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Q&A

Influence of Molecular Testing on Influenza Diagnosis

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Influenza viruses infect millions of people each year, leading to several hundred thousand hospitalizations and thousands of deaths annually in the US. Early antiviral therapy reduces illness duration, complications, and mortality associated with influenza. Yet, antivirals are consistently used at a suboptimal rate. Patients with positive influenza diagnostic testing results are more likely to receive antiviral therapy and less likely to be prescribed unnecessary antibiotics. Thus, access to reliable influenza testing in both ambulatory and inpatient settings is critical to facilitate both optimal patient outcomes and antimicrobial stewardship. Recently, the first point-of-care (POC)[7] molecular diagnostic test was cleared by the US Food and Drug Administration (FDA) for the detection of influenza. At the same time, concerns about the performance of commonly used rapid antigen tests, particularly the test sensitivity, led to modified regulatory requirements for these devices. The landscape of influenza diagnostics is rapidly evolving, and clinical laboratorians are certain to face pressure regarding new testing modalities. In this article, 5 experts that span the continuum of influenza diagnosis from the clinical laboratory to industry to public health and regulatory agencies discuss recent advances and ongoing challenges in influenza diagnostics.

During influenza season, how does rapid influenza diagnostic testing affect clinical management and clinical workflows?

Neil Anderson: During influenza season, most infected individuals will present to 1 of 2 places: an outpatient clinic or an emergency department (ED). These initial interactions with the healthcare system are often very brief. During this short amount of time, clinicians must make many decisions. Should the patient be given antibiotics, antivirals, or neither? Should the patient be admitted? Given the overlap in symptomatology of different respiratory pathogens, these questions can be very difficult to answer on presentation alone. In this situation, a rapid influenza diagnostic test is an essential component of patient management during influenza season. In both outpatient and ED settings, the identification of patients who tested positive for influenza enhances the likelihood that antiviral treatment is promptly initiated, if appropriate. Additionally, real-time influenza diagnosis promotes antimicrobial stewardship by avoiding unnecessary antibacterial therapy. Finally, if the patient is admitted, a rapid diagnosis of influenza can help inform early appropriate infection prevention measures to prevent nosocomial influenza virus transmission to vulnerable inpatients.

Ritu Banerjee: Rapid influenza diagnostics can provide rapid, actionable results that aid clinical decision-making for patients with respiratory symptoms who present during cold and flu season. In the outpatient setting, when patients have positive influenza test results but relatively mild infections that do not require hospitalization, providers are more likely to prescribe antivirals like oseltamivir and less likely to prescribe unnecessary antibiotics or perform ancillary testing like blood tests and chest radiographs. A high-risk immunocompromised patient with a positive influenza test result may be followed more closely or even hospitalized. Providers are more likely to prescribe antiviral prophylaxis for high-risk contacts of the known positive patients and reinforce the importance of staying home from school or work to limit influenza virus spread in the com-

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[7] Nonstandard abbreviations: POC, point-of-care; FDA, US Food and Drug Administration; ED, emergency department; RIDT, rapid influenza diagnostic (antigen) tests; RSV, respiratory syncytial virus.

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munity. Rapid influenza testing also has direct implications for patient flow, as rapid results enable faster discharge from EDs or outpatient clinics, which is especially important during winter months when respiratory viruses are prevalent and clinics are busy.

Christine Ginocchio: During traditional "flu seasons," influenza is responsible for anywhere from <5% to approximately 35% of respiratory tract infections. Depending upon the epidemiology of a given flu season, many respiratory tract infections denoted as influenza-like illness are due to other circulating respiratory viruses that cannot be reliably distinguished from influenza on clinical symptoms alone. Therefore, rapid influenza tests can assist with clinical care and treatment decisions for patients in a variety of settings, including outpatient clinics, chronic care facilities, EDs, and hospitals. Rapid results (15 min to a few hours) allow for appropriate treatment within a time frame that is clinically relevant, as the most benefit from treatment of influenza is obtained if initiated within 48 h of symptom onset. Rapid results for influenza alone or as part of larger multiplex syndromic panels affect clinical decisions to admit or discharge, shorten time in the ED, reduce the number of other ancillary tests, shorten length of stay, and promote more effective infection control practices. Finally, rapid identification of an outbreak in a community or chronic care facility allows for appropriate public health measures.

What are some important considerations for clinical laboratories regarding the use of rapid influenza antigen assays? What are the strengths, limitations, and logistical challenges of these assays?

Neil Anderson: The greatest appeal of rapid influenza diagnostic (antigen) tests (RIDTs) is their ease of use. Because many of these tests are CLIA-waived, they can be performed by virtually any member of the healthcare team with appropriate training. Thus, rapid antigen testing has become commonplace in a variety of patient settings during influenza season. Unfortunately, challenges with test sensitivity have been well documented. The performance of RIDTs can be affected by the amount of virus present and the antigenic makeup of the circulating strains. Sensitivity varies and is estimated to be lower than 50% for some RIDTs. It is important to note that many RIDTs have acceptable levels of specificity. A positive result during influenza season in a symptomatic patient is highly suggestive of influenza. This leads many to the conclusion that rapid influenza antigen testing is an acceptable standalone approach. However, many clinicians are unaware of the low sensitivity of these assays. Laboratories may issue results with comments regarding test limitations, but this is likely to have little effect, as most testing is performed at the POC. The reality is that antigen testing is frequently deployed in many settings where providers do not fully understand test limitations.

Christine Ginocchio: The benefits of RIDTs are fast time to results (generally 15 min), ease of use requiring minimal training, availability of CLIA-waived tests for office and bedside use, and relatively low cost. However, there are several important factors that should be considered if opting to use an RIDT, including for whom and when testing should be performed. Sensitivity can be suboptimal (ranging from 50% to 70%) depending on the patient population tested (generally perform better in children than in the elderly), time of sample collection after onset of symptoms (best within 3–4 days), quality of sample (preferably nasopharyngeal swab, aspirate, or wash), and the influenza virus strain (generally lower for influenza B viruses). Importantly, RIDTs may not detect emerging strains or novel variants. Specificities of RIDTs are approximately 90%–95%; hence, false-negative results occur more commonly than false-positive results during times of high influenza activity. Conversely, false positives are more likely when influenza viruses are not circulating, and RIDTs are therefore are not recommended for use outside influenza season when pretest probability is low. A negative RIDT is insufficient to exclude influenza infection in persons with a high clinical suspicion. Healthcare personnel must be educated on the "real-life" performance of RIDTs, including positive and negative predictive values during periods of high and low influenza activity. The laboratory should also be prepared to offer molecular testing, either frontline or as a reflex test, when an RIDT is negative but the confirmation of influenza is indicated (high-risk persons, hospitalized patients, institutional outbreaks, risk for novel influenza A virus), to confirm a positive RIDT in low-prevalence times, or if subtyping is indicated.

Kimberly Hanson: Of highest concern regarding the use of rapid antigen tests for influenza is the lack of sensitivity. Test performance varies by assay, specimen type, adequacy of collection, host, and influenza type (i.e., sensitivity is generally lower for influenza B). Notably, influenza A sub-

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type information is not provided by RIDTs, and these tests do not differentiate seasonal strains from potentially novel strains. Thus, when a patient has compatible symptoms and influenza is known to be circulating in the community, a negative rapid test does not rule out infection, and additional testing may still be required. The main advantages of RIDTs include the rapid turnaround time and the ability to perform testing at the POC. However, use of RIDTs at the POC also presents several logistical challenges regarding training nonlaboratory clinical staff to appropriately collect, perform, and interpret testing.

Timothy Uyeki: Clinical laboratory staff should be knowledgeable about proper specimen collection, transport, and processing, as well as what information is provided by RIDTs. RIDTs can differentiate between influenza A and B virus antigens in respiratory specimens but cannot differentiate among influenza A virus subtypes or distinguish seasonal influenza A viruses from novel influenza A viruses of animal origin. If subtyping information is needed or if novel influenza A virus infection is suspected in a patient, specimens should be sent to a public health laboratory for specialized molecular testing. Clinical laboratory staff should be familiar with the level of influenza activity in the community. Information sources can include local influenza surveillance data, positive results of influenza tests in outpatients and hospitalized patients, and reports of influenza outbreaks, including in long-term care facilities. Staff should also understand that during periods of influenza activity in a community, a negative RIDT result does not exclude influenza virus infection. For hospitalized patients with suspected influenza, the CDC does not recommend use of RIDTs, so clinicians should be advised not to order these tests for patients who are being admitted to the hospital or who are already hospitalized with suspected influenza and to order a molecular assay for influenza instead.

The FDA recently reclassified rapid influenza testing devices from Class I to Class II devices. What prompted this change? What is the significance of this change for clinical laboratories and will it affect patient management?

Ritu Banerjee: The lack of sensitivity of RIDTs during the 2009 H1N1 pandemic led to recognition by the FDA that RIDTs were contributing to missed diagnoses, treatment delays, and poor outcomes for patients. Reclassification of RIDTs by the FDA from Class I to Class II devices will improve overall test quality, as these devices must now pass minimum performance requirements and meet compliance with additional controls to ensure accuracy and reliability. The effects of this change are not yet clear, but it may confer clinical benefit by improving detection of influenza-infected patients, which will facilitate directed therapy and reduce unnecessary use of antibiotics for uncomplicated influenza and enable appropriate infection control measures in the inpatient setting to prevent further spread of disease.

Christine Ginocchio: During the 2009 H1N1 pandemic, numerous studies demonstrated suboptimal sensitivity of many RIDTs. Sensitivity for the 2009 pandemic virus strain varied significantly from 20% to 85% depending on the assay. This gap highlighted a need for better regulatory oversight of RIDTs. Until 2017, RIDTs were classified by the FDA as Class I (low likelihood of harm and general controls are required), and there was no regulatory requirement for manufacturers to continually verify the performance of FDA-cleared RIDTs. However as circulating influenza virus strains routinely undergo genetic drift or shift (as seen in 2009), the ability of RIDTs to detect new strains may vary considerably. Therefore, the FDA reclassified antigen-based RIDT systems as Class II devices to help improve the overall quality of influenza testing and remove poorly performing devices from the market. Manufacturers are now required to continually monitor antigen-based RIDT performance, including accuracy, reliability, and clinical relevance. Testing must be done by the manufacturer on an annual basis and in certain emergency situations, such as emergence of a new strain. The FDA reclassification means that the burden of monitoring test performance for acceptability now appropriately resides with the manufacturer of the device, not solely with the laboratory. Improved performance of RIDTs may lead to a reduction in the amount of reflex testing to a molecular diagnostic test following a negative RIDT, which delays time to results and requires additional technical time and costs.

Timothy Uyeki: Before reclassification, for FDA clearance of any new RIDT, manufacturers only had to demonstrate equivalent performance to existing FDA-cleared tests. There were no standard levels of sensitivity and specificity to achieve. Now manufacturers must demonstrate that RIDTs can meet improved sensitivity and specificity standards set by the FDA. Overall, this is a very positive development and long overdue. More accurate RIDTs, and importantly, RIDTs with higher sensitivity, will be very good for clinical management of influenza patients, primarily outpatients, because fewer false-

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negative results will occur, especially during peak influenza activity. It will also be good for more accurate detection of influenza outbreaks, such as at long-term care facilities.

What are the strengths, limitations, and logistical challenges of molecular assays for influenza? What preanalytical or postanalytical factors should laboratories consider for rapid molecular testing performed at the POC?

Neil Anderson: The newly described CLIA-waived rapid molecular tests rival their antigen counterparts in terms of speed and simplicity. The primary benefit of rapid molecular tests is superior sensitivity over RIDTs, which may have a significant positive effect on overall influenza management. However, adoption of rapid influenza molecular testing requires justification for the added cost. This may be challenging, as hospitals currently using RIDTs may perceive that they are already using a viable rapid test while underestimating the limitations of antigen testing. Emphasis should be placed on the benefits of added sensitivity, such as facilitating earlier treatment, improving outcomes, and preventing unnecessary hospital stays. These hidden costs may be difficult to capture but should be taken into account. Other challenges for clinical laboratories implementing POC molecular testing include procedures for proper instrument maintenance, including stringent cleaning protocols and periodic environmental testing, adherence to sterile technique, and training in all aspects of testing from preanalytical factors to postanalytical reporting of results.

Christine Ginocchio: As of June 2018, there are 7 CLIA-waived rapid molecular tests that include detection of influenza, either alone or in combination with respiratory syncytial virus (RSV), and one multiplex syndromic panel for a variety of respiratory pathogens. Rapid molecular tests are performed in enclosed cartridges or pouches, with a simple sample-to-answer approach, requiring a few minutes of hands-on time with results in approximately 15 min to 1 h. The strength of this testing is that it affords all healthcare organizations, including laboratories, physician practices, clinics, urgent care centers, and EDs, the ability to perform a simple yet very sensitive and specific test. Rapid molecular tests allow for round-the-clock near-patient testing, where clinical and infection control decisions can be rapidly made, rather than classically in a central laboratory, where result delays may occur. The major drawbacks of rapid molecular tests are increased cost over RIDTs and the need for instrumentation. However, the clinical benefits of an accurate rapid result may outweigh the increased cost.

Despite the simplicity of CLIA-waived rapid molecular tests, compliance with the test manufacturer's instructions regarding all preanalytical and postanalytical phases of testing is still essential. Users must be trained, observed, and have knowledge of the information in the package insert, including all disclaimers and warnings. Quality control should be performed as recommended by the manufacturer. Appropriate collection of approved sample types must be followed to ensure assay performance. Since rapid molecular tests are performed in enclosed cartridges or pouches, amplicon contamination is virtually eliminated, but there is still a risk of environmental or user contamination. For example, administration of intranasal influenza vaccine in a room where samples are collected and tested could lead to false-positive results. Healthcare workers with respiratory symptoms should refrain from testing or wear masks and clean gloves when collecting and testing samples to prevent self-contamination of patient samples and testing areas. Testing areas and equipment surfaces should be appropriately cleaned, as recommended by the manufacturer. Users should also be familiar with reviewing test results to identify unusual patient results that should prompt repeat testing or an investigation. An unusually high number of invalid results may indicate user failure requiring supervision and retraining or reagent failure that should trigger an inquiry with the test manufacturer. Users must also be aware of and comply with local influenza reporting requirements.

Timothy Uyeki: Major strengths of rapid influenza molecular assays include high sensitivity, fast results (approximately 15–30 min), and the ability of some assays to also detect RSV nucleic acids. This last feature is especially helpful for testing young children with respiratory illness during the winter respiratory virus season. The limitations of rapid molecular assays are similar to those for the RIDTs and include the inability to determine whether infectious virus is present, to differentiate influenza A virus subtypes, and to distinguish seasonal influenza A viruses from novel influenza A viruses. Despite improved sensitivity, end users of rapid molecular assays must keep in mind that a negative result does not altogether exclude influenza virus infection, although a negative result from a rapid molecular assay has much higher negative predictive value than for RIDTs.

Should influenza testing be performed in the setting of a centralized laboratory or available at the POC? Are there certain situations in which a dedicated influenza molecular test would be preferred over a multiplex assay that detects multiple agents of upper respiratory infection?

Ritu Banerjee: The clinical setting determines the preferred type of influenza testing. POC influenza testing is particularly useful in EDs and outpatient clinics, where

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timely results affect patient flow and clinical decisions. Influenza testing in a centralized laboratory is not ideal for these outpatient settings, as this requires specimen transport and increases turnaround time. However, centralized laboratories should still perform molecular tests for influenza, as more sensitive molecular tests are often needed when rapid antigen tests are negative, particularly with hospitalized, critically ill, and/or immunocompromised patients. During influenza season, when virus is circulating in the community and pretest probability of influenza virus infection is high, in most patients presenting with respiratory illness, use of a dedicated molecular test for influenza may be more useful and cost-effective than use of a multiplex assay containing several targets. However, during months when other respiratory viruses are circulating, or in immunocompromised patients who often harbor multiple pathogens, multiplex tests capable of detecting several targets may be useful.

Neil Anderson: There are many ways to implement molecular influenza testing. Although POC testing carries its own unique challenges, many hospitals may be willing to address these challenges in return for the benefit of faster results. The improvement in turnaround time can be particularly dramatic if a hospital normally relies on testing sent to an offsite, centralized laboratory. If the difference in turnaround time between POC testing and a centralized laboratory is clinically negligible, it is preferable to test in a controlled environment by staff familiar with diagnostic testing, features that more commonly apply to centralized laboratories.

Another decision that must be made regarding implementation of influenza molecular testing is the breadth of the testing offered. Current testing options range from tests that detect influenza viruses only to broadly multiplexed tests detecting 20 (or more) respiratory pathogens. Broad panels are typically more expensive and have lower analytical sensitivity than dedicated reverse transcription PCR tests. Broadly multiplexed tests continue to play an important role in the diagnosis of illness in patients at risk for severe respiratory disease from multiple pathogens, particularly immunocompromised patients.

Christine Ginocchio: Influenza testing is appropriate in both settings, depending on the patient population tested and the time to results. Ideally influenza testing should be performed at the POC so that treatment decisions can be made in an appropriate timeframe to affect patient care. However, testing in a centralized laboratory can be as effective, particularly in the outpatient setting. High-throughput, random-access platforms are available that reduce technical time and provide results within hours.

Dedicated influenza testing is usually sufficient in the outpatient or ED setting or in an immunocompetent patient with no comorbidities when documented influenza is in the community. However, even in these settings, if the response to a negative influenza test is to automatically prescribe an antibiotic, a more comprehensive panel that identifies additional respiratory viruses should prevent antibiotic administration in a person with no risk factors for a concomitant bacterial infection. Additionally, in a patient with an unusual clinical presentation (such as pertussis in an adult), limiting the testing to influenza alone may miss a treatable disease. In the inpatient setting, the use of multiplex syndromic assays has been shown to decrease hospital length of stay, days of antibiotic and antiviral therapy, and number of ancillary tests and affect decisions to hospitalize or not. Multiplex syndromic assays have shown that coinfections with 1 or multiple respiratory viruses are not rare (up to 30%–35% in children and 10%–15% in adults), indicating the need to identify all pathogens if cohorting of patients is necessary, especially during peak respiratory virus season. Finally, significant costs savings have been demonstrated with appropriate discontinuation of infection control measures when a respiratory pathogen aside from influenza was identified that did not require isolation. Notably, highly multiplexed syndromic testing is usually available through a centralized laboratory, rather than at the POC.

Timothy Uyeki: For outpatients with a clinical diagnosis of influenza, empiric antiviral treatment can be prescribed without influenza testing, especially for persons who are at high risk for complications from influenza or those with progressive disease. In the ambulatory care clinic setting, influenza testing using RIDTs or CLIA-waived rapid molecular assays is beneficial if having a rapid result will change clinical management. POC test results are usually available sooner than testing performed in a centralized laboratory because of the time required for specimen transport and processing, analysis, and result reporting. For most patients evaluated in an outpatient or ED setting who do not require hospital admission, a multiplex assay that detects multiple respiratory pathogens is not necessary, as there are no specific treatments available for respiratory viruses except for influenza virus infection. In hospitalized patients, particularly young children and the elderly, knowing whether a patient has influenza virus or RSV infection can be useful for diagnostic and infection prevention and control measures.

Kimberly Hanson: Rapid influenza testing should be available at the POC to enable clinical decision-making in real time. However, central laboratory testing is also useful for confirming a negative RIDT, subtyping, and for validating and testing lower respiratory tract specimen types such as bronchial alveolar lavage fluid. Addi-

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tionally, current recommendations are that all hospitalized patients with influenza-like illness should have molecular testing performed. For most immunocompetent patients, influenza testing (with or without RSV) alone is likely adequate. For immunocompromised hosts and potentially critically ill patients (especially if rapid influenza testing is negative) a larger multiplex is preferred given the breadth of respiratory viruses than can cause severe disease.

During influenza season, what is the effect of rapid molecular assays for influenza on the public health response?

Neil Anderson: Rapid molecular assays play a pivotal role in the public health response to influenza. The beginning of "influenza season" is often heralded by an increase in influenza-testing positivity. This trigger is essential because it allows for the implementation of infection prevention, testing, and treatment protocols. The best illustration of the importance of this process is when it breaks down, as it did during the 2009 H1N1 influenza pandemic. During this time, most rapid influenza testing was performed using antigen-based assays that demonstrated extremely poor sensitivity for the circulating virus. These limitations resulted in delayed implementation of infection prevention measures and missed opportunities for patient treatment. Fortunately, much has changed in the past decade. A shift of rapid testing to more sensitive molecular methods decreases the likelihood of being caught off guard with the beginning of influenza season. Additionally, several manufacturers of rapid molecular tests offer methods for centralized monitoring of results across multiple sites. This allows hospital systems to set up their own network for influenza virus detection, a useful tool that further aids public health efforts by both predicting the beginning of influenza season and monitoring for activity throughout.

Timothy Uyeki: The high sensitivity and rapidity of results produced by influenza molecular assays increases the potential for more accurate and expedient recognition of an influenza outbreak, particularly in an institutionalized setting such as a hospital or long-term care facility. Positive influenza testing results should prompt rapid implementation of infection prevention and control measures to decrease spread of influenza viruses in healthcare settings. Wider use of rapid molecular assays will detect more influenza virus infections and provide more accurate information than RIDTs for patients with influenza seeking medical care. Such data, if made available in a timely manner across the country, can be combined with traditional influenza surveillance data to provide public health officials with better situational awareness of high influenza activity in order to better direct response efforts. For example, medical countermeasures such as influenza vaccines and antivirals can be targeted to influenza "hotspots." More accurate diagnosis of influenza can also contribute toward antimicrobial stewardship by reducing inappropriate empiric antibiotic prescriptions in patients who have influenza without severe illness. This can benefit public health by reducing unnecessary antibiotic use. Lastly, available molecular assays that distinguish among influenza A virus subtypes may facilitate recognition of suspected novel influenza A virus infections [i.e., influenza A positive, nonsubtypeable (H1, H3 negative results)]. Clinicians and laboratory staff who suspect detection of a novel influenza A virus infection should contact local or state public health officials as soon as possible to arrange specific testing by reverse transcription PCR; sequencing and further confirmation may be needed at the CDC.

What does the future hold for influenza diagnostic testing? What types of tests will be available and in what settings will they be performed (central laboratories, clinics, pharmacies, homes, etc.)?

Ritu Banerjee: The future will likely see the development of even more sensitive, timely, and simple-to-use molecular POC tests for influenza detection. We will also likely see testing using self-collected specimens. Testing may even be performed at home, with accompanying provider consultation using telemedicine, or at community clinics or pharmacies, rather than in traditional hospital or clinic settings.

Christine Ginocchio: As both molecular testing prices and test turnaround times decrease, I anticipate that molecular assays will slowly but eventually replace most RIDTs because of better performance and overall cost savings when clinical impact is considered in the analyses. I also see an increase in more multiplex syndromic panels, for both hospitalized patients and in the outpatient setting, where there is the greatest opportunity to reduce the unnecessary use of antibiotics for persons with uncomplicated viral infections. A comprehensive diagnostic in combination with a POC assay for biomarkers of viral and/or bacterial disease will be essential to meet this goal. Additionally, as newer treatments become available for noninfluenza viral infections, comprehensive diagnostics will be necessary to target therapy. Influenza testing of the future should be available as CLIA-waived or moderate complexity molecular tests that can be performed in a large variety of settings, ranging from the central laboratory (high throughput, fully automated, random access) to simple-to-use individual POC tests done in rapid response laboratories, EDs, clinics, and urgent care centers. Pharmacies should be able to test for influenza and immediately prescribe an antiviral. CLIA-waived diagnos-

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tics should be easily implemented in areas of "high-risk" exposure and transmission such as military bases and ships, college health centers, school nurses' offices, company health units, and cruise ships. Rapid determination of the start of an influenza outbreak can help to reduce spread in the community. In-home testing by visiting nurses could ensure rapid recognition and treatment of an elderly, immunocompromised, or chronically ill patient at risk for rapidly progressing disease.

Kimberly Hanson: I envision home testing as a viable option in the future. Additionally, POC diagnostics will continue to improve in terms of sensitivity and simplicity and may potentially include subtype information, which can inform treatment choice.

Timothy Uyeki: As molecular technologies continue to advance, we will likely see further decreases in turnaround time and increased sensitivity. Influenza tests in the future will likely provide more actionable information, especially if based upon next-generation sequencing technology, and be able to distinguish among influenza A virus subtypes. The availability of tests that can detect infection with influenza viruses that are resistant to available antivirals will be important for clinical management. Some influenza molecular tests might be very portable ("laboratory in a box") or even handheld devices for use in field investigations. Influenza tests could be available for over-the-counter use in the future, although a key issue will be the proper interpretation and use of the results. Having an over-the-counter influenza test might facilitate early antiviral treatment for some patients, as antiviral medications for influenza currently must be prescribed by a physician. Importantly, wider availability of testing does not replace clinical examination and assessment. Use of highly accurate influenza tests at pharmacies for patients with mild illness who are not at high risk for influenza complications, combined with antiviral treatment without the need for a prescription, could be considered under specific circumstances with sufficient supplies of antivirals. This strategy could alleviate the surge in patients at emergency rooms during seasonal epidemics and rare pandemics.

Neil Anderson: Although molecular influenza assays are likely to become faster and even more user-friendly, the real "breakthroughs" will be how these tools are used to better patient care and public health. Future directions for improvement likely lie in greater patient access to testing and results. Rapid antigen tests for a variety of infectious diseases found their greatest utility when they were used to bring testing to patients outside of the hospital. As molecular assays become more user-friendly and cost-effective, they may be offered through mobile clinics, pharmacies, schools, grocery stores, and gyms. In the future, small rapid molecular platforms may even reside in personal residences.

Examples of increased patient access to results already exist, as many healthcare systems now provide real-time access to portions of the medical record, including test results. Some laboratories have even more proactive approaches such as sending patients text messages when their results are ready. As many rapid molecular tests feed results into a centralized data repository, these tests are already poised for electronic reporting. The prospect of cloud-based data aggregation for influenza is particularly exciting. Imagine an app that reports your influenza test result in addition to real-time positivity rates in your local area. In this digital age, it is natural and desirable that reporting mechanisms and clinical laboratories should evolve with the capabilities of technology.

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