

Diagnostic Testing of Influenza

<p>Policy Number: AHS – G2119 – Diagnostic Testing of Influenza</p>	<p>Prior Policy Name and Number, as applicable:</p> <ul style="list-style-type: none"> • G2119 – Rapid Flu Tests in the Outpatient Setting • Also included influenza coverage from prior M2097 – Identification of Microorganisms Using Nucleic Acid Probes
<p>Initial Presentation Date: 09/18/2015 Revision Date: 09/01/2021</p>	

I. Policy Description

Influenza is an acute respiratory illness caused by influenza A or B viruses resulting in upper and lower respiratory tract infection, fever, malaise, headache, and weakness. It mainly occurs in outbreaks and epidemics during the winter season, and is associated with increased morbidity and mortality in certain high-risk populations (Dolin, 2020).

Rapid influenza diagnostic tests (RIDTs) refer to clinical laboratory improvement amendments (CLIA) waived immunoassays that can detect influenza viruses during the outpatient visit, giving results in a clinically relevant time period to inform treatment decisions (CDC, 2017). Besides RIDTs, influenza can be detected using polymerase chain reaction (PCR)-based assays as well as culture testing; however, the former is not often used in initial clinical management due to time constraints. Serologic testing is not used in outpatient settings for diagnosis (Dolin, 2021).

II. Related Policies

Policy Number	Policy Title
AHS-G2149	Pathogen Panel Testing
AHS-G2174	Coronavirus Testing in the Outpatient Setting

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual’s benefit coverage at the time of the request

1. One single rapid flu test—including either a point-of-contact rapid nucleic acid amplification test (NAAT) or a rapid antigen test—OR one single traditional NAAT in the outpatient setting for a patient in a single visit, but not both an antigen and NAAT

for a single patient in a single visit, **MEETS COVERAGE CRITERIA** for diagnosis of patients who present with signs and symptoms consistent with influenza disease (See Note 1 below) when influenza activity has been documented in the community or geographic area.

2. Viral culture testing for influenza in an outpatient setting **DOES NOT MEET COVERAGE CRITERIA**.
3. Outpatient influenza testing, including rapid antigen flu tests, rapid NAAT or RT-PCR tests, traditional RT-PCR tests, and viral culture testing **DOES NOT MEET COVERAGE CRITERIA** in asymptomatic patients.
4. Serology testing for influenza **DOES NOT MEET COVERAGE CRITERIA** under any circumstance.

Note 1: Typical Influenza Signs and Symptoms (CDC, 2020a)

- Fever: A 100.4°F or higher temperature or feeling feverish/chills AND one or more:
 - Cough
 - Sore throat
 - Headaches and/or body aches
 - Difficulty breathing or shortness of breath
 - Fatigue
 - Runny or stuffy nose

IV. Scientific Background

The influenza virus causes seasonal epidemics that result in severe illnesses and death every year. Influenza characteristically begins with the abrupt onset of fever, headache, myalgia, and malaise (Dolin, 1976; Kilbourne & Loge, 1950; Loeb et al., 2012; Nicholson, 1992), accompanied by manifestations of respiratory tract illness, such as nonproductive cough, sore throat, and nasal discharge (Dolin, 2020).

High titers of influenza virus are often present in respiratory secretions of infected persons. Influenza is transmitted primarily via respiratory droplets produced from sneezing and coughing (Brankston, Gitterman, Hirji, Lemieux, & Gardam, 2007; Dolin, 2020; Mubareka et al., 2009) which requires close contact with an infected individual. The typical incubation period for influenza is one to four days (average two days) (CDC, 2017; Cox & Subbarao, 1999). The serial interval among household contacts is three to four days (Cowling et al., 2010). When initiated promptly (within the first 24 to 30 hours), antiviral therapy can shorten the duration of influenza symptoms by approximately one-half to three days (Cooper et al., 2003; Dobson, Whitley, Pocock, & Monto, 2015; Hayden et al., 1997; Heneghan et al., 2014; Jefferson et al., 2014; Nicholson et al., 2000; Zachary, 2021).

In certain circumstances, the diagnosis of influenza can be made clinically, such as during an outbreak. At other times, it is important to establish the diagnosis using laboratory testing. Viral diagnostic test options include rapid antigen tests, immunofluorescence assays, and reverse-transcriptase polymerase chain reaction (RT-PCR)-based testing (CDC, 2017). Among these, RT-PCR is the most sensitive and specific (Dolin, 2021). Rapid influenza antigen tests are immunoassays that can identify influenza A and B viral nucleoprotein antigens in respiratory specimens (CDC, 2017) which yield qualitative results in approximately 15 minutes or less. However, they have much lower sensitivity (CDC, 2017; Harper et al., 2009; Hurt, Alexander, Hibbert, Deed, & Barr, 2007; Ikenaga et al., 2008). A recent meta-analysis found that the sensitivity of these immunoassays was 62.3 percent and the specificity was 98.2 percent (Chartrand, Leeflang, Minion, Brewer, & Pai, 2012). Furthermore, detectable viral shedding in respiratory secretions peaks at 24 to 48 hours of illness and then rapidly declines (Dolin, 2021).

A decision analysis by Sintchenko, Gilbert, Coiera, and Dwyer (2002) concluded that treatment based on rapid diagnostic testing results was appropriate first over empirical antiviral treatment, except during influenza epidemics. When the probability of a case being due to influenza reached 42 percent, the two strategies were equivalent. Further, a separate meta-analysis found that rapid diagnostic testing did not add to the overall cost-effectiveness of treatment if the probability of influenza was greater than 25 to 30 percent (Call, Vollenweider, Hornung, Simel, & McKinney, 2005; Dolin, 2021).

Analytical Validity

Viral culture is a gold standard for influenza diagnosis, but it is very time-consuming with an average 7-day turnaround time; on the other hand, real-time RT-PCR and shell vial (SV) testing require only an average of 4 hours and 48 hours, respectively. A study by Lopez Roa et al. (2011) compared real-time RT-PCR and SV testing against conventional cell culture to detect pandemic influenza A H1N1. The sensitivity of real-time RT-PCR as compared to viral culture testing was 96.5%, and SV had a sensitivity of 73.3% and 65.1%, depending on the use of either A549 cells or Madin-Darby Canine Kidney (MDCK) cells, respectively. The authors conclude, “Real-time RT-PCR displayed high sensitivity and specificity for the detection of influenza A H1N1 in adult patients when compared with conventional techniques” (Lopez Roa et al., 2011).

Clinical Validity and Utility

In 2017, Yoon, Yun, Nam, Choi, and Lim (2017) investigated the use of saliva specimens for detecting influenza A and B using RIDTs. Both saliva and nasopharyngeal swab (NPS) samples were analyzed from 385 patients; each sample was assayed using four different RIDTs—the Sofia Influenza A+B Fluorescence Immunoassay, ichroma TRIAS Influenza A+B, SD Bioline Influenza Ag, and BinaxNOW Influenza A/B antigen kit—as well as real-time RT-PCR. Using real-time RT-PCR as a standard, 31.2% of the patients tested positive for influenza A and 7.5% for influenza B. All four RIDTs had “slightly higher” diagnostic sensitivity in NPS samples than saliva samples; however, both Sofia and ichroma “were significantly superior to those of the other conventional influenza RIDTs with both types of sample” (Yoon et al., 2017). The authors note that the sensitivity of diagnosis improves if both saliva and NPS testing is performed (from 10% to 13% and from 10.3% to 17.2% for A and B, respectively). The researchers conclude, “This study demonstrates that saliva is a useful specimen for influenza detection, and that the combination of saliva and NPS could improve the sensitivities of influenza RIDTs” (Yoon et al., 2017).

Ryu et al. (2016) investigated the efficacy of using instrument-based digital readout systems with RIDTs. In their 2016 paper, the authors included 314 NPS samples from patients with suspected influenza and tested each sample with the Sofia Influenza A+B Fluorescence Immunoassay and BD Veritor System Flu A+B, which use instrument-based digital readout systems, as well as the SD Bioline assay (a traditional immunochromatographic assay) and PCR, the standard. Relative to the RT-PCR standard, for influenza A, the sensitivities for the Sofia, BD Veritor, and SD Bioline assays were 74.2%, 73.0%, and 53.9%, respectively; likewise, for influenza B, the sensitivities, respectively, were 82.5%, 72.8%, and 71.0%. All RIDTs show 100% specificities for both subtypes A and B. The authors conclude, “Digital-based readout systems for the detection of the influenza virus can be applied for more sensitive diagnosis in clinical settings than conventional [RIDTs]” (Ryu et al., 2016). Similar research was performed in 2018 on NPS using RIDTs with digital readout systems—Sofia and Veritor as before along with BUDDI—as compared to standard RT-PCR and the SD Bioline immunochromatographic assay (n=218). The four RIDTs were also tested with diluted solutions from the National Institute for Biological Standards and Control (NIBSC) to probe lower detection limits for each testing method. Again, the digital-based assays exhibited higher sensitivity for influenza. “Sofia showed the highest sensitivity for influenza A and B detection. BUDDI and Veritor showed higher detection sensitivity than a conventional RIDT for influenza A detection. Further study is needed to compare the test performance of RIDTs according to specific, prevalent influenza subtypes” (Ryu et al., 2018).

Another study compared the Alere iNAT, a rapid isothermal nucleic acid amplification assay, to the Sofia Influenza A+B and the BinaxNOW Influenza A&B immunochromatographic (ICT) assay. Using RT-PCR as the standard for 202 NPS samples, the “Alere iNAT detected 75% of those positive by RT-PCR, versus 33.3% and 25.0% for Sofia and BinaxNOW, respectively. The specificity of Alere iNAT was 100% for influenza A and 99% for influenza B” (Hazelton et al., 2015). BinaxNOW also had a sensitivity of only 69% for influenza as compared to RT-PCR in another study of 520 NPS from children under the age of 5 (Moesker et al., 2016).

Young, Illescas, Nicasio, and Sickler (2017) investigated the accuracy of using point-of-care (POC) nucleic acid amplification test (NAAT)-based assays on NPS as compared to the US Food and Drug Administration (FDA)-cleared in vitro PCR test, GenMark Dx Respiratory Viral Panel. Their study consisted of 87 NPS samples from adults. As compared to the RT-PCR gold standard, the cobas Liat Influenza A/B POC test had an overall sensitivity and specificity of 97.9% and 97.5%, respectively, whereas the Alere i Influenza A&B POC test’s sensitivity was only 63.8% with a specificity of 97.5% (Young et al., 2017). Taken together, the authors conclude that “the cobas Influenza A/B assay demonstrated performance equivalent to laboratory-based PCR, and could replace rapid antigen tests” (Young et al., 2017). These results are corroborated by another study that measured the specificity of the cobas POC assay as 100% for influenza A/B with a sensitivity of 96% for influenza A and 100% for influenza B (Melchers, Kuijpers, Sickler, & Rahamat-Langendoen, 2017). Further, a third study reported a 6.5% invalid rate (as defined by as a failure on a first-run assay) by the cobas POC assay; however, “the sensitivities and specificities for all assays [cobas, Xpert Xpress Flu/RSV, and Aries Flu A/B & RSV] were 96.0 to 100.0% and 99.3 to 100% for all three viruses [influenza A, influenza B, and respiratory syncytial virus]” (Ling et al., 2018).

Antoniol et al. (2018) aimed to evaluate the usage of rapid influenza diagnostic tests (RIDTs) in adults, particularly the OSOM® Ultra Flu A&B on viral strains of influenza A/B in the emergency department. The diagnostic evaluation of this test was compared against the Xpert® Flu PCR test. The PCR test

had a sensitivity of 98.4%, specificity of 99.7%, positive predictive value (PPV) of 99.2% and a negative predictive value (NPV) of 99.5% , whereas the OSOM[®] Ultra Flu A&B RIDT had a sensitivity of 95.1%, specificity of 98.4%, positive predictive value of 95.1%, and negative predictive value of 98.4%. However, “there was no difference in test performance between influenza A and B virus nor between the influenza A subtypes,” thereby solidifying the use of both the PCR and RIDT in diagnosing influenza strains in adult and elderly patients (Antoniol et al., 2018).

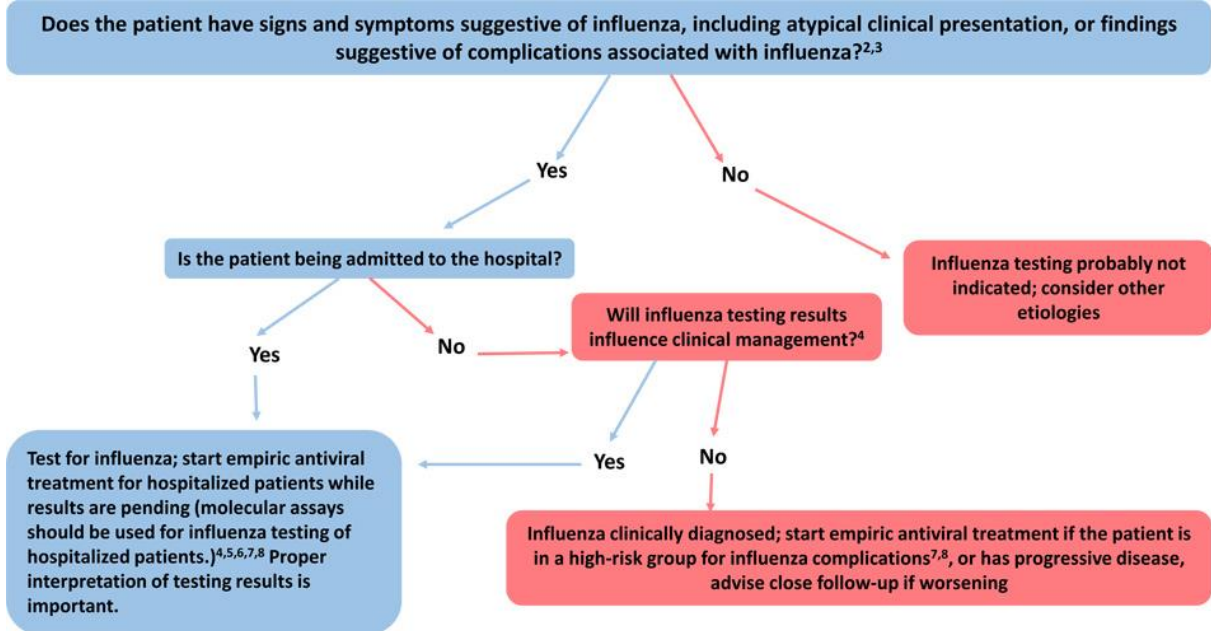
Lee et al. (2019) conducted a systematic review and meta-analysis on point-of-care tests (POCTs) for influenza in ambulatory care settings. After screening, seven randomized studies and six non-randomized studies from studies mostly from pediatric emergency departments were included. The researchers concluded that “in randomized trials, POCTs had no effect on admissions (RR 0.93, 95% CI 0.61-1.42, I2 = 34%), returning for care (RR 1.00 95% CI = 0.77-1.29, I2 = 7%), or antibiotic prescribing (RR 0.97, 95% CI 0.82-1.15, I2 = 70%), but increased prescribing of antivirals (RR 2.65, 95% CI 1.95-3.60; I2 = 0%). Further testing was reduced for full blood counts (FBC) (RR 0.80, 95% CI 0.69-0.92 I2 = 0%), blood cultures (RR 0.82, 95% CI 0.68-0.99; I2 = 0%) and chest radiography (RR 0.81, 95% CI 0.68-0.96; I2 = 32%), but not urinalysis (RR 0.91, 95% CI 0.78-w1.07; I2 = 20%).” Among the non-randomized studies, fewer reported these outcomes, with some showing inconsistency with the randomized trial outcomes, such as there being fewer antibiotic prescriptions and less urinalysis testing. This demonstrated the use of POCTs for influenza and how they influence clinical treatment and decision making (Lee et al., 2019).

Kanwar, Michael, Doran, Montgomery, and Selvarangan (2020) compared three rapid, POC molecular assays for influenza A and B detection in children: the ID Now influenza A & B assay, the Cobas influenza A/B NAAT, and Xpert Xpress Flu. Each of the three aforementioned tests are CLIA-waived influenza assays. PCR was used to compare results from each. NPS Samples from 201 children were analyzed for this study. The researchers note that “The overall sensitivities for the ID Now assay, LIAT, and Xpert assay for Flu A virus detection (93.2%, 100%, and 100%, respectively) and Flu B virus detection (97.2%, 94.4%, and 91.7%, respectively) were comparable. The specificity for Flu A and B virus detection by all methods was >97%” (Kanwar et al., 2020).

V. Guidelines and Recommendations

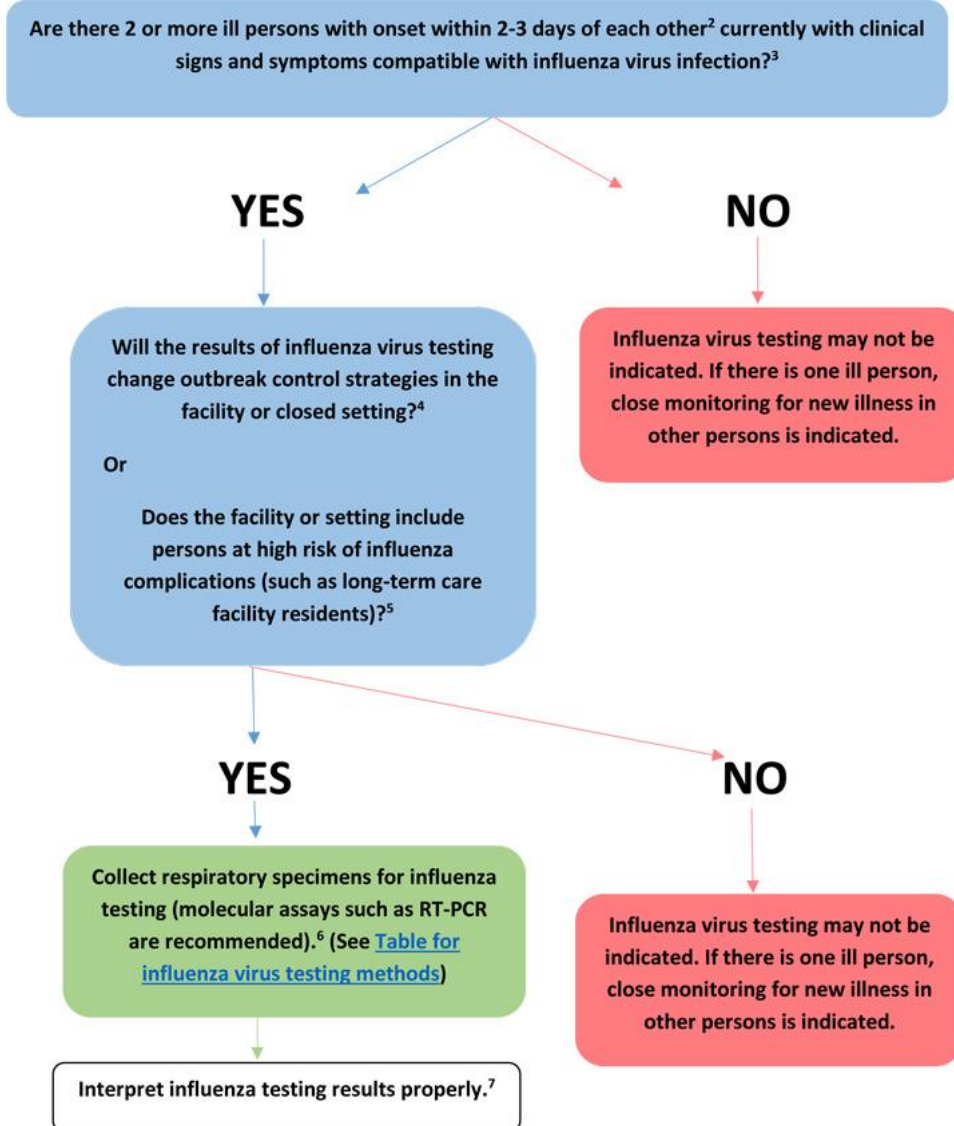
Centers for Disease Control and Prevention (CDC) (CDC, 2016, 2017, 2019, 2020a, 2020b)

The CDC gives two sets of guidelines concerning testing for influenza. If influenza is known to be circulating in the community, they give the algorithm displayed in the figure below (CDC, 2020b):



If the patient is asymptomatic for influenza, then they do not recommend testing. If the patient is symptomatic and is being admitted to the hospital, then they recommend testing; on the other hand, if a symptomatic patient is not being admitted to the hospital, they recommend testing if the results of the test will influence clinical management. Otherwise, if the test results are not going to influence the clinical management, then do not test but do administer empiric antiviral treatment for any patient in high-risk categories (CDC, 2020b). [For a list of typical signs and symptoms of influenza according to the CDC, please refer to Note 1 within the Coverage criteria section above (CDC, 2020a).]

For possible outbreaks in a closed setting or institution, the CDC issued the guideline algorithm in the figure below (CDC, 2019):



If only one person is showing signs and symptoms of influenza, then testing is not recommended but he/she should be closely monitored. If multiple people are showing signs of influenza, then RT-PCR testing is recommended if the results would change control strategies or if there are persons at high risk of complications within the facility or closed setting (CDC, 2019). [For a list of signs and symptoms and a list of high-risk populations, please see Notes 1 and 2, respectively, in the Coverage criteria section above] (CDC, 2020a).

The CDC notes the usefulness of RIDT influenza testing given the rapid testing time (less than 15 minutes on the average) and that some have been cleared for point-of-care use, but they note the limited sensitivity to detect influenza as compared to the reference standards for laboratory confirmation testing, RT-PCR or viral culture. Disadvantages of RIDTs include high false negative results, especially during outbreaks, false positive results during times when influenza activity is low, and the lack of parity in RIDTs in detecting viral antigens. “Testing is not needed for all patients with signs and symptoms of influenza to make antiviral treatment decisions...Once influenza activity has

been documented in the community or geographic area, a clinical diagnosis of influenza can be made for outpatients with signs and symptoms consistent with suspected influenza, especially during periods of peak influenza activity in the community (CDC, 2016).”

The CDC notes the practicality of using RIDTs to detect possible influenza outbreaks, especially in closed settings. “RIDTs can be useful to identify influenza virus infection as a cause of respiratory outbreaks in any setting, but especially in institutions (i.e., nursing homes, chronic care facilities, and hospitals), cruise ships, summer camps, schools, etc. Positive RIDT results from one or more ill persons with suspected influenza can support decisions to promptly implement infection prevention and control measures for influenza outbreaks. However, negative RIDT results do not exclude influenza virus infection as a cause of a respiratory outbreak because of the limited sensitivity of these tests. Testing respiratory specimens from several persons with suspected influenza will increase the likelihood of detecting influenza virus infection if influenza virus is the cause of the outbreak, and use of molecular assays such as RT-PCR is recommended if the cause of the outbreak is not determined and influenza is suspected. Public health authorities should be notified promptly of any suspected institutional outbreak and respiratory specimens should be collected from ill persons (whether positive or negative by RIDT) and sent to a public health laboratory for more accurate influenza testing by molecular assays and viral culture.” The CDC recommends using a molecular assay, such as RT-PCR, to test any hospitalized individual with suspected influenza rather than using an RIDT (CDC, 2016).

Infectious Diseases Society of America (IDSA) (Miller et al., 2018; Uyeki et al., 2018)

The IDSA published an update to seasonal influenza in adults and children in 2018. The following three recommendations relating to outpatient influenza testing were published:

- “Clinicians should use rapid molecular assays (ie, nucleic acid amplification tests) over rapid influenza diagnostic tests (RIDTs) in outpatients to improve detection of influenza virus infection.”
- “Clinicians should not use viral culture for initial or primary diagnosis of influenza because results will not be available in a timely manner to inform clinical management (A-III), but viral culture can be considered to confirm negative test results from RIDTs and immunofluorescence assays, such as during an institutional outbreak, and to provide isolates for further characterization.”
- “Clinicians should not use serologic testing for diagnosis of influenza because results from a single serum specimen cannot be reliably interpreted, and collection of paired (acute/convalescent) sera 2–3 weeks apart are needed for serological testing (Uyeki et al., 2018).”

The 2018 IDSA guidelines for the diagnosis of infectious diseases by microbiology laboratories (Miller et al., 2018) under viral pneumonia respiratory infections, specifically including influenza, state: “Rapid antigen tests for respiratory virus detection lack sensitivity and depending upon the product, specificity. A recent meta-analysis of rapid influenza antigen tests showed a pooled sensitivity of 62.3% and a pooled specificity of 98.2%. They should be considered as screening tests only. At a minimum, a negative result should be verified by another method... Several US Food and Drug

Administration (FDA)-cleared NAAT platforms are currently available and vary in their approved specimen requirements and range of analytes detected (Miller et al., 2018).” Moreover, they state that the “IDSA/American Thoracic Society (ATS) practice guidelines (currently under revision) consider diagnostic testing as optional for the patient who is not hospitalized.” For children, though, they do recommend testing for viral pathogens in both outpatient and inpatient settings. In the section on general influenza virus infection, again they recommend the use of rapid testing assays, noting the higher sensitivity of the NAAT-based methods over the rapid antigen detection assays. They also state: Serologic testing is not useful for the routine diagnosis of influenza due to high rates of vaccination and/or prior exposure (Miller et al., 2018).”

American Academy of Emergency Medicine (AAEM) (Abraham, Perkins, Vilke, & Coyne, 2016)

The AAEM approved a clinical practice paper on influenza in the emergency department: vaccination, diagnosis, and treatment. This document gives a “Level B” recommendation that states: “Testing for influenza should only be performed if the results will change clinical management. If a RAD [rapid antigen diagnostic] testing method is utilized, the provider should be aware of the limited sensitivity and the potential for false negatives. If clinical suspicion is moderate to high and RAD test is negative, one should consider sending a confirmatory RT-PCR or proceeding with empiric treatment for suspected influenza (Abraham et al., 2016).”

Committee on Infectious Diseases, American Academy of Pediatrics (AAP), 32nd Edition (2021-2024, Red Book)

The Committee on Infectious Diseases released joint guidelines with the American Academy of Pediatrics. These joint guidelines recommend that “influenza testing should be performed when the results are anticipated to influence clinical management (eg, to inform the decision to initiate antiviral therapy or antibiotic agents, to pursue other diagnostic testing or to implement infection prevention and control measures)” (AAP, 2021).

Regarding types of testing, the AAP states that “The decision to test is related to the level local influenza activity, clinical suspicion for influenza, and the sensitivity and specificity of commercially available influenza tests... These include rapid molecular assays for influenza RNA or nucleic acid detection, reverse transcriptase-polymerase chain reaction (RT-PCR) single-plex or multiplex assays, real time or other RNA-based assays, immunofluorescence assays (direct [DFA] or indirect [IFA] fluorescent antibody staining) for antigen detection, rapid influenza diagnostic tests (RIDTs) based on antigen detection, rapid cell culture (shell vial culture), and viral tissue cell culture (conventional) for virus isolation. The optimal choice of influenza test depends on the clinical setting” (AAP, 2021).

National Institute of Health (NIH) (NIH, 2017)

The NIH published a webpage on influenza diagnoses. This page notes that “Diagnostics that enable healthcare professionals to quickly distinguish one flu strain from another at the point of patient care and to detect resistance to antiviral drugs would ensure that patients receive the most appropriate care” (NIH, 2017).

VI. State and Federal Regulations, as applicable

On 1/12/2017, the FDA released the following concerning the reclassification of influenza testing systems: “The Food and Drug Administration (FDA) is reclassifying antigen based rapid influenza virus antigen detection test systems intended to detect influenza virus directly from clinical specimens that are currently regulated as influenza virus serological reagents from class I into class II with special controls and into a new device classification regulation” (Kux, 2017). The effective date is 2/13/2017. This reclassification now requires new minimum standards and annual reactivity testing. “Consequently, many previously available RIDTs can no longer be purchased in the United States” (Azar & Landry, 2018).

A list of tests granted waived status under CLIA (Clinical Laboratory Improvement Amendments of 1988) according to CPT codes is maintained by the Centers for Medicare & Medicaid Services (CMS) website (CMS, 2018). As of 7/24/2018, 27 different influenza tests are listed with the 87804 CPT code for influenza immunoassay with direct optical observation.

A search of the FDA’s Device Database on 7/23/2021 yielded 121 approved records for “influenza” (FDA, 2021). Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA ’88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

VII. Applicable CPT/HCPCS Procedure Codes

Code Number	Code Description
87804	Infectious agent antigen detection by immunoassay with direct optical (ie, visual) observation; Influenza
87400	Infectious agent antigen detection by immunoassay technique, (eg, enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA], fluorescence immunoassay [FIA], immunochemiluminometric assay [IMCA]) qualitative or semiquantitative; Influenza, A or B, each
87501	Infectious agent detection by nucleic acid (DNA or RNA); influenza virus, includes reverse transcription, when performed, and amplified probe technique, each type or subtype
87502	Infectious agent detection by nucleic acid (DNA or RNA); influenza virus, for multiple types or sub-types, includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, first 2 types or sub-types
87503	Infectious agent detection by nucleic acid (DNA or RNA); influenza virus, for multiple types or sub-types, includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, each additional influenza

	virus type or sub-type beyond 2 (List separately in addition to code for primary procedure)
86710	Antibody; influenza virus
87275	Infectious agent antigen detection by immunofluorescent technique; influenza B virus
87276	Infectious agent antigen detection by immunofluorescent technique; influenza A virus
87631	Infectious agent detection by nucleic acid (DNA or RNA); respiratory virus (eg, adenovirus, influenza virus, coronavirus, metapneumovirus, parainfluenza virus, respiratory syncytial virus, rhinovirus), includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, multiple types or subtypes, 3-5 targets
87254	Virus isolation; centrifuge enhanced (shell vial) technique, includes identification with immunofluorescence stain, each virus

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Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

VIII. Evidence-based Scientific References

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