R. Shah, M.D., M.P.H.
Commissioner

Sue Kelly
Executive Deputy Commissioner

May 16, 2013

Re: Interim Guidelines for Laboratories on the use of a new Diagnostic Testing Algorithm for Human Immunodeficiency Virus (HIV) Infection

Dear Laboratory Director and Management Staff:

The purpose of this letter is to provide information to New York State (NYS) Permitted Clinical Laboratories regarding a new laboratory testing algorithm for the diagnosis of HIV infection. This new algorithm, presented in Clinical Laboratory Standards Institute (CLSI) guideline document M53-A entitled *"Criteria for Laboratory Testing and Diagnosis of Human Immunodeficiency Virus Infection"* as 'Algorithm I', will be referred to as the 'HIV Diagnostic Testing Algorithm' throughout these interim guidelines[1].

The HIV Diagnostic Testing Algorithm offers several advantages over the conventional strategy of HIV antibody screening followed by Western blot confirmation of preliminary positive results, including earlier and more accurate detection of HIV infections and the ability to differentiate between HIV-1 and HIV-2 infections[2]. The performance of this algorithm has been verified through scientific studies[3], and recommendations from the Centers for Disease Control and Prevention (CDC) for use of this new HIV testing algorithm are anticipated. However, while awaiting CDC recommendations, the New York State Department of Health (NYSDOH) has elected to provide interim guidance to NYS-permitted laboratories. These guidelines are intended to provide clarification on the test methods that are suitable for the new algorithm and guidance on how to report test results to health care providers and to the NYSDOH to meet public health reporting requirements.

Four attachments accompany this letter.

- Attachment 1 The HIV Diagnostic Testing Algorithm
- Attachment 2 FDA-approved Test Methods Applicable to the HIV Diagnostic Testing Algorithm
- Attachment 3 Guidance for Reporting Results from the HIV Diagnostic Testing Algorithm to Health Care Providers and to the NYSDOH
- Attachment 4 New York State Reportable HIV Related Tests

A. <u>Description of the test methods for the HIV Diagnostic Testing Algorithm</u>

A flowchart and step-by-step description of the HIV Diagnostic Testing Algorithm is shown in **Attachment 1**. This algorithm differs significantly from the conventional Western blot strategy which relies on the result of a single confirmatory test for the final interpretation. The HIV Diagnostic Testing Algorithm is a multi-test algorithm and the final interpretation is based on a combination of results from two or more tests. The tests that may be used in this algorithm must be approved with the stated intended use for aiding in the diagnosis of HIV infection by the Food and Drug Administration (FDA) or by the NYSDOH Clinical Laboratory Evaluation Program (CLEP) and must meet additional criteria specific to each step of the algorithm. Currently available FDA-approved tests that meet the specific criteria for each step of the HIV Diagnostic Testing Algorithm are provided in **Attachment 2**.

The algorithm begins with an HIV-1/2 immunoassay capable of detecting HIV antigens (Ag) and antibodies (Ab), commonly referred to as an Ag/Ab combo or 4th generation immunoassay. An HIV-1/2 Ag/Ab combo immunoassay is preferred for the initial test because this technology can detect HIV-1 during the acute stage as well as chronic stages of infection. An HIV-1/2 immunoassay with IgM and IgG antibody detection capability (i.e. 3rd generation) is also currently acceptable as the initial test for this algorithm, but 3rd generation immunoassays will not detect HIV-1 infection in the very early stage of infection. When the 4th generation (or 3rd generation) test result is 'Reactive' this is considered to be a preliminary positive result and a specific sequence of supplemental tests is indicated for confirmation.

B. <u>Settings in which the HIV Diagnostic Testing Algorithm may be used</u>

The tests that may be used at each step of the HIV Diagnostic Testing Algorithm (Attachment 2) must be performed at a clinical laboratory holding a NYS Clinical Laboratory permit in the appropriate categories and must begin with a laboratory-based 4th (or 3rd) generation HIV-1/2 immunoassay. There are also several FDA-approved rapid test kits which may be used for HIV antibody screening[4]. These include rapid tests that have been waived by the FDA under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and may be performed at facilities with a Limited Service Laboratory Registration. All preliminary positive HIV rapid test results require additional testing for confirmation. Permitted Clinical Laboratories may use the HIV Diagnostic Testing Algorithm for rapid test confirmation; however, the laboratory must begin testing the specimen at step 1 using a 4th (or 3rd) generation HIV-1/2 immunoassay*. If this test is non-reactive, no further testing is required and the rapid test result is considered a false positive. If the 4th (or 3rd) generation HIV-1/2 immunoassay is reactive, the laboratory should continue to step 2 and, if needed, step 3 of the algorithm to obtain a final result.

*Note: It is currently acceptable to use a 3rd generation immunoassay in step 1 when confirming a rapid test result because the currently available rapid tests are less sensitive than the 3rd generation, laboratory-based immunoassays. However, a 4th generation immunoassay is preferred for this step to avoid the possibility of a false-negative result, especially if more sensitive rapid tests become available.

Laboratories may continue to confirm reactive rapid test results using a FDA-approved Western blot; however it should be noted that the HIV-1 Western blot tests are less sensitive than most available HIV screening tests. Therefore, if the Western blot result is negative or indeterminate, an HIV-1 RNA test should be performed on the specimen to resolve the discrepancy. If it is not possible to perform the HIV-1 RNA test directly, the test report should include a statement recommending collection of a specimen for HIV-1 RNA testing as soon as possible.

C. <u>Guidance on reporting test results to health care providers</u>

The HIV Diagnostic Testing Algorithm includes combinations of HIV test results that may be unfamiliar to health care providers. Therefore, in addition to the results of all tests, the laboratory report that is returned to the ordering clinician should include a final interpretation statement and, when appropriate, recommendations for follow-up testing. A list of the different combinations of test results and the recommended interpretation statements is provided in **Attachment 3**. The test results and interpretations in **Attachment 3** are based on initial testing with a 4th generation HIV-1/2 Ag/Ab combo immunoassay. Minor modifications should be applied if the initial test in the algorithm is a 3rd generation HIV-1/2 immunoassay. The CLEP Laboratory Standards of Practice for reporting preliminary positive HIV test results to providers (Diagnostic Immunology standard DI S5) in accordance with NYSDOH regulation section 58-8.4 remains in effect and applies to a preliminary positive result obtained from the test performed at step 1 of the algorithm.

D. Instructions for reporting HIV test results to the NYSDOH via the Electronic Clinical Laboratory Reporting System (ECLRS) for public health reporting

All laboratories conducting HIV-related testing on NYS residents and/or for NYS clinicians are required by regulation to electronically report to the NYSDOH any laboratory test, tests or series of tests approved for the diagnosis of HIV or for the periodic monitoring of HIV infection along with complete patient identifiers and address. The requirements to submit test results from all confirmed positive HIV antibody tests, all HIV nucleic acid (RNA and DNA) detection tests (qualitative and quantitative), all CD4 lymphocyte values and all HIV genotypic sequences continue to be in effect (**Attachment 4**). In addition, optimal public health intervention will depend on reporting specific combinations of test results from the HIV Diagnostic Testing Algorithm via ECLRS (**Attachment 3**). To meet public health reporting requirements for the HIV Diagnostic Testing Algorithm, the initial HIV-1/2 immunoassay result and all supplemental test results must be reported for any specimen with a final outcome of HIV positive or any specimen with an unresolved status. The test results that must be reported via ECLRS for different testing scenarios are listed in **Attachment 3**.

The testing laboratory is responsible for submitting the reportable test results to the NYSDOH electronically using ECLRS. Because of the reporting requirements imposed by this algorithm, some laboratories that did not previously report HIV test results to the NYSDOH may need to implement laboratory reporting. For example, results from EIA/CIA tests were not previously reportable, but now must be reported to the NYSDOH in specific circumstances. To assist laboratories with identifying appropriate Logical Observation Identifiers Names and Codes (LOINC) codes for laboratory reporting of these test results, a list of preferred LOINC codes is included in **Attachment 2**. Additional information regarding LOINC codes can be accessed at http://loinc.org.

Questions regarding the new HIV diagnostic testing algorithm may be directed to the NYSDOH by email to hivtesting@health.state.ny.us.

Questions regarding ECLRS reporting of HIV-related results should be directed to the Bureau of HIV/AIDS Epidemiology at 518-474-4284 or by email to BHAELab@health.state.ny.us.

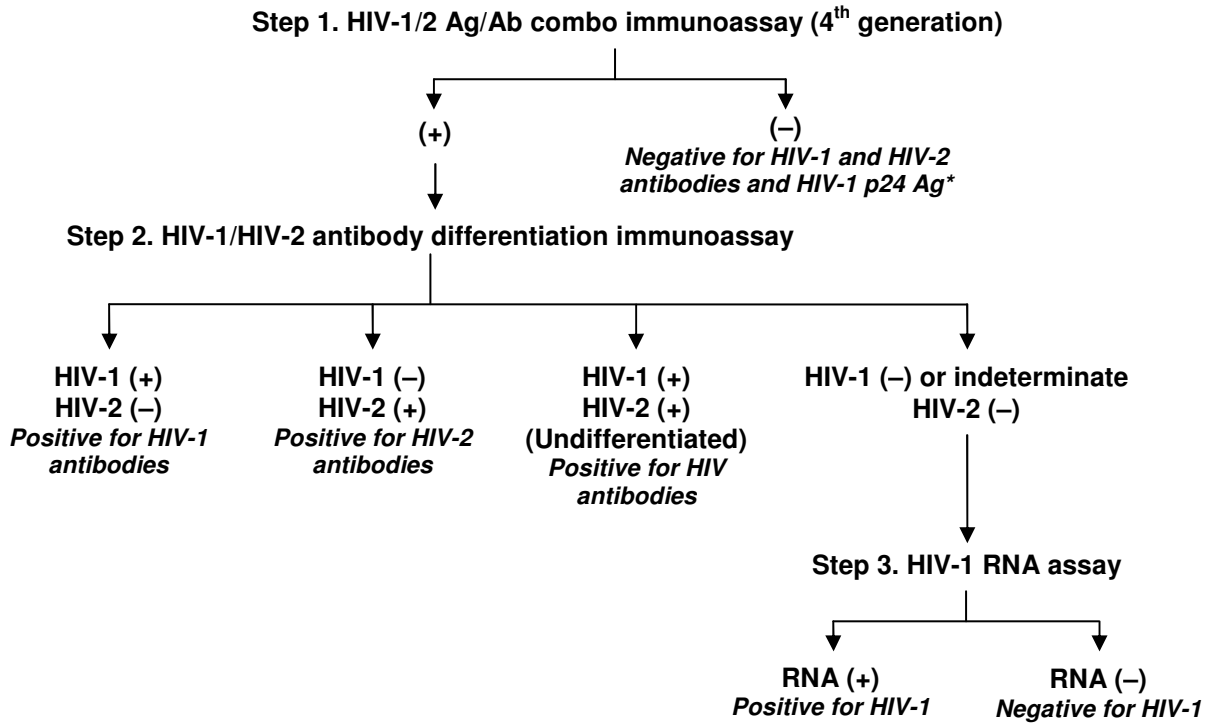
Sincerely,

Stephanie H. Shulman, M.P.H., M.S., M.T. (ASCP)
Director
Clinical Laboratory Evaluation Program
Wadsworth Center

Monica M. Parker, Ph.D.
Director
Bloodborne Viruses Laboratory
Wadsworth Center

References

1. CLSI. Criteria for Laboratory Testing and Diagnosis of Human Immunodeficiency Virus Infection; Approved Guideline. CLSI Document M-53A, 2011.
2. Branson, BM. The Future of HIV Testing. J Acquir Immune Defic Syndr 2010;55:S102-S105.
3. Update on HIV Diagnostic Testing Algorithms. Journal of Clinical Virology Vol 52, Supplement 1, pp. S1-S90
4. Diagnostic, Monitoring, and Resistance Laboratory Tests for HIV; http://www.hivguidelines.org/clinical-guidelines/adults/diagnostic-monitoring-and-resistance-laboratory-tests-for-hiv



(+) = Reactive (or repeatedly reactive) test result, in accordance with manufacturer's instructions
(–) = Nonreactive test result, in accordance with manufacturer's instructions
Italics = Final interpretation; No further testing indicated for the specimen
*For 3rd generation HIV-1/2 immunoassay, interpretation is 'Negative for HIV-1 and HIV-2 antibodies'.

Step 1. 4th generation HIV-1/2 Ag/Ab combo immunoassay (preferred) or 3rd generation HIV-1/2 immunoassay (acceptable). If the result from this test is 'Nonreactive', no further testing of the specimen is indicated. If the result is 'Reactive', this is considered to be a preliminary positive result and supplemental testing must be performed, beginning with an HIV-1/HIV-2 antibody differentiation immunoassay (step 2).

Step 2. HIV-1/HIV-2 antibody differentiation immunoassay. If the initial HIV-1/2 immunoassay (step 1) was reactive and the result of HIV-1/HIV-2 antibody differentiation immunoassay is 'Reactive' for HIV-1 or HIV-2 antibodies, the interpretation is 'Positive for HIV-1 antibodies' or 'Positive for HIV-2 antibodies', respectively. No further testing of the specimen is required and medical care is recommended. If the result is 'Reactive' for both HIV-1 and HIV-2 antibodies (i.e. HIV Positive, Undifferentiated), the interpretation is 'Positive for HIV antibodies' and medical care is recommended. Additional testing for HIV-1 RNA and HIV-2 RNA or DNA is recommended at the initial clinical evaluation to verify or rule-out HIV-1/HIV-2 dual infection. If the result of the HIV-1/HIV-2 antibody differentiation test is 'Nonreactive' or 'Indeterminate', testing of the specimen should reflex to an HIV-1 RNA assay (step 3).

Step 3. HIV-1 RNA assay. If the initial HIV-1/2 immunoassay (step 1) was reactive and HIV-1 RNA is detected, the final interpretation is 'Positive for HIV-1' and medical care should be initiated. If HIV-1 RNA is not detected, the final interpretation is 'Negative for HIV-1'. The initial HIV-1/2 immunoassay result was most likely a false positive. If there is reason to suspect recent HIV-2 infection, follow-up testing for HIV-2 RNA or DNA should be considered.

FDA-Approved Test Methods Applicable to the HIV Diagnostic Testing Algorithm

Clinical laboratories must adhere to the manufacturer's specifications for all tests that have been approved by the FDA. Any modification to the manufacturer's package insert must be validated, and validation data for the modification must be submitted to the NYSDOH Clinical Laboratory Evaluation Program (CLEP) for approval prior to use on clinical specimens.

As of May 16, 2013, the following test kits have been approved by the FDA to aid in the diagnosis of HIV infection and meet the criteria specified for each step of the HIV Diagnostic Testing Algorithm. The Department's preferred LOINC codes for reporting test results in the Electronic Clinical Laboratory Reporting System (ECLRS) are listed. Updates to this table will be posted on http://www.health.ny.gov/diseases/aids/regulations and http://www.wadsworth.org/labcert/clep/clep.html.

Test Kit Name	Test Manufacturer	Preferred LOINC
Step 1. HIV-1/HIV-2 Ag/Ab combo immunoassay (4th Generation)		
Abbott Architect HIV Ag/Ab Combo Assay	Abbott Laboratories	56888-1
GS HIV Ag/Ab Combo EIA	Bio-Rad Laboratories	56888-1
Step 1. HIV-1/HIV-2 immunoassay (3rd Generation)		
Abbott PRISM HIV O Plus Assay	Abbott Laboratories	48345-3, 57975-5
ADVIA Centaur HIV 1/O/2 Enhanced Assay	Siemens Healthcare Diagnostics	48345-3, 57975-5
GS HIV-1/HIV-2 + O EIA	Bio-Rad Laboratories	48345-3, 57975-5
Ortho Vitros Anti HIV 1+2	Ortho-Clinical Diagnostics	31201-7
Step 2. HIV-1/HIV-2 antibody differentiation immunoassay		
Multispot HIV-1/HIV-2 Rapid Immunoassay[1]	Bio-Rad Laboratories	69668-2
Step 3. HIV-1 RNA assay[2]		
Aptima HIV-1 RNA Qualitative Assay	Hologic Gen-Probe	5018-7, 5017-9, 25835-0

[1] The Multispot test was originally approved by the FDA in 2004 as a laboratory rapid test to detect and differentiate antibodies to HIV-1 and HIV-2. The manufacturer has received approval from the FDA for a modification to the package insert that includes instructions for use of the Multispot test in the HIV Diagnostic Testing Algorithm. Consult the package insert for detailed instructions on use of the test.

[2] The currently available FDA-approved quantitative HIV-1 RNA tests (i.e. viral load tests) are not labeled for diagnostic use.

Note: There are no FDA-approved HIV-2 RNA or DNA tests currently available. A laboratory-developed HIV-2 RNA test that has been approved for diagnostic use is available at the NYSDOH Wadsworth Center. **If HIV-2 RNA testing is warranted, contact the Wadsworth Center at (518) 474-2163.**

Guidance for Reporting Results from the HIV Diagnostic Testing Algorithm to Health Care Providers and to the NYSDOH

	Test Method	Test Result	Final Interpretations for the Provider Report	Test Results to be Reported to NYSDOH via ECLRS
A	1. HIV-1/2 Ag/Ab combo immunoassay	1. Nonreactive	Negative for HIV-1 antigen and HIV-1/HIV-2 antibodies. No laboratory evidence of HIV infection.	Reporting of this test result via ECLRS is NOT required.
B	1. HIV-1/2 Ag/Ab combo immunoassay 2. HIV-1/HIV-2 antibody differentiation immunoassay	1. Reactive 2. HIV-1 Positive	Positive for HIV-1 antibodies. Laboratory evidence of HIV-1 infection is present. *Add provider case reporting statement**	Report test results 1 and 2 to NYSDOH via ECLRS.
C	1. HIV-1/2 Ag/Ab combo immunoassay 2. HIV-1/HIV-2 antibody differentiation immunoassay	1. Reactive 2. HIV-2 Positive	Positive for HIV-2 antibodies. Laboratory evidence of HIV-2 infection is present. *Add provider case reporting statement**	Report test results 1 and 2 to NYSDOH via ECLRS
D	1. HIV-1/2 Ag/Ab combo immunoassay 2. HIV-1/HIV-2 antibody differentiation immunoassay 3. HIV-1 RNA assay	1. Reactive 2. Nonreactive or Indeterminate 3. Not detected	HIV antibodies were not confirmed and HIV-1 RNA was not detected. No laboratory evidence of HIV-1 infection. Further testing is recommended if warranted by clinical evaluation or risk factors.	Report test result 3 to NYSDOH via ECLRS
E	1. HIV-1/2 Ag/Ab combo immunoassay 2. HIV-1/HIV-2 antibody differentiation immunoassay 3. HIV-1 RNA assay	1. Reactive 2. Nonreactive or Indeterminate 3. Detected	Positive for HIV-1. Laboratory evidence of HIV acute HIV-1 infection is present. *Add provider case reporting statement**	Report test results 1, 2 and 3 to NYSDOH via ECLRS
F	1. HIV-1/2 Ag/Ab combo immunoassay 2. HIV-1/HIV-2 antibody differentiation immunoassay	1. Reactive 2. HIV Positive (Undifferentiated)	Positive for HIV antibodies. Laboratory evidence of HIV infection is present. HIV antibodies could not be differentiated as HIV-1 or HIV-2. Additional testing for HIV-1 RNA and HIV-2 RNA or DNA is warranted. *Add provider case reporting statement**	Report test results 1 and 2 to NYSDOH via ECLRS
G	1. HIV-1/2 Ag/Ab combo immunoassay 2. HIV-1/HIV-2 antibody differentiation immunoassay	1. Reactive 2. Nonreactive or Indeterminate	HIV-1 antibodies were not confirmed and HIV-1 RNA testing was not performed. Testing of this specimen is incomplete. Follow-up testing for HIV antibodies and HIV-1 RNA is recommended as soon as possible.	Report test results 1 and 2 to NYSDOH via ECLRS

**Provider case reporting statement*: Under public health law, medical providers are required to report to the NYSDOH cases of HIV infection, HIV-related illness, AIDS and, for newly diagnosed cases, the names of all contacts known to the provider. Please contact the NYSDOH at (518) 474-4284 for additional information and reporting forms.

Attachment 4

Guidance to Facilitate the Public Health Reporting of HIV-related Laboratory Tests to New York State Department of Health (NYSDOH)

New York State Reportable HIV Related Tests:

As of September 1, 2010, laboratories, blood and tissue banks conducting HIV-related testing on New York residents and/or for New York State clinicians (regardless of patient residence) are required by regulation to electronically report to the NYSDOH any laboratory test, tests or series of tests approved for the diagnosis of HIV or for the periodic monitoring of HIV infection with complete patient identifiers and address.

The following results or combination of results are to be reported to the NYSDOH via the Electronic Clinical Laboratory Reporting System (ECLRS):

(1) All initial and supplemental test results of the multi-test algorithm (sensitive HIV-1/2 immunoassay followed by HIV-1/HIV-2 antibody differentiation immunoassay) for HIV detection, unless the multi-test algorithm resolves to negative[1];
(2) positive or indeterminate HIV Western Blot (WB) or Immunofluorescent Assay (IFA) tests[1];
(3) positive HIV detection tests (culture, P24 antigen);
(4) all HIV nucleic acid tests (NAT) for RNA or DNA detection (qualitative and quantitative), including tests on individual specimens for confirmation of NAT screening;
(5) all CD4 lymphocyte counts and percentages, unless known to be ordered for a condition other than HIV illness;
(6) HIV subtype and antiviral resistance. This reporting requirement can be met with the electronic submission of the protease, reverse transcriptase and integrase nucleotide sequence determined through genotypic resistance testing.

All HIV related reporting, including New York City, is directly to the New York State Department of Health. For questions regarding HIV reporting please call (518) 474-4284.

[1] Residuals from the original HIV-1 antibody positive diagnostic test specimen should be submitted for HIV incidence surveillance testing. Please contact the HIV Incidence Coordinator at (518) 474-4284 in the Bureau of HIV/AIDS Epidemiology to arrange for specimen transfer to the appropriate laboratory.

New York State HIV/AIDS Data Elements:

The federal funding available for care and monitoring of persons with HIV/AIDS is directly impacted by the surveillance case counts created by laboratory reports. CDC case confirmation and eligibility are dependent on the complete and accurate submission of the following variables in addition to the laboratory test result and ordering physician information that you submit.

For case confirmation, surveillance records must contain a known value for the following:
Patient name
Date of birth
Sex
Race and ethnicity[2]
Patient residence at time of test

We appreciate your attention to the submission of these crucial identifying and demographic variables. If you are aware of specific providers or clients who are delinquent in providing you these critical variables for NYS reporting, please contact us for assistance. The ECLRS manual is a resource outlining a complete listing of all required, critical and preferred data elements and the appropriate formatting of each data element.

[2] NB: Race and ethnicity are distinct concepts and should be ascertained separately at intake and reported as distinct variables via ECLRS.

Attachment 4

OMB RACE AND ETHNICITY FEDERAL REPORTING GUIDELINES

RACE AND ETHNICITY STANDARDS FOR FEDERAL STATISTICS AND ADMINISTRATIVE REPORTING (as adopted on May 12, 1977)

This Directive provides standard classifications for record keeping, collection, and presentation of data on race and ethnicity in Federal program administrative reporting and statistical activities.

The standards have five categories for data on race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, and White. There are two categories for data on ethnicity: "Hispanic or Latino," and "Not Hispanic or Latino."

Categories and Definitions

The minimum categories for data on race and ethnicity for Federal statistics, program administrative reporting, and civil rights compliance reporting are defined as follows:

Race:

- **American Indian or Alaska Native.** A person having origins in any of the original peoples of North and South America (including Central America), and who maintains tribal affiliation or community attachment. **Report to ECLRS as race=I**[3]
- **Asian.** A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. **Report to ECLRS as race=A**[3]
- **Black or African American.** A person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American." **Report to ECLRS as race=B**[3]
- **Native Hawaiian or Other Pacific Islander.** A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands. **Report to ECLRS as race=P**[3]
- **White.** A person having origins in any of the original peoples of Europe, the Middle East, or North Africa. **Report to ECLRS as race=W**[3]

Ethnicity:

- **Hispanic or Latino.** A person of Cuban, Mexican, Puerto Rican, Cuban, South or Central American, or other Spanish culture or origin, regardless of race. The term, "Spanish origin," can be used in addition to "Hispanic or Latino." **Report to ECLRS as ethnicity=H**[3]
- **Not Hispanic.** A person of not of Hispanic origin. **Report to ECLRS as ethnicity=N**[3]

Respondents shall be offered the option of selecting one or more racial designations. Recommended forms for the instruction accompanying the multiple response question are "Mark one or more" and "Select one or more."

For additional information, please see: http://www.whitehouse.gov/omb/fedreg/directive_15.html

[3] New York State Electronic Clinical Laboratory Reporting System (ECLRS). Use these codes if reporting to ECLRS via file transfer.