



December 9, 2009

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Dear Dr. Rosenfeld:

This letter is in response to your request that the Food and Drug Administration (FDA) issue an Emergency Use Authorization (EUA) for emergency use of the GeneSTAT 2009 A/H1N1 Influenza Test for the diagnosis of 2009 H1N1 influenza virus infection in patients with signs and symptoms of respiratory infection, pursuant to section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. §360bbb-3), by CLIA High Complexity Laboratories, which are laboratories certified under the Clinical Laboratory Improvement Amendments of 1988, 42 U.S.C. §263a, to perform high complexity tests.

On April 26, 2009, pursuant to section 564(b)(1)(C) of the Act (21 U.S.C. §360bbb-3(b)(1)(C)), the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency under 42 U.S.C. §247d that affects, or has a significant potential to affect, national security, and that involves a specified biological, chemical, radiological, or nuclear agent or agents, or a specified disease or condition that may be attributable to such an agent or agents - in this case, 2009 H1N1 influenza virus.¹ Pursuant to section 564(b) of the Act (21 U.S.C. §360bbb-3(b)), and on the basis of such determination, the Secretary of HHS then declared an emergency justifying the authorization of the emergency use of certain in vitro diagnostics for the detection of 2009 H1N1 influenza virus, subject to the terms of any authorization issued under 21 U.S.C. §360bbb-3(a).

Having concluded that the criteria for issuance of this authorization under section 564(c) of the Act (21 U.S.C. §360bbb-3(c)) are met, I am authorizing the emergency use of the GeneSTAT 2009 A/H1N1 Influenza Test (as described in the scope section of this letter (Section II)) for the diagnosis of 2009 H1N1 influenza virus infection in individuals with signs and symptoms of respiratory infection, subject to the terms of this authorization.

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of the GeneSTAT 2009 A/H1N1 Influenza Test for the diagnosis of 2009 H1N1 influenza virus infection in individuals with signs and symptoms of respiratory infection meets the criteria for issuance of an authorization under section 564(c) of the Act, because I have concluded that:

¹ Memorandum, Determination Pursuant to § 564 of the Federal Food, Drug, and Cosmetic Act (April 26, 2009).

1. The 2009 H1N1 influenza virus can cause influenza, a serious or life threatening disease or condition to humans infected by this virus;
2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that the GeneSTAT 2009 A/H1N1 Influenza Test may be effective for the diagnosis of 2009 H1N1 influenza virus infection, and that the known and potential benefits of the GeneSTAT 2009 A/H1N1 Influenza Test, when used in the diagnosis of 2009 H1N1 influenza virus infection, outweigh the known and potential risks of such product; and
3. There is no adequate, approved, and available alternative to the emergency use of the GeneSTAT 2009 A/H1N1 Influenza Test for the diagnosis of 2009 H1N1 influenza virus infection.²

II. Scope of Authorization

I have concluded, pursuant to section 564(d)(1) of the Act, that the scope of this authorization is limited to the use of the authorized GeneSTAT 2009 A/H1N1 Influenza Test for the diagnosis of 2009 H1N1 influenza virus infection in individuals with signs and symptoms of respiratory infection.

The Authorized GeneSTAT 2009 A/H1N1 Influenza Test:

The GeneSTAT 2009 A/H1N1 Influenza Test is a reverse-transcription polymerase chain reaction assay for the *in vitro* qualitative detection of 2009 H1N1 influenza viral RNA in nasopharyngeal swabs or nasal swabs from patients with signs and symptoms of respiratory infection. The GeneSTAT 2009 A/H1N1 Influenza Test is to be used in combination with the Roche High Pure RNA Isolation Kit and the GeneSTAT Analytical Platform. The assay is composed of two principal steps: (1) extraction of RNA from patient specimens, (2) one-step reverse transcription and PCR amplification using fluorogenic probes for detection.

The GeneSTAT 2009 A/H1N1 Influenza Test includes the following primer and probe sets:

- **H1:** a primer-probe set designed to detect the presence of the hemagglutinin gene specifically found in the 2009 H1N1 influenza A virus.
- **N1:** a primer-probe set designed to detect the presence of the neuraminidase gene specifically found in the 2009 H1N1 influenza A virus.
- **MA:** a primer-probe set designed to detect the presence of a well conserved region of the matrix gene found in both, seasonal human influenza A virus and 2009 H1N1 influenza A virus.
- **P28:** a primer-probe set designed to detect the presence of the Caprine Arthritis-Encephalitis Virus core polypeptide p28 gene (Exogenous Reaction Control).

The GeneSTAT 2009 A/H1N1 Influenza Test also includes the following control materials:

- **Influenza A Matrix-Positive Control Swab.**

² No other criteria of issuance have been prescribed by regulation under section 564(c)(4) of the Act.

- **H1-Positive Control Swab (2009 H1N1 specific).**

The GeneSTAT 2009 A/H1N1 Influenza Test requires the following hardware with corresponding software:

- GeneSTAT Analytical Platform.

The GeneSTAT 2009 A/H1N1 Influenza Test requires the use of the following additional reagents/materials:

- GeneSTAT H1N1 Test Module.
- GeneSTAT Sample Prep Vial.
- Roche High Pure RNA Isolation Kit.

The above described GeneSTAT 2009 A/H1N1 Influenza Test, when labeled consistently with the labeling authorized by FDA, entitled GeneSTAT™ 2009 A/H1N1 Influenza Test Package Insert, (see <http://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm>), as may be revised with written permission of FDA, is authorized to be distributed to CLIA High Complexity Laboratories under this EUA, despite the fact that it does not meet certain requirements otherwise required by federal law.

The above described GeneSTAT 2009 A/H1N1 Influenza Test is authorized to be accompanied by the following information pertaining to the emergency use, which is authorized to be made available to healthcare providers and patients:

- **Fact Sheet for Healthcare Providers: Interpreting GeneSTAT 2009 A/H1N1 Influenza Test Results**
- **Fact Sheet for Patients: Understanding the GeneSTAT 2009 A/H1N1 Influenza Test Results**

As described in section IV below, DxNA, LLC, is also authorized to make available additional information relating to the emergency use of the authorized GeneSTAT 2009 A/H1N1 Influenza Test that is consistent with, and does not exceed, the terms of this letter of authorization.

I have concluded, pursuant to section 564(d)(2) of the Act, that it is reasonable to believe that the known and potential benefits of the authorized GeneSTAT 2009 A/H1N1 Influenza Test in the specified population, when used for diagnosis of 2009 H1N1 influenza virus infection, outweigh the known and potential risks of such a product.

I have concluded, pursuant to section 564(d)(3) of the Act, based on the totality of scientific evidence available to FDA, that it is reasonable to believe that the authorized GeneSTAT 2009 A/H1N1 Influenza Test may be effective in the diagnosis of 2009 H1N1 influenza virus infection pursuant to section 564(c)(2)(A) of the Act. The FDA has reviewed the scientific information available including the information supporting the conclusions described in Section I above, and concludes that the authorized GeneSTAT 2009 A/H1N1 Influenza Test, when used to diagnose 2009 H1N1 influenza virus infection in the specified population, meets the criteria set forth in section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of the authorized GeneSTAT 2009 A/H1N1 Influenza Test under this EUA must be consistent with, and may not exceed, the terms of this letter, including the scope and the conditions of authorization set forth below. Subject to the terms of this EUA and under the circumstances set forth in the Secretary of HHS' determination under section 564(b)(1)(C) described above and the Secretary of HHS' corresponding declaration under section 564(b)(1), the GeneSTAT 2009 A/H1N1 Influenza Test described above is authorized to diagnose 2009 H1N1 influenza virus infection in individuals with signs and symptoms of respiratory infection.

This EUA will cease to be effective when the declaration of emergency is terminated under section 564(b)(2) of the Act or when the EUA is revoked under section 564(g) of the Act.

III. Waiver of Certain Requirements

I am waiving the following requirements for the GeneSTAT 2009 A/H1N1 Influenza Test during the duration of this emergency use authorization:

- Current good manufacturing practice requirements, including the quality system requirements under 21 CFR Part 820 with respect to the design, manufacture, packaging, labeling, storage, and distribution of the GeneSTAT 2009 A/H1N1 Influenza Test.
- Labeling requirements for cleared, approved, or investigational devices, including labeling requirements under 21 CFR 809.10 and 809.30, except for the intended use statement (21 CFR 809.10(a)(2), (b)(2)), adequate directions for use (21 U.S.C. 352(f)), (21 CFR 809.10(b)(5) and (8)), any appropriate limitations on the use of the device including information required under 21 CFR 809.10(a)(4), and any available information regarding performance of the device, including requirements under 21 CFR 809.10(b)(12).

IV. Conditions of Authorization

Pursuant to section 564 of the Act, I am establishing the following conditions on this authorization:

DxNA, LLC

- A. DxNA, LLC will distribute the authorized GeneSTAT 2009 A/H1N1 Influenza Test with the authorized labeling, as may be revised with written permission of FDA, only to CLIA High Complexity Laboratories.
- B. DxNA, LLC will provide to the CLIA High Complexity Laboratories the authorized GeneSTAT 2009 A/H1N1 Influenza Test Fact Sheets for Healthcare Providers and the authorized GeneSTAT 2009 A/H1N1 Influenza Test Fact Sheets for Patients.
- C. DxNA, LLC will make available on its website the authorized GeneSTAT 2009 A/H1N1 Influenza Test Fact Sheets for Healthcare Providers and the authorized GeneSTAT 2009 A/H1N1 Influenza Test Fact Sheets for Patients.
- D. DxNA, LLC will inform state and/or local public health authority(ies) of this EUA, including the terms and conditions herein.

- E. All advertising and promotional descriptive printed matter relating to the use of the authorized GeneSTAT 2009 A/H1N1 Influenza Test shall be consistent with the Fact Sheets and authorized labeling, as well as the terms set forth in this EUA and other requirements set forth in the Act and FDA regulations.
- F. All advertising and promotional descriptive printed matter relating to the use of the authorized GeneSTAT 2009 A/H1N1 Influenza Test shall clearly and conspicuously state that:
- This test has not been FDA cleared or approved;
 - This test has been authorized by FDA under an Emergency Use Authorization;
 - This test has been authorized only for the detection of 2009 H1N1 influenza virus and not for any other viruses or pathogens;
 - This test is only authorized for the duration of the declaration of emergency under section 564(b)(1) of the Act, 21 U.S.C. §360bbb-3(b)(1); and
 - The declaration of emergency will expire on April 26, 2010, unless it is terminated or revoked sooner or renewed.
- G. No advertising or promotional descriptive printed matter relating to the use of the authorized GeneSTAT 2009 A/H1N1 Influenza Test may represent or suggest that this test is safe or effective for the diagnosis of 2009 H1N1 influenza virus.
- H. DxNA, LLC will ensure that CLIA High Complexity Laboratories using the authorized GeneSTAT 2009 A/H1N1 Influenza Test have a process in place for reporting test results to healthcare providers and federal, state and/or local public health authorities, as appropriate.
- I. DxNA, LLC will track adverse events and report to FDA as required under 21 CFR part 803.
- J. Through a process of inventory control, DxNA, LLC will maintain records of device usage.
- K. DxNA, LLC will collect information on the performance of the assay and report to FDA any suspected occurrence of false positive or negative results of which DxNA, LLC becomes aware.

CLIA High Complexity Laboratories

- L. CLIA High Complexity Laboratories will include with reports of the results of the GeneSTAT 2009 A/H1N1 Influenza Test the authorized Fact Sheets for Healthcare Providers and the authorized Fact Sheets for Patients.

- M. CLIA High Complexity Laboratories will use the Roche High Pure RNA Isolation Kit for nucleic acid extraction and perform the assay on the GeneSTAT Analytical Platform, ensuring that at least once per day that specimens are to be tested, a known sample (2009 H1N1 positive or influenza A positive specimen) is tested as a positive control for RNA extraction and subsequent protocol steps.
- N. CLIA High Complexity Laboratories will have a process in place for reporting test results to healthcare providers and federal, state and/or local public health authorities, as appropriate.
- O. CLIA High Complexity Laboratories will collect information on the performance of the assay, and report to DxNA, LLC any suspected occurrence of false positive or false negative results of which CLIA High Complexity Laboratories become aware.

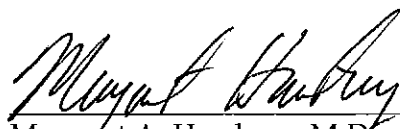
DxNA, LLC and CLIA High Complexity Laboratories

- P. DxNA, LLC is authorized to make available additional information relating to the emergency use of the authorized GeneSTAT 2009 A/H1N1 Influenza Test that is consistent with, and does not exceed, the terms of this letter of authorization.
- Q. Only DxNA, LLC may request changes to the authorized GeneSTAT 2009 A/H1N1 Influenza Test Fact Sheet for Healthcare Providers or the authorized GeneSTAT 2009 A/H1N1 Influenza Test Fact Sheet for Patients. Such requests will be made by contacting FDA concerning FDA review and approval.
- R. DxNA, LLC will ensure that any records associated with this EUA are maintained until notified by FDA. Such records will be made available to FDA for inspection upon request.

The emergency use of the authorized GeneSTAT 2009 A/H1N1 Influenza Test as described in this letter of authorization must comply with the conditions above and all other terms of this authorization.

V. Duration of Authorization

This EUA will be effective until the declaration of emergency is terminated under section 564(b)(2) of the Act or the EUA is revoked under section 564(g) of the Act.


Margaret A. Hamburg, M.D.
Commissioner of Food and Drugs

Fact Sheet for Healthcare Providers: Interpreting GeneSTAT 2009 A/H1N1 Influenza Test Results

December 9, 2009

A public health emergency has been declared by the Secretary of Health and Human Services because of the outbreak of the 2009 H1N1 influenza virus (previously referred to as swine influenza (H1N1) virus). This Fact Sheet will refer to the virus as 2009 H1N1 influenza virus. The Food and Drug Administration (FDA) has authorized the emergency use of the GeneSTAT 2009 A/H1N1 Influenza assay to test for the presence of the 2009 H1N1 influenza virus in clinical respiratory specimens. These specimens should be collected via nasopharyngeal swabs or nasal swabs from patients with signs and symptoms of respiratory infection. This authorization will terminate on April 26, 2010, when the emergency declaration is terminated (unless it is renewed), or when the authorization has been revoked, whichever is earlier. The information in this Fact Sheet is the minimum necessary to inform you of the significant known and potential risks and benefits of the emergency use of the GeneSTAT 2009 A/H1N1 Influenza Test.

At this time, there are no FDA-approved/cleared tests that identify the existence of the 2009 H1N1 influenza virus in clinical specimens. Previously, the FDA granted Emergency Use Authorization for other tests intended to diagnose 2009 H1N1 influenza virus, see <http://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm> for more information. To augment existing testing capacity, and to make available a faster, more portable test, the FDA has authorized the emergency use of the GeneSTAT 2009 A/H1N1 Influenza Test on the GeneSTAT Analytical Platform, to detect 2009 H1N1 influenza virus infection. Current information on 2009 H1N1 influenza virus, including case definitions and infection control guidelines, is available at <http://www.cdc.gov/h1n1flu/>. All information and guidelines, including those on testing for 2009 H1N1 influenza virus, may change as we continue to learn more about this disease. Please check CDC's 2009 H1N1 influenza virus website regularly for the most current information.

The GeneSTAT 2009 A/H1N1 Influenza Test should be ordered only to diagnose 2009 H1N1 influenza virus infection in patients with signs and symptoms of respiratory infection. This test is authorized for use with nasopharyngeal swabs and nasal swabs. Specimen collection should be conducted according to the manufacturer's instructions for the specimen collection device and sent to a qualified laboratory for analysis.

What does it mean if the specimen tests positive for the 2009 H1N1 influenza virus?

A positive test for 2009 H1N1 influenza virus using the GeneSTAT 2009 A/H1N1 Influenza Test indicates that the patient has been infected with the 2009 H1N1 influenza virus. The test does not indicate the stage of infection. Laboratory test results should always be considered in the context of clinical observations and epidemiologic data in making a final diagnosis. For guidelines on managing patients please refer to *Interim Guidance on Infection Control Measures for 2009 H1N1 Influenza in Healthcare Settings, Including Protection of Healthcare*

Personnel” and “Updated Interim Recommendations for the Use of Antiviral Medications in the Treatment and Prevention of Influenza for the 2009-2010 Season” at <http://www.cdc.gov/h1n1flu/guidance/>.

The GeneSTAT 2009 A/H1N1 Influenza Test for 2009 H1N1 influenza virus has been designed to minimize the likelihood of false positive test results. However, in the event of a false positive result, the risks to patients could include any or all of the following: recommendations to limit contact with uninfected persons (including at home or at the workplace), a prescription of antiviral medication or other therapy, the impaired ability to detect and receive appropriate medical care for the true infection causing the flu-like symptoms, or other unintended adverse effects.

What does it mean if the specimen tests negative for the 2009 H1N1 influenza virus?

Negative GeneSTAT 2009 A/H1N1 Influenza Test results do not preclude influenza virus infection and should not be used as the sole basis for treatment or other patient management decisions. The clinical features of the illness and the type and risk of exposure are the keys to making patient management decisions. A negative result from the GeneSTAT 2009 A/H1N1 Influenza Test should not be interpreted as demonstrating that the patient does not have 2009 H1N1 Influenza virus infection, if other aspects of the patient’s clinical presentation or recent epidemiologic exposures indicate that 2009 H1N1 Influenza virus infection is likely, and diagnostic tests for other causes of acute respiratory illness are negative.

Contact Information:

DxNA; 3879 South River Road. Saint George, Utah 84790
Phone: 801.628.0324

Healthcare providers will be contacted by DxNA in the event of any significant new findings observed during the course of the emergency use of the GeneSTAT 2009 A/H1N1 Influenza Test. Updated information on the GeneSTAT 2009 A/H1N1 Influenza Test will also be made available at the DxNA website.

Fact Sheet for Patients: Understanding the GeneSTAT 2009 A/H1N1 Influenza Test Results

December 9, 2009

A public health emergency has been declared by the Secretary of Health and Human Services because of the outbreak caused by the 2009 H1N1 influenza virus. This virus has also been referred to as swine influenza (H1N1) virus. This Fact Sheet will refer to the virus as 2009 H1N1 influenza virus. The Food and Drug Administration (FDA) has authorized the emergency use of the GeneSTAT 2009 A/H1N1 Influenza assay to test for the presence of the 2009 H1N1 influenza virus in clinical respiratory specimens collected from the upper respiratory track (nasopharyngeal swabs and nasal swabs) from patients with signs and symptoms of respiratory infection. This authorization will terminate on April 26, 2010, when the emergency declaration is terminated (unless it is renewed), or when the authorization has been revoked, whichever is earlier. The information in this Fact Sheet is the minimum necessary to inform you of the significant known and potential risks and benefits of the emergency use of the GeneSTAT 2009 A/H1N1 Influenza test.

Why is my sample being tested with the GeneSTAT 2009 A/H1N1 Influenza Test?

Your sample is being tested using the GeneSTAT 2009 A/H1N1 Influenza Test, because you may have been infected with the 2009 H1N1 flu virus. This test could help to determine whether you are infected. The results of this test, along with other information, may also help your doctor take better care of you.

What is 2009 H1N1 flu?

The 2009 H1N1 flu is a respiratory disease caused by type A influenza virus. Human cases of 2009 H1N1 influenza virus infection have been identified in the United States and internationally. The Centers for Disease Control and Prevention (CDC) has determined that this virus is contagious and is spreading from person to person. Like seasonal flu, the 2009 H1N1 flu in humans can vary in severity from mild to severe.

What is the GeneSTAT 2009 A/H1N1 Influenza Test?

The GeneSTAT 2009 A/H1N1 Influenza Test is a test performed to detect the 2009 H1N1 influenza virus. The FDA has not cleared or approved this test and there are no FDA cleared or approved tests that can identify the 2009 H1N1 influenza virus. Based on data submitted to FDA, the FDA has granted an Emergency Use Authorization for the GeneSTAT 2009 A/H1N1 Influenza Test.

What are the known risks and benefits of the GeneSTAT 2009 A/H1N1 Influenza Test?

Besides minimal potential discomfort during sample collection, there is a very small risk of a reported incorrect result (see next paragraphs for more information). The results of this test from upper respiratory tract samples (nasopharyngeal swabs and nasal swabs), along with other information, can help your doctor take better care of you. Knowing your test results may help you prevent the spread of the virus to your family or others.

If this test is positive, does that mean that I have 2009 H1N1 flu?

Yes, although there is a very small chance that this test can give a result that is wrong. There is a small chance of an incorrect positive test result (false positive). Your doctor may decide how to care for you based on the test results along with other factors.

If this test is negative, does that mean that I do not have 2009 H1N1 flu?

Most, but not all, people infected with the 2009 H1N1 influenza virus will have a positive test. Therefore, if your test is negative, something else may be responsible for your illness. However, there is a small chance that this test can give a negative result that is wrong (called a false negative) meaning you could possibly still have 2009 H1N1 flu even though the test is negative. Therefore, while a negative test most likely means you don't have flu, your doctor must consider the test result together with all other aspects of your illness in deciding how to treat you.

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GeneSTAT™ 2009 A/H1N1 Influenza Test

INTENDED USE

The GeneSTAT™ 2009 A/H1N1 Influenza Test is intended for the *in vitro* qualitative detection of 2009 H1N1 Influenza A viral RNA using RNA extracted with the Roche High Pure RNA Isolation Kit from nasopharyngeal and nasal swabs of patients with signs and symptoms of respiratory infection. This test is to be used in CLIA High Complexity Laboratories with access to the GeneSTAT Analytical Platform.

Testing with the GeneSTAT™ 2009 A/H1N1 Influenza Test should not be performed unless the patient meets clinical and epidemiologic criteria for testing suspect specimens. The identification of 2009 H1N1 influenza virus should be made in conjunction with clinical and epidemiological information.

Negative results from the GeneSTAT™ 2009 A/H1N1 Influenza Test do not preclude influenza virus infection and should not be used as the sole basis for treatment or other patient management decisions.

SUMMARY AND EXPLANATION

Influenza is a highly contagious, acute respiratory illness. Influenza symptoms include but are not limited to, fever, muscle ache and pain, headache, cough, sore throat and nasal inflammation. Seasonal, geographic patterns have historically characterized the illness, but international travel precipitates influenza becoming a year-round disease. Recent significant public health concerns associated with emergence of the novel 2009 H1N1 influenza A virus pandemic, have elevated the need for improved screening tools intended to detect specific seasonal and novel influenza A viruses infecting humans.¹ In that regard, the U.S. Food and Drug Administration has issued a document entitled "Guidance for Industry and FDA Staff - In Vitro Diagnostic 2009 H1N1 Tests for Use in the 2009 H1N1 Emergency" that delineates criteria for Emergency Use Authorization (EUA) requests for *in vitro* diagnostic devices to be used in detecting 2009 H1N1 Influenza virus².

Three major influenza pandemics occurred in the 20th Century, predictions of the imminence of a future pandemic³ were recently verified by the declaration of the H1N1 influenza pandemic in June, 2009. The GeneSTAT™ 2009 A/H1N1 Influenza Test is an *in vitro* diagnostic test designed to detect influenza A, via an influenza A matrix gene target, and 2009 H1N1 influenza A RNA, via HA1 and NA1 gene targets specific to the 2009 A/H1N1 influenza virus.

The GeneSTAT System can provide valuable information to assist medical professionals in diagnosing 2009 A/H1N1 Influenza virus infection and consequently implementing appropriate therapeutic and control measures.

PRINCIPLE

The test comes as two components, the GeneSTAT Sample Prep Vial and GeneSTAT Test Module. The Test Module can only be analyzed using the GeneSTAT Analytical platform.

The Sample Prep Vial contains a pre-measured amount of buffer. An extracted test specimen (obtained from a nasal or nasopharyngeal swab) is added to the liquid in the Sample Prep Vial, after which, it is attached to the Test Module. The Test Module is then inserted in the GeneSTAT Analyzer. All subsequent procedural steps, from sample preparation to result reporting, are analyzer-controlled and proceed without user intervention.

The Test Module contains all of the necessary PCR chemistry in lyophilized format. There are two reaction wells. One reaction well contains the necessary reagents to individually detect sequences in the H1 hemagglutinin gene and N1 neuraminidase gene specific for the 2009 H1N1 influenza A virus using separate fluorophores. The other well contains reagents to individually detect the presence of the Influenza A matrix gene plus an internal or exogenous control gene, the Caprine Arthritis-Encephalitis Virus (CAEV) core polypeptide p28 gene (which is spiked into each specimen prior to sample processing).

The required testing conditions (e.g., duration and temperature) and specific test/reagent information are encoded on an RFID tag that is attached to the Test Module and recognized automatically by the system. The user is not required to select an assay routine from a menu of assays and is not able or to define testing conditions.

Results are generated from typical RT-PCR amplification curves that exhibit sufficient amplification and typical characteristics. Test results are scored as positive, meaning that specific nucleic acid sequences of the target analyte (H1, N1, and Matrix) were "Detected"; or as negative, meaning that such specific sequences were "Not Detected."

As with all diagnostic procedures exhibiting a limit of detection, a negative result does not preclude the possibility of the specific target being present at concentrations below the assay's detection limit.

Negative test results should be followed up by additional diagnostic testing. Cell culture requires a Biosafety Level 2 or higher designated facility.

As with other PCR tests, negative results do not preclude influenza virus infection and should not be used as the sole basis for treatment or other management decisions.

STORAGE

Optimally, the product should be stored refrigerated (2-8°C), but may be kept at temperatures ranging from 2°C to 25°C until the expiration date printed on the box. Do not freeze or overheat.

PRECAUTIONS

- For *In Vitro* Diagnostic Use Only.
- This is a "closed test system" (except for the extraction procedure) that employs a unique test module. The test module is designed to only run on a GeneSTAT PCR Analyzer.
- Directions and user manual must be read and followed carefully.
- Do not use tests or components beyond printed expiration date.
- Do not use cotton swabs or swabs with wooden shafts to collect nasal or nasopharyngeal specimens. These can introduce chemistry that may compromise and confound PCR amplification.
- Follow the established safety procedures when working with patient specimens.
- Opening of the cartridge and removal of specimen after initial specimen insertion is not recommended and may invalidate the test. Biological hazards and/or amplicon contamination might compromise subsequent test results.
- Suspected novel virulent specimens should be collected with infection control precautions and sent to state or local health departments for further testing.
- Used test modules should be disposed of using standard biohazard material handling protocols (autoclaving or 10% bleach).

SPECIMEN COLLECTION AND TRANSPORT

Acceptable specimens for use with the GeneSTAT 2009 A/H1N1 Influenza Test are nasal and nasopharyngeal swabs. All collected specimens should be obtained as early as possible after onset of symptoms. Ideally, the swab should be inserted immediately into a tube containing 1-ml viral transport media and stored at 2-4 C for less than 4 days or otherwise at -70°C to prevent contamination or degradation of the sample.

Inadequate or inappropriate specimen collection and storage may yield false results. No analytical system can compensate for an inadequate test specimen. Multiple references describe in detail how to properly obtain adequate nasal and nasopharyngeal swab samples⁴.

The sample should be processed, placed in a test module and then inserted into the GeneSTAT Analyzer as soon as possible for the best results. If a positive result for 2009 H1N1 influenza is indicated, reporting should be forwarded to the CDC as per current reportable disease guidelines.

SAMPLE TRANSPORT OR STORAGE MEDIA

The GeneSTAT 2009 A/H1N1 Influenza Test has been successfully validated using Brain Heart Infusion Transport Medium and *Chlamydia*, Viruses and *Mycoplasma* Transport Medium from Hardy Laboratories. Performance of the test using other virus transport and storage media has not been established.

Testing on the GeneSTAT can be done at or near the specimen collection site if the appropriate equipment and personnel capabilities are in place. However, if a sample must be sent to a testing site, transport should be arranged in accordance with international, federal and/or state requirements and local laboratory protocols. DxNA recommends following the protocols outlined by Centers for Disease Control and Prevention or the World Health Organization for transport of suspected Human and Animal specimens suspected of containing 2009 A/H1N1 Influenza virus infection.⁵

NUCLEIC ACID EXTRACTION

Performance of RT-PCR amplification-based assays in the GeneSTAT System using nucleic acid extracted samples depends on the amount and quality of sample template RNA. DxNA routinely uses the Roche High Pure RNA Isolation Kit (Roche Diagnostics, Germany; Cat. No. 11 828 665 001) for extraction of purified RNA for the GeneSTAT System. The manufacturer's 1X protocol should be followed with 200-µL samples used for extraction. Nucleic acid is eluted into a final volume of 200 µL and either used immediately or stored at -70°C.

Note:

Extraction of a 200-µL sample aliquot typically comprises about 20% of the total volume of a sample contained in sample transport or storage medium.

For other RNA-based detection assays, commercially available procedures including QIAamp® viral RNA Mini Kit, or RNeasy® Mini Kit (Qiagen), Roche MagNA Pure Compact RNA Isolation Kit, MagNA Pure LC RNA Isolation Kit II and Roche MagNA Pure Total Nucleic Acid Kit have been shown to generate highly purified RNA appropriate for analysis when following manufacturer's recommended procedures. Performance of the GeneSTAT 2009 A/H1N1 Influenza Test using any RNA extraction procedure other than the Roche High Pure RNA Isolation Kit has not been established.

REAGENTS AND MATERIALS SUPPLIED

1. GeneSTAT H1N1 Test Module. Each GeneSTAT Test Module contains within it all of the measured reagents and materials necessary to do RT-PCR. No additional measuring or manipulation of reagents is necessary.

2. GeneSTAT Sample Prep Vial. The Sample Prep Vial for use with extracted RNA contains a pre-measured volume (900 μ L) of distilled water.

3. Influenza A Matrix - Positive Control Swab

4. H1 Positive Control Swab (2009 H1N1 specific).

MATERIALS REQUIRED OR RECOMMENDED BUT NOT SUPPLIED

1. Disposable, powder-free gloves

2. Laboratory coat

3. Pipette and pipette tips capable of handling 200- μ L volumes

4. 10% Bleach Solution

PROCEDURE

It is recommended that a lab coat and powder-free disposable gloves (not previously used) be worn when running assays. Change gloves between samples and whenever you suspect that these may be contaminated. Also, remember to keep samples capped or covered as much as possible prior to use. Work surfaces, pipettes and the GeneSTAT Analyzer should be cleaned and decontaminated with cleaning products like 5% bleach, UltraClean™ Lab Cleaner, DNAzap™ or RNase AWAY® to minimize the risk of nucleic acid contamination.

1. Have ready a 200- μ L aliquot of an extracted RNA sample. If more than 5 minutes will transpire before adding it to a GeneSTAT Sample Prep vial, keep the samples on ice or refrigerated at 4-8°C until used.

2. Open the foil pouch containing the Test Module but do not remove it from the pouch at this time.

3. Remove the Sample Prep Vial from its pouch and remove the cap.

4. With a pipette, dispense the 200- μ L aliquot of an extracted RNA sample into the liquid contained in the Sample Prep Vial. Remove the pipette tip from the liquid and discard it in 10% bleach.

5. Remove the Test Module from its pouch and screw on the Sample Prep Vial as shown below. It will lock in place which will be obviated by an ability to screw on no further. The fully-assembled Test Module is self-contained and does not vent to the external environment.



6. Open the lid of the analyzer and position the Test Module as shown below.



7. Close the lid and push the Start Button (●) on the analyzer.
8. The assay will proceed without any further user input. Results will be displayed after the run is completed. The following screens indicate assay progress (i.e., what is happening to the sample): (a) Lysing [which will actually be turned off when used with extracted RNA samples], (b) RT [= Reverse Transcriptase], (c) Pre-Denature, (d) Cycles to go: # [Progress of DNA Amplification], Test Results
9. Read and record the test results from the display screen on the analyzer.

Notes:

1. See the GeneSTAT Operator's Manual to set the local date and time.
2. The lot number and expiration date of the Test Module will be read from the Radio Frequency ID (RFID) tag on the Test Module. Test names and cycling conditions (e.g., duration and temperature.) are also read from the RFID memory and cannot be altered by the operator.
3. Error screens will indicate the problem and give instruction as 'what to do' if necessary.

INTERPRETATION AND REPORTING OF RESULTS

All of the three targets (N1 neuraminidase, H1 hemagglutinin, and Influenza A matrix) must be positive to determine that 2009 A/H1N1 Influenza RNA has been detected in a sample. In case of an indeterminate result (i.e., when one or more of the three aforementioned targets is not detected), retesting and/or other diagnostic follow up is recommended.

The cut-off Ct value for a GeneSTAT assay was set at 38 in order to maximize detection of any and all influenza A subtypes. This cut-off value was validated during the clinical evaluation of the assay. Clinical samples should present reaction curves that cross the threshold line at or before 38 cycles. It is possible that certain samples will fail to yield positive reactions due to low cell numbers in the original clinical samples. Below are the acceptance criteria for the interpretation of the results.

1. If N1 & H1 have a Ct \leq 38 and Matrix has a Ct \leq 38, then 2009 A/H1N1 Influenza RNA is reported as **Detected**.
2. If N1 & H1 have a Ct \leq 38 and Matrix is not detected within 38 cycles, then 2009 A/H1N1 Influenza RNA is reported as **Indeterminate**. Repeat testing is required.
3. If N1 or H1 (i.e., only one not both targets) has a Ct \leq 38 and Matrix is detected within 38 cycles, then 2009 A/H1N1 Influenza RNA is reported as **Indeterminate**. Repeat testing is required.
4. If N1 or H1 (only one of them) has a Ct \leq 38 and Matrix is not detected within 38 cycles, then an "Indeterminate Test Result" is obtained. Repeat testing is required.
5. If N1 and H1 are not detected within 38 cycles and Matrix has a Ct \leq 38, then 2009 A/H1N1 Influenza RNA is reported as **Not Detected**; Influenza-A RNA is considered **Detected**.

6. If N1 and H1 are not detected within 38 cycles and Matrix is not detected within 38 cycles, then 2009 A/H1N1 Influenza RNA is reported as **Not Detected**; Influenza-A RNA is considered **Not Detected**.

Quality Control:

1. If Matrix is not detected within 38 cycles and p28 is also not detected within 38 cycles, the test is Invalid. Repeat testing is required.
2. If Matrix is detected within 38 cycles, the test is valid regardless of p28 status.
3. At least once per day that specimens are to be tested, a known sample (2009 H1N1 positive or influenza A positive specimen) should be tested as a positive control for RNA extraction and subsequent protocol steps. If the positive control fails, any specimen result obtained since the last positive control result needs to be retested.

4. LIMITATIONS

1. Individuals performing analyses should be trained and familiar with testing procedures and interpretation of results prior to doing a GeneSTAT assay.
2. Results from this test must be interpreted in conjunction with the clinical history, epidemiological data, clinical signs and symptoms, and other data available to the clinician evaluating the patient.
3. The prevalence of infection will affect the test's predictive value.
4. Performance characteristics may vary due to emerging influenza A viruses.
5. As with other tests, negative results do not rule out Influenza A or 2009 H1N1 influenza infection, and should not be used as the sole basis for patient clinical management decisions.
6. Analyte targets (viral nucleic acid) may persist *in vivo*, independent of virus viability. Detection of analyte target(s) does not imply that the corresponding virus(es) are infectious, or are the causative agents of the clinical symptoms.
7. A false negative result may outfall when inadequate amounts of viral RNA are present in samples due to low viral loads, improper collection, transportation, poor storage conditions and other deficiencies in handling.
8. False negative results may occur when the infecting organism has genomic mutations, insertions, deletions, or rearrangements or when performed late in the course of illness.
9. There is a risk of false positive values resulting from cross-contamination by target organisms or their nucleic acid.
10. The performance of this test has not been established for screening of blood or blood products for the presence of Influenza A or 2009 H1N1 influenza.
11. This test cannot rule out diseases caused by other bacterial or viral pathogens.

ANALYTICAL PERFORMANCE CHARACTERISTICS

ANALYTICAL SENSITIVITY/LIMIT OF DETECTION (LOD)

The Limit of Detection was determined with samples of virus cultured in chicken eggs: a 2009 H1N1 influenza virus strain (A/California/04/2009) and a seasonal strain of H1N1 (A/Memphis/37/2009), both obtained from the WHO Collaborating Center for Studies on the Ecology of Influenza in Animals Virology (Department of Infectious Disease, St. Jude Children's Research Hospital, Memphis, TN).

These primary or minimally-passed viral stocks were titered (both initially testing at 10^8 EID₅₀/mL), serially diluted, and then extracted in 5 replicates of each dilution to determine a tentative LoD EID₅₀/mL dilution yielding positive

values 95% of the time (Table 1). A final dilution confirming a 95% LoD of 2×10^2 EID₅₀/mL or $10^{2.3}$ EID₅₀/mL was run in 20 replicates (Table 2).

Table 1. Serial Dilutions of 2009 A/H1N1 Influenza and Seasonal Influenza A/H1N1 Viruses Assayed in the DxNA GeneSTAT System. Values are expressed as Ct values. Primary virus cultures were obtained from the WHO Collaborating Center for Studies on the Ecology of Influenza in Animals Virology (Department of Infectious Disease, St. Jude Children's Research Hospital, Memphis, TN). Five aliquots of each virus dilution were assessed as log₁₀ serial dilutions and RNA was extracted for assay processing.

CONC. refers to the concentration of extracted viral RNA present in a GeneSTAT rRT-PCR reaction expressed as EID₅₀/mL. N1 = N1 neuraminidase for 2009 A/H1N1 Influenza; H1 = H1 hemagglutinin for 2009 A/H1N1 Influenza; MA = Influenza A matrix; p28 = P28 Caprine Arthritis-Encephalitis Virus (Exogenous Reaction Control); ND = Not Detected

2009 A/H1N1		Influenza, A/California/04/2009 -- Concentration of Undiluted Virus Culture = 10^8 EID ₅₀ /mL																			
CONC.	N1-1	N1-2	N1-3	N1-4	N1-5	H1-1	H1-2	H1-3	H1-4	H1-5	MA-1	MA-2	MA-3	MA-4	MA-5	p28-1	p28-2	p28-3	p28-4	p28-5	
10 ⁸	24	26	23	25	23	28	23	25	26	26	25	31	26	28	27	34	36	33	34	33	
10 ⁷	27	28	27	27	29	27	28	27	28	28	27	32	30	30	28	31	37	34	30	35	
10 ⁶	29	31	28	30	29	28	31	33	30	30	30	35	33	33	33	32	32	31	34	34	
10 ⁵	36	37	ND	36	ND	ND	38	35	36	36	ND	38	37	ND	35	30	31	30	33	35	
10 ⁴	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	33	30	32	30	31	
Averages																					
CONC.	N1	H1	MA	p28																	
10 ⁸	24.2	25.6	27.4	34.0																	
10 ⁷	27.6	27.6	29.4	33.4																	
10 ⁶	29.4	30.4	32.4	32.6																	
10 ⁵	36.3	36.3	36.7	31.2																	

Seasonal A/H1N1 Influenza, A/Memphis/37/2009 -- Concentration of Undiluted Virus Culture = 10^8 EID ₅₀ /mL																					
CONC.	N1-1	N1-2	N1-3	N1-4	N1-5	H1-1	H1-2	H1-3	H1-4	H1-5	MA-1	MA-2	MA-3	MA-4	MA-5	p28-1	p28-2	p28-3	p28-4	p28-5	
10 ⁸	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	22	24	27	23	25	35	34	33	35	32	
10 ⁷	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	27	27	31	27	28	31	30	35	34	36	
10 ⁶	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	30	29	33	29	32	34	38	29	34	31	
10 ⁵	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	32	34	ND	32	ND	32	30	31	36	29	
10 ⁴	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	34	32	32	30	31	
Averages																					
CONC.	N1	H1	MA	p28																	
10 ⁸	ND	ND	24.2	33.8																	
10 ⁷	ND	ND	28.0	33.2																	
10 ⁶	ND	ND	30.6	33.2																	
10 ⁵	ND	ND	32.7	31.9																	

Table 2. Limit of Detection Replicates (n = 20) for 2009 A/H1N1 Influenza and Seasonal Influenza A/H1N1 Viruses Assayed in the DxNA GeneSTAT System. Shown herein are Ct values of the lowest virus concentration that still yielded positive detection of at least 19 out of 20 replicates for each influenza virus. **The Limit of Detection was 2×10^2 EID₅₀/mL or $10^{2.3}$ EID₅₀/mL.**

N1 = N1 neuraminidase for 2009 A/H1N1 Influenza; H1 = H1 hemagglutinin for 2009 A/H1N1 Influenza; MA = Influenza A matrix; p28 = P28 Caprine Arthritis-Encephalitis Virus (Exogenous Reaction Control); ND = Not Detected

2009 A/H1N1 Influenza – A/California/04/2009

TARGET	REPLICATE																			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
N1	30	31	29	29	31	30	30	30	32	29	33	31	32	31	32	30	31	30	33	29
H1	29	33	30	31	32	31	30	31	ND	30	35	31	36	33	32	31	32	32	35	29
MA	29	30	30	30	31	31	32	ND	36	34	33	33	33	34	30	30	31	30	31	29
P28	30	30	30	31	30	31	31	29	29	33	33	28	28	28	28	30	31	30	30	38
						N1	H1	MA	P28											
Target Not Detected						0	1	1	0											
Total						20	20	20	20											
% Reproducibility at LOD						100	95	95	100											

Seasonal A/H1N1 Influenza – A/Memphis/37/2009

TARGET	REPLICATE																			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
MA	27	27	29	30	32	30	32	33	30	ND	32	31	31	35	32	34	33	30	32	31
P28	34	30	35	28	28	28	29	36	29	36	29	29	33	30	30	28	30	29	28	28
						MA	P28													
Target Not Detected						1	0													
Total						20	20													
% Reproducibility at LOD						95	100													

ANALYTICAL REACTIVITY/INCLUSIVITY

The analytical reactivity of the GeneSTAT 2009 A/H1N1 Influenza Test was evaluated using nucleic acid extracted (following the GeneSTAT protocol) from multiple strains of influenza A virus and tested near the limit of detection. The reactivity panel included four seasonal influenza A subtype H1N1 strains, two seasonal influenza A subtype H3N2 strains, two avian influenza A/H5N1 recombinant viruses, and one 2009 H1N1 influenza A isolate.

All tested positive for the Influenza A matrix gene but remained negative for the H1 hemagglutinin and N1 neuraminidase genes elucidated for the 2009 A/H1N1 Influenza virus.

Viral Strain	Target	Culture Titer	2009 H1N1	Flu A (M)
Seasonal A/H1N1 Salt Lake City, Utah - 2008/2009	Seasonal H1	10 ⁶ TCID ₅₀ /mL	-	+
Seasonal A/H1N1 Salt Lake City, Utah - 2007/2008	Seasonal H1	10 ⁵ TCID ₅₀ /mL	-	+
Seasonal A/H3N2 A/Salt Lake City, Utah - 2008/2009	Seasonal H3	10 ⁴ TCID ₅₀ /mL	-	+
Seasonal A/H3N2 A/Salt Lake City, Utah - 2007/2008	Seasonal H3	10 ⁵ TCID ₅₀ /mL	-	+
2009 H1N1 A/California/04/2009	2009 H1N1	10 ² EID ₅₀ /mL	+	+

ANALYTICAL SPECIFICITY/CROSS-REACTIVITY

Nucleic acid from a panel of 14 cultures (9 non-Influenza A viral, 3 bacterial (3) and 2 yeast strains) representing pathogens commonly found in respiratory samples were extracted and tested for cross-reactivity using the GeneSTAT 2009 A/H1N1 Influenza Test. Samples had concentrations ranging from 10⁴ to 10⁸ TCID₅₀/mL or EID₅₀/mL for viruses, 10⁸ CFU/mL for bacteria and 10⁶ CFU/mL for yeast. Each sample was examined as analytical triplicates.

No cross-reactivity was observed between the non-Influenza A viruses, bacteria or fungi and the 2009 H1 or N1 or the Influenza A Matrix targets of the GeneSTAT 2009 A/H1N1 Influenza Test.

Viruses	Concentration	2009 H1N1	Flu A (Matrix)
Adenovirus 1	10 ⁶ TCID ₅₀ /mL	-	-
Epstein-Barr Virus (EBV)	10 ⁵ TCID ₅₀ /mL	-	-
Herpes Simplex Virus Type 1 (HSV1)	10 ⁶ TCID ₅₀ /mL	-	-
Human Cytomegalovirus (CMV)	10 ⁸ TCID ₅₀ /mL	-	-

Influenza B (B/Lee/40)	10 ⁸ EID ₅₀ /mL	-	-
Parainfluenza Virus 1	10 ⁶ TCID ₅₀ /mL	-	-
Primate Polyoma Virus SV40	10 ⁶ TCID ₅₀ /mL	-	-
Respiratory Syncytial Virus Serotype A	10 ⁶ TCID ₅₀ /mL	-	-
Varicella Zoster Virus	10 ⁴ TCID ₅₀ /mL	-	-
Bacteria			
Group B <i>Streptococcus</i>	10 ⁸ CFU/mL	-	-
<i>Bacillus subtilis</i>	10 ⁸ CFU/mL	-	-
<i>Escherichia coli</i>	10 ⁸ CFU/mL	-	-
Yeast			
<i>Aspergillus flavus</i>	10 ⁶ CFU/mL	-	-
<i>Candida albicans</i>	10 ⁶ CFU/mL	-	-

CLINICAL PERFORMANCE CHARACTERISTICS

A total of 79 samples were assessed. Samples from patients presenting with apparent symptoms of 2009 A/H1N1 Influenza virus infection were received from clinics affiliated with the Saint Mark's Hospital (Salt Lake City, UT; obtained under Institutional Review Board approval). Other samples were received from the Utah State Department of Health and the WHO Collaborating Center for Studies on the Ecology of Influenza in Animals Virology (Department of Infectious Disease, St. Jude Children's Research Hospital, Memphis, TN). All samples were randomized and run blindly in the GeneSTAT and FDA-authorized CDC rRT-PCR Tests for the 2009 A/H1N1 Influenza virus.

These samples encompassed 23 samples positive for the 2009 A/H1N1 Influenza virus (as ascertained by the CDC FDA-authorized test) and 55 samples that were negative with the same authorized reference test. The negative samples include 26 influenza A specimens, 22 of which are seasonal A/H1N1 and 4 seasonal A/H3N2 specimens, all confirmed positive by both, CDC reference test and GeneSTAT test (matrix genes), 19 of the remaining negative samples were no influenza-virus specimens; 3 were influenza B positive cultures; 3 blank swabs, and 3 were streptococcus culture swab specimens.

Results of comparison of the GeneSTAT Test and the CDC reference rRT-PCR Test for 2009 A/H1N1 Influenza are presented in Table 3.

Table 3. 2X2 contingency table comparing results of the GeneSTAT 2009 A/H1N1 Influenza Test and the CDC FDA-authorized rRT-PCR Test for 2009 H1N1 Influenza A RNA.

		CDC rRT-PCR 2009 H1N1			Totals
		Positive	Indeterminate ^a	Negative	
GeneSTAT	Positive	22	1	0	23
	Indeterminate ^a	1 ^b	1		
	Negative	0	0	55	55
Totals		23	1	55	79

	Result	95% Confidence Interval
Positive Percent Agreement	95.7% (22/23)	78.0% - 99.9%
Negative Percent Agreement	98.2% (55/56)	90.4% - 100%

^a All discrepant indeterminate results (total of 2) from both GeneSTAT and reference method are tallied against the performance of the GeneSTAT test.

^b This sample was actually positive for H1 and N1, but negative for matrix gene in the GeneSTAT 2009 A/H1N1 Influenza Test.

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3. Utah Pandemic Influenza Response Plan, November 2, 2005

4. Reference examples:

- http://cdc.gov/nchs/data/nhanes/nhanes_01_02/specimen_collection_year_3.pdf
- <http://www.nyc.gov/html/doh/downloads/pdf/cd/asopnar-specimen-guide.pdf>
- <http://www.phac-aspc.gc.ca/cpip-pclcp/>
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- <http://www.dhh.state.la.us/offices/miscdocs/docs-249/Manual/Nasopharyngeal%20Swab%20Collection.pdf>
- http://www.who.int/csr/disease/avian_influenza/guidelines/humanspecimens/en/

5. www.cdc.gov/h1n1/specimencollection.htm

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