1  Cost-Effective Respiratory Virus Testing

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3  Running Title: Cost-Effective Respiratory Virus Testing

4  Pinsky BA¹,# and Hayden RT²

5 ¹Departments of Pathology and Medicine, Stanford University School of Medicine, Stanford, CA, ²Department of Pathology, St. Jude Children’s Research Hospital, Memphis, TN.

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7  #To whom correspondence should be addressed: 3375 Hillview Ave, Room 2913, Palo Alto, CA 94304; Phone: +001 (650) 721-1896; Fax: +001 (650) 723-6918; E-mail: bpinsky@stanford.edu
Abstract

The timely and accurate diagnosis of respiratory virus infections has the potential to optimize downstream (post-testing) use of limited healthcare resources, including antibiotics, antivirals, ancillary testing, and inpatient and emergency room beds. Cost-effective algorithms for respiratory virus testing must take into consideration numerous factors, including which patients should be tested, what testing should be performed (for example, antigen versus RT-PCR, or influenza A/B versus a comprehensive respiratory virus panel), and the turnaround time necessary to achieve the desired post-testing outcomes. Despite the clinical impact of respiratory virus infections, the cost-effectiveness of respiratory virus testing is incompletely understood. In this manuscript, we review the literature pertaining to the cost-effectiveness of respiratory virus testing in pediatric and adult patient populations, and in emergency department, outpatient, and inpatient clinical settings. Furthermore, we consider the cost-effectiveness of a variety of testing methods, including rapid antigen, direct fluorescent antibody (DFA), and nucleic acid amplification tests (NAATs).
The goal of cost-effective respiratory virus testing is to ensure patient health while optimizing the use of limited healthcare resources.

Decision to Test

The first decision-point encountered in the quest for cost-effective respiratory virus testing is the determination of whether a patient requires testing. This involves a clinical interpretation that considers presenting signs and symptoms, the day of illness at presentation given the diminished efficacy of anti-influenza therapies after 48 hours, and risk factors such as the extremes of age or immunocompromise that may predispose to severe respiratory disease. The U.S. Centers for Disease Control and Prevention (CDC) encapsulates this process for influenza virus testing in a decision tree that includes clinical presentation, hospital admission, and whether the testing results will influence clinical management (https://www.cdc.gov/flu/professionals/diagnosis/consider-influenza-testing.htm).

Note that the clinical signs and symptoms that define influenza-like-illness (ILI) are neither sensitive (~60%) nor specific (0-90%) (1). Furthermore, these ILI definitions differ slightly based on which agency or research group sets the case definition (https://www.cdc.gov/vaccines/pubs/surv-manual/chpt06-influenza.html) (1). For example, the U.S. CDC defines ILI as fever of 100°F (37.8 °C) or greater and cough and/or sore throat, whereas the World Health Organization (WHO) defines ILI as an acute respiratory illness with a measured temperature of ≥ 38°C and cough, with onset within the past 10 days. How ILI is de-
fined impacts influenza surveillance (2) and oseltamivir use (3), and therefore may also effect 
decision-tree-based models for cost-effective respiratory virus testing.

Nevertheless, cost-benefit modeling suggests that a test and then treat approach, com-
pared with no testing/empiric therapy, is the most cost-effective strategy during moderate influ-
enza prevalence (4, 5) or low influenza prevalence combined with a low-to-moderate risk of 
hospitalization (6). Another cost-benefit model demonstrated that using RT-PCR to guide antivi-
ral therapy in older adults (≥65 years old) was the most cost-effective strategy when influenza 
prevalence was moderate-to-high (7). These models predict that the cost-effectiveness of influenza 
testing varies significantly based on disease prevalence, highlighting the importance of epidemiologic monitoring to optimize test utilization. Limitations of the modeling approach include 
the use of parameters that may not represent real-world clinical behavior, such as assuming testing does not affect hospital admission, or omitting certain considerations of cumulative costs, 
such as the cost of unnecessary testing in a missed diagnosis of influenza. However, extending 
these models to account for additional respiratory viruses will likely further refine our under-
standing of the variables that impact the cost-effectiveness of respiratory virus testing; and may 
allow us to provide more sophisticated decision-trees for cost-effective clinical management.

Practical recommendations for cost-effective testing include testing only once per episode, unless 
signs and/or symptoms change, and eliminating repeat testing to confirm co-infections.

**Specimen Selection**

Once a decision has been made to test, the appropriate respiratory tract specimen must be col-
lected [reviewed in detail in (8)]. In order to maximize detection of respiratory viruses in the upper respiratory tract, sampling of the posterior nasopharynx via nylon flocked swab, wash or as-
pirate is recommended. Though a number of studies demonstrate that nasopharyngeal aspirates are more sensitive than specimens collected with flocked swabs, other studies show that these collection methods result in similar diagnostic performance (9-12). Nasal swabs generally result in lower overall sensitivity compared to collection methods that sample the nasopharynx, however, performance may vary based on the virus evaluated, the patient population tested, and method used for detection (13). If using an FDA-cleared respiratory virus detection assay, the manufacturer’s instructions for collection, transport and processing should be verified and followed. Lower respiratory tract specimens, such as bronchoalveolar lavage fluid (BAL), are frequently validated by laboratories, particularly for immune compromised patients. A syndromic pneumonia panel (BioFire FilmArray), including both viruses and bacteria, has been FDA-cleared for lower tract specimens. Non-respiratory specimen types are not recommended for routine testing.

**Testing Methods**

Once the specimen type has been decided, the type of respiratory virus test to perform must also be considered. Methods for clinical testing of respiratory viruses are comprised primarily of rapid antigen and NAATs, though some laboratories continue to perform direct fluorescent antibody (DFA) testing and viral culture (14). The technical details of these methods are described elsewhere (15, 16). Reagent and instrument costs, as well as labor costs to run the testing, are also important components of the cost-effectiveness analysis. Reagent costs are test-volume dependent, and for tests that require instrumentation, reagent costs may differ if the capital equipment is purchased or obtained via reagent rental. In addition, the labor markets differ markedly through-
out the U.S. and globally, so high reagent costs may be justified in some high-cost labor markets if the need for staffing is reduced.

A list of FDA-cleared rapid antigen tests are provided in Table 1 (see also [link] for the most up to date information). This table includes both waived and non-waived rapid antigen tests. As defined by the Clinical Laboratory Improvement Amendments (CLIA), waived tests are categorized as “simple laboratory examinations and procedures that have an insignificant risk of an erroneous result.” From a practical perspective, tests with a waiver from the FDA can be performed at outpatient clinics and other facilities that have obtained a CLIA certificate of waiver. These sites are therefore not subject to the same regulatory requirements as laboratories that perform moderate and high complexity testing.

Table 2 includes FDA-cleared, CLIA-waived sample-to-answer respiratory virus NAATs, whereas Table 3 includes selected FDA-cleared, non-waived respiratory virus NAATs. For additional details regarding these tests, as well as other FDA-cleared reagents for the molecular detection of respiratory viruses, please review the microbial tests tab at [link].

It is important to note, that critical components of cost-benefit analyses are the performance characteristics of the test being evaluated, as this data allows for an estimation of the impact of false positive and false negative results. For example, a rapid antigen test with lower sensitivity and similar specificity compared to a NAAT may be less cost-effective despite lower costs for reagents, equipment, and labor.
As has been well described in the literature, rapid antigen tests for influenza demonstrate poor-to-moderate sensitivity, depending on the particular assay and the circulating strain. Meta-analysis of influenza rapid antigen tests revealed pooled sensitivities of 64.6% for influenza A (95% confidence interval [CI], 59.0% to 70.1%) and 52.2% for influenza B (CI, 45.0% to 59.3%), with a combined pooled specificity of 98.2% (CI, 97.5% to 98.7%) (17). This analysis was completed prior to the introduction of the next-generation digital antigen immunoassays with automated detection, such as the Quidel Sofia and BD Veritor systems, which generally show improved sensitivity compared to conventional lateral flow rapid immunoassays that rely on visual detection by human readers (15, 18). A subsequent meta-analysis reported digital antigen immunoassay pooled sensitivities of 80.0% (95% credible interval [CrI], 73.4% to 85.6%) for influenza A and 76.8% (CrI, 65.4% to 85.4%) for influenza B, with combined pooled specificity >98% (19). Using the same methodology these authors described pooled sensitivities for conventional rapid antigen immunoassays of 54.4% ([CrI], 48.9% to 59.8%) for influenza A and 53.2% (CrI, 41.7% to 64.4%) for influenza B, with similarly high pooled specificity. An additional meta-analysis also observed higher pooled sensitivity for digital antigen immunoassays than conventional rapid influenza antigen tests (20). Nevertheless, the CDC does not yet distinguish between these antigen detection methods and recommends that patients presenting with a syndrome consistent with influenza and that have a negative rapid antigen test, should either receive a confirmatory RT-PCR test or be treated as if they have influenza due to the overall limited sensitivity of antigen testing. Influenza rapid antigen tests were recently reclassified by the FDA in order to meet minimum performance standards, and compliance was mandatory by 12 January 2018 (21).
Meta-analysis of RSV rapid antigen tests that included assays with automated readers revealed a pooled sensitivity of 80.0% (CI, 76.0% to 83.0%) and pooled specificity of 97.0% (CI, 96.0% to 98.0%) (22). Interestingly, the American Academy of Pediatrics does not recommend testing for RSV or other respiratory viruses in children with a clinical diagnosis of bronchiolitis (23), as the authors assert that at an individual patient level, the value of identifying a specific viral etiology has not been demonstrated. However, monitoring the start and end of the RSV season is acknowledged to be important for the optimal administration of RSV passive immunization (palivizumab) in high-risk pediatric patients (24).

As the field of clinical virology has transformed into clinical molecular virology, NAATs have become the reference method for the diagnosis of respiratory virus infections, generally demonstrating superior sensitivity without loss of specificity compared to rapid antigen testing (16, 18, 25). With the development of numerous sample-to-answer systems, including the Cepheid GeneXpert, BioFire FilmArray, and GenMark ePlex, as well as the FDA-approval of waived respiratory virus NAATs such as the Alere i (26-35), Cobas Liat (26, 34, 36-43), and Xpert Xpress (35, 39, 41-48), laboratories and facilities using point-of-care testing no longer need to compromise performance for simplicity, ease of use, and rapid test turn around (49, 50).

Meta-analysis revealed that rapid NAATs have pooled sensitivities of 91.6% (CrI, 84.9% to 95.9%) for influenza A and 95.4% (CrI, 87.3% to 98.7%) for influenza B, with pooled specificities of >99% (19). There remain, however, further considerations in developing algorithms for cost-effective respiratory virus testing; the number of targets required to be included in the panel and the rapidity with which results must be reported.

Determining the optimal panel for the diagnosis of respiratory virus infections continues to be an area of active discussion (51-54). Options include primary testing for influenza A/B,
primary syndromic respiratory panel testing, or some combination, for example, influenza A/B

testing with reflex to a respiratory virus panel, if influenza negative (Figure 1). Variables that
may be considered include patient age, immune status, location (inpatient v. outpatient), the acu-
ity of infection, influenza vaccination status, and virus prevalence/seasonality. For inpatients,
infection control and prevention factors must also be considered, including decisions about isola-
tion and cohorting.

Data regarding the utility and cost-effectiveness of these potential algorithmic approaches
are relatively limited, though a recent observational study of adult outpatients at a large VA med-
cical center suggest that testing for influenza viruses alone may be more cost-effective than multi-
plex respiratory pathogen testing in this patient population (55). In contrast, a retrospective,
case-control study of pediatric inpatients revealed that multiplex testing with BioFire FilmArray
was associated with reduced antibiotic use and decreased chest radiographs (56). However, a
prospective assessment of multiplex respiratory panel testing in hospitalized adults revealed that
the diagnosis of influenza virus infection was associated with reduced duration of hospitalization
and appropriate antiviral management, but that detection of other respiratory viruses was not sig-
nificantly associated with study outcome measures (57). Another study using a decision-analysis
approach in a pediatric patient population concluded that testing using the Luminex xTag Res-
piratory Virus Panel (RVP) NAAT was less costly than other testing strategies when the prev-
ance of infection was ≥11%, with savings primarily due to a reduction in the duration of hospi-
talization (58). Other groups have demonstrated potential laboratory cost-savings associated
with syndromic respiratory virus testing (59, 60), or a two-stage algorithm comprised of Quidel
Sofia influenza antigen testing with negative samples reflexed to BioFire FilmArray (61). Nev-
Nevertheless, the contributions of the myriad co-infections diagnosed by syndromic testing to cost-effective respiratory virus testing remains an area of active investigation.

Cost-Effectiveness of Rapid Testing

The final variable to consider for cost-effective respiratory virus testing is turnaround time, which has been studied primarily in the context of rapid antigen tests, though data is beginning to be collected using NAATs, with both targeted testing and large respiratory virus panels. Given the large number of studies on this topic, this section has been divided into subsections describing observational and randomized controlled trials (RCTs), and then further organized based on the clinical setting: emergency department/outpatient versus inpatient testing.

Observational Studies

Emergency Departments and Outpatient Clinics

In emergency department (EDs) and outpatient clinics, the clinical utility and effectiveness of rapid respiratory virus testing has been studied in several observational studies. Patients in these settings with positive rapid influenza antigen immunoassays have been shown to receive fewer antibiotics, undergo fewer diagnostic tests, are more likely to receive antiviral therapy, and are less likely to be hospitalized than patients whose rapid tests are negative. One or more of these outcomes have been demonstrated in both pediatric (62, 63) and adult patient populations (64). Similar findings have been observed when positive influenza results were reported before rather than after ED discharge (65), and when positive influenza results were available before as opposed to after the ED physician’s exam (66). Furthermore, in both adult patients with specimens submitted within 48 hours of presentation (67) and pediatric patients admitted from the ED...
(68), the rapid diagnosis of influenza using the FilmArray Respiratory Virus Panel was associated with decreased length of stay and duration of antimicrobial use. An economic modeling analysis of rapid influenza diagnosis using the FilmArray in a pediatric ED setting indicated that rapid NAAT for influenza was the most cost-effective strategy compared to conventional influenza NAAT, DFA, and rapid antigen testing (69). In addition, a prospective study evaluating the impact of rapid Cobas Liat Influenza A/B testing on physician decision-making in a mixed adult/pediatric ED and adult ED, suggested the potential for significant cost-savings (70) and reductions in hospital acquired influenza (71), respectively. Finally, the implementation of the Cepheid Xpert Flu A/B/RSV XC assay in outpatient, clinic-based physician laboratories improved anti-viral utilization (72). These studies support the clinical utility and cost-effectiveness of timely influenza testing.

Inpatient settings

Similarly, observational case-control studies of inpatients demonstrate that positive rapid respiratory virus testing is associated with less antibiotic use in both pediatric (73-75) and adult study populations (76), as well as increased, appropriate antiviral use in pediatric and adult populations compared to patients with negative testing (75-77). When respiratory virus diagnosis was available within 24 hours via DFA, significant reductions in the duration of hospitalization and antibiotic therapy, as well as the number of microbiological investigations have also been observed (78). A simple calculation taking the cost of hospital days saved and subtracting the cost of offering DFA yielded a net savings of 400,000 Hong Kong dollars per year in this pediatric population (78). This study was replicated at a US hospital serving a mixed adult and pediatric patient population and the results were confirmed (79). These findings have not been limited to
DFA panels and conventional influenza rapid antigen tests. Implementation the Cepheid Xpert Flu A/B/RSV XC test for hospitalized adults was associated with decreased length of stay and reduced laboratory utilization (80). In addition, using a laboratory-developed 16-member respiratory virus real-time PCR panel performed within 24 hours, hospitalized pediatric patients with positive panel results received fewer antibiotic prescriptions than patients with negative testing (81). The decreased use of antibiotics for patients with viral infections is an important antimicrobial stewardship endeavor, which decreases the overall antibiotic pressure in an environment (e.g., a hospital), which, in turn, decreases the emergence of antibiotic resistant bacteria.

**Randomized Controlled Trials**

While these observational studies suggest that timely respiratory virus testing may be cost-effective, the results of RCTs have been mixed.

**Emergency Departments and Outpatient Clinics**

RCTs investigating rapid viral diagnosis in the ED have been primarily performed in pediatric populations. For example, RCTs using rapid influenza antigen tests or a respiratory virus DFA panel have been evaluated in otherwise healthy pediatric patients presenting to the ED in three RCTs (82-84) and one quasi-RCT (85). A meta-analysis showed a significant reduction in the number of chest radiographs, but only a trend toward reductions in the length of ED stay, blood or urine testing, and ED antibiotic use (86). The meta-analysis concluded that there was insufficient evidence to support the use of routine rapid respiratory virus testing in the pediatric ED, though statistical significance for the major outcome measures may not have been reached due to lack of power (86).
Similarly, an RCT in a pediatric ED evaluating the availability of results from a 17-249 member respiratory pathogen real-time PCR panel within 12-36 hours showed no statistically significant difference in hospital admissions, length of hospital stay, or antibiotic use (87). Furthermore, a prospective, 2-arm randomized study of point-of-care testing using the Cobas Liat Flu A/B in both the pediatric and adult EDs of an academic medical center demonstrated no significant difference in time to discharge or antibiotic use (88). While formal cost analyses were not performed in these studies, the absence of significant differences between study arms suggests that routine rapid viral testing of otherwise healthy children in the pediatric ED may not provide substantial cost-savings.

In contrast, the single RCT of rapid influenza testing in the ED that included children with underlying diseases, showed that patients with positive influenza results were significantly less likely to undergo routine blood testing or receive antibiotic prescriptions than those patients that were not tested, though costs were not evaluated (89). Future trials specifically investigating high-risk pediatric populations, including the immune compromised, as well as children with underlying chronic respiratory and cardiac conditions, may be required to clearly demonstrate statistically significant outcome measures.

Additional RCTs will also be required to investigate the role of rapid respiratory virus testing in the outpatient pediatric setting. In a cluster RCT performed in French outpatient clinics, pediatricians with access to rapid influenza antigen testing prescribed significantly more antivirals, but also utilized more antibiotics and performed more chest radiographs than pediatricians that did not perform rapid antigen tests (90). While the increased use of antibiotics and ancillary testing was primarily in patients with negative rapid antigen tests, the medical necessity of these interventions was not investigated. In the pediatric outpatient setting, the use of rapid tests...
may therefore increase costs.

The single randomized controlled trial of adults presenting to the ED with acute respiratory illness demonstrated that rapid molecular point-of-care influenza A/B testing did not reduce overall antibiotic use, though it was associated with a reduced length of stay and improved influenza detection and antiviral use (91).

Inpatient settings

To date, a limited number of RCTs have been performed in hospitalized patients. In a trial of non-immune suppressed, hospitalized adults with lower respiratory tract infection, the availability of results from a 14-member real-time PCR panel within 48 hours did not reduce antibiotic use or costs (92). In fact, PCR testing increased average costs 318€ per patient. In a quasi-randomized-controlled trial in both inpatient and outpatient settings, and including adults and teenagers, near-care testing with the BioFire FilmArray did not reduce hospital length of stay, though influenza positive patients received antiviral therapy more rapidly than those patients that received routine laboratory-based testing (93). Additional RCTs enrolling low and high-risk adult and pediatric inpatients will be needed to further evaluate the utility and cost-effectiveness of respiratory virus testing in this clinical setting.

Conclusions

As described herein, the data supporting the cost-effectiveness of respiratory virus testing is suggestive, but far from conclusive. Additional studies are critically important to inform the decision-making of microbiology and virology laboratory medical directors, clinicians, and hospital administrators as they work together to implement respiratory virus testing algorithms that en-
sure quality, cost-effective clinical care of patients with suspected respiratory virus infections. In the future, perhaps clinically validated, sophisticated decision-analytics incorporating patient age and key risk factors, patient location, test performance and turn-around time, and real-time respiratory virus prevalence data will be available to physicians at the time of test ordering to help optimize the clinical utility and cost-effectiveness of respiratory virus testing.
Key Points

- The determination of whether a patient requires respiratory virus testing involves a clinical interpretation that considers presenting signs and symptoms, the day of illness at presentation, and risk factors such as the extremes of age or immunocompromise that may predispose to severe respiratory disease.

- The timely availability of epidemiologic surveillance data may inform clinical decision-making, as respiratory virus prevalence impacts the utility of testing.

- The Centers for Disease Control and Prevention recommend that patients presenting with a syndrome consistent with influenza and that have a negative rapid antigen test, should either receive a confirmatory RT-PCR test or be treated as if they have influenza.

- The American Academy of Pediatrics does NOT recommend RSV testing in children presenting with bronchiolitis.

- The cost-effectiveness of syndromic panels for respiratory pathogen detection remains an area of active investigation.

- Observational studies suggest that a rapid turnaround time for respiratory virus testing, particularly for influenza, may be a cost-effective testing strategy.

- Randomized controlled trials evaluating a rapid turnaround time for respiratory virus testing in a variety of clinical settings have generated mixed results regarding the clinical utility and cost-effectiveness consistently demonstrated in observational studies.
REFERENCES


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Figure 1. Respiratory virus testing algorithms. (A) All patients with influenza-like illness (ILI) are tested using an influenza A/B test. (B) All patients with ILI are tested with a respiratory pathogen panel. (C) Patients with ILI are tested with an influenza A/B test and if negative, reflex testing with a respiratory pathogen panel is performed. (D) Patients with ILI are tested with an influenza A/B test or a respiratory pathogen panel up front, depending on underlying diseases and severity of the presentation.
Table 1. FDA-cleared Influenza A/B Rapid Antigen Tests

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Product</th>
<th>Platform/Instrument</th>
<th>Approved Specimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott</td>
<td>Binax Now Influenza A &amp; B Card 2</td>
<td>Alere Reader</td>
<td>NPS, NS direct</td>
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<tr>
<td>Becton Dickinson &amp; Co.</td>
<td>BD Veritor Flu A + B</td>
<td>BD Veritor Reader, BD Veritor Plus Analyzer</td>
<td>NPS, NS direct, NPW, NA, NPS in VTM</td>
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<tr>
<td>Quidel Corp.</td>
<td>Sofia Influenza A + B FIA</td>
<td>Sofia FIA Analyzer, Sofia 2 FIA Analyzer</td>
<td>NS, NPS, NPA, NPW direct, NP, NPA, NPW in VTM</td>
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<td>Quidel Corp.</td>
<td>QuickVue Influenza A + B</td>
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<td>NPS, NS direct</td>
</tr>
<tr>
<td>Princeton BioMeditech Corp.</td>
<td>BioSign Flu A &amp; B</td>
<td>N/A</td>
<td>NS, NPS direct, NPA, NPW</td>
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<td></td>
<td>LABSCO Advantage Flu A &amp; B</td>
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<td></td>
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<td></td>
<td>LifeSign LLC Status Flu A &amp; B</td>
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<td></td>
<td>OrcaSure QuickFlu Rapid A + B</td>
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<td>Polymedco Poly stat Flu A &amp; B</td>
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<td>N/A</td>
<td>Nasal wash</td>
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NPS, nasopharyngeal swab; NS, nasal swab; NA, nasal aspirate; NFA, nasopharyngeal aspirate; NPW, nasopharyngeal wash; VTM, viral transport media. Specimen types listed in BOLD are CLIA-waived.
<table>
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<th>Product</th>
<th>Platform/Instrument</th>
<th>Approved Specimens</th>
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<td>Alere i (ID NOW)</td>
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<tr>
<td>Abbott</td>
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<td>Alere i (ID NOW)</td>
<td>NPS direct, NPS</td>
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<td>BioFire Diagnostics</td>
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<td>Sekisui Diagnostics</td>
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NPS, nasopharyngeal swab; NS, nasal swab
Table 3. Selected FDA-cleared Respiratory Virus NAATs: Non-Waived

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<td>BioFire FilmArray</td>
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<td>BioFire Diagnostics</td>
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<td>BioFire FilmArray</td>
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<tr>
<td>BioFire Diagnostics</td>
<td>BioFire FilmArray Pneumonia Panel</td>
<td>BioFire FilmArray</td>
<td>IS, TRA, BAL</td>
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<td>Xpert Xpress Flu</td>
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<td>VERIGENE Reader and Processor SP</td>
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<td>Solana</td>
<td>NS, NPS</td>
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</table>

NPS, nasopharyngeal swab; NS, nasal swab; NPA, nasopharyngeal aspirate; NPW, nasopharyngeal wash; IS, induced/expectorated sputum; TRA, tracheal aspirate; BAL, bronchoalveolar lavage
A. Patient with ILI
   Influenza A/B

B. Patient with ILI
   Respiratory Pathogen Panel

C. Patient with ILI
   Influenza A/B
   Reflex if Influenza A/B Negative

D. Patient with ILI
   Otherwise Healthy
   Immunocompromised
   Underlying heart and/or lung disease
   Considering Admission
   Influenza A/B
   Respiratory Pathogen Panel