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Influence of Molecular Testing on Influenza Diagnosis

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Guest: Drs. Melanie Yarbrough and Neil Anderson are from the Department of Pathology and Immunology at the School of Medicine of Washington University in St. Louis.

Bob Barrett: This is a podcast from *Clinical Chemistry,* sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I am Bob Barrett.

Influenza viruses affect millions of people each year, leading to several hundred thousand hospitalizations and thousands of deaths annually in the U.S. Early antiviral therapy reduces the duration of illness, complications and mortality associated with the flu, yet antivirals are often underutilized. However, patients with a positive influenza diagnostic test results are more likely to receive appropriate antiviral therapy and less likely to be prescribed unnecessary antibiotics. Access to reliable influenza testing is critical to facilitate both optimal patient outcomes and antimicrobial stewardship.

Recently, the first point-of-care molecular diagnostic test was cleared by the U.S. Food and Drug Administration for detection of the flu. At the same time, concerns about the performance of commonly used rapid antigen tests have surfaced. The landscape of influenza diagnostics is rapidly evolving and clinical laboratories are certain to face pressure regarding new testing modalities.

A Q&A feature in the November 2018 issue of *Clinical Chemistry* asked five experts with different roles in this field to discuss recent advances and ongoing challenges in influenza diagnostics. We are joined in this podcast by one of the moderators of that Q&A, Dr. Melanie Yarbrough, and one of the expert panelists, Dr. Neil Anderson. Both of them are from the Department of Pathology and Immunology at the School of Medicine of Washington University in St. Louis.

And Dr. Anderson, we'll start with you. Every year as the flu season approaches, there is increased media coverage of the role of vaccinations and testing. What should clinical laboratorians and physicians know about influenza diagnosis?

Neil Anderson: Well, one the most important things to keep in mind each flu season is that not all diagnostic assays are created

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equal, so it's very important to know your tests. A large proportion of influenza testing is currently performed using rapid antigen tests. These tests provide a diagnosis within minutes, are relatively inexpensive, and are very easy to perform. This makes them very attractive options for point-of-care and near patient testing in settings such as hospital emergency departments and outpatient clinics. In these settings, quick test results allow for physicians to make some very important decisions such as, "should our patient be admitted or should I give antivirals?"

Although on the surface, rapid antigen testing, based on what I just said, may sound like a great thing for patient care, one must keep in mind that these tests have a very significant Achilles' heel. They have very poor sensitivity. This is because their accuracy is highly dependent on the amount of virus in a patient sample and the antigen makeup of a circulating virus each year. Because of these factors, antigen-based assays have in some cases been shown to have sensitivities even lower than 50% when compared to molecular methods. Although there have been efforts from both the FDA and the manufacturers themselves to address these sensitivity issues, the fact remains that antigen-based testing is still less sensitive than other methods.

So, you may ask yourself, "what's the cost of not recognizing this limitation?" Well, patients with early influenza and falsely negative antigen tests are often not treated with targeted antivirals. This creates an important gap in patient care, particularly since antivirals show best efficacy when administered early in the course of infection. A patient may end up developing severe influenza disease requiring hospitalization, and even if the correct diagnosis is eventually made, the best opportunity for effective treatment would have been missed. Because of this, over recent years, many healthcare settings have gravitated towards using more sensitive molecular methods.

Bob Barrett: So, Dr. Yarbrough, let's go to you. In what settings are molecular diagnostic assays for influenza performed, and when are they appropriate?

Melanie Yarbrough: Well, molecular diagnostic assays for influenza were first introduced several years ago. Since the setup for many of these assays was highly complex and required specialized instruments, testing was usually offered in centralized laboratories, or even had to be sent out to reference labs. So, results were often not available in real time, and this really limited their utility because during flu season, we know that most infected individuals present either in outpatient clinics or the emergency department. And the long turn-around time that is associated with these assays often means that they have no immediate effect on patient

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management. This has changed recently when the first point-of-care molecular diagnostic test was cleared by the FDA for the detection of flu.

The availability of rapid molecular testing has the potential to shift the burden of testing out of the clinical lab and into the wild, so to speak. While this may sound scary to many of us clinical laboratorians, there are several potential advantages to rapid flu molecular tests. For example, there are now several FDA-cleared assays that are also CLIA-waived and available at the point-of-care. Most require only a few minutes of hands-on time to set up, and results are typically available in less than half an hour. So, they rival their antigen counterparts in terms of their speed and their simplicity, and this allows for round-the-clock near patient testing where clinical and infection control decisions can be rapidly made as opposed to in a central laboratory where results may take longer.

Of course, the biggest benefit of rapid molecular assays over antigen tests is their superior sensitivity, which will likely have a significant positive effect on overall influenza management. All this means that the landscape of influenza diagnostics is rapidly evolving and clinical laboratorians are certain to face pressure from providers to offer this newer, faster, and more sensitive tests.

Bob Barrett: So, it sounds like molecular testing for influenza has lots of advantages, but are there any challenges or disadvantages to consider?

Melanie Yarbrough: Yes. Although these are CLIA-waived tests with the sample to answer format, there are several technical challenges that should be overcome before one implements one of these assays. For instance, many users of these tests have probably not received specialized training in laboratory methods. So, these means that they may be unfamiliar with the ins and outs of molecular testing, such as the importance of sterile technique, or the need for periodic environmental testing to ensure that their testing areas are not contaminated with any nucleic acid.

So, this lack of experience may also prevent users from recognizing unusual results that should prompt further investigation before those results get reported. Another potential disadvantage to molecular flu testing is the increased costs over rapid antigen tests. This may prevent some hospitals from adopting molecular methods in spite of their advantages.

Bob Barrett: So, Dr. Anderson, can laboratories justify the added cost associated with molecular testing?

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Neil Anderson: Given what we know about the limitations of antigen testing, the value of molecular testing has become much more apparent. Patients with definitive diagnosis of influenza have been shown to be less likely to receive unnecessary antibacterial therapy. This can help with antibiotic stewardship, it may even result in decreased rates of Clostridium difficile infection. Prompt and accurate patient screening may also help implement appropriate infection prevention measures, preventing crippling hospital outbreaks.

Being able to avoid having to close down an entire hospital wing because of an initially unrecognized flu outbreak may easily justify the financial cost of testing. Finally, as stated previously, screening using a more sensitive approach allows for overall better management of patients with influenza. This benefit can be hard to quantify, though when one considers the financial and human cost of a week-long stay in the ICU because of delayed antiviral treatment, the value of molecular testing becomes much more concrete.

Bob Barrett: So finally, Dr. Yarbrough, it sounds like the field of influenza diagnostics is really evolving. What changes can clinical laboratories expect in the future?

Melanie Yarbrough: Well, I think that in the future, clinical laboratories can actually expect to perform less diagnostic testing for influenza, particularly if the cost of molecular testing continues to decrease and the tests become even more user-friendly. If this happens, I think that rapid molecular assays will eventually replace other testing modalities and will be offered in a variety of places such as urgent care clinics, EDs, pharmacies, school nurse's offices, or maybe even at home.

Even better would be a companion diagnostic test that detects biomarkers for rapid ID of viral versus bacterial disease, because if we know right away if the patient has a virus or a bacterial infection, this can promote antibiotic stewardship by helping providers determine if a prescription for antibiotics is indicated while the patient is still in the office. One thing is for sure, the flu virus is always evolving, so it's important for clinical laboratorians and clinicians to try to keep up, both with new technology and with making sure that that technology detects the strain of flu that's circulating each year. Even with great diagnostics, flu season is inevitable, thus I want to remind everyone to be sure to get your flu vaccine, cover your cough, and wash your hands.

Bob Barrett: That was Dr. Melanie Yarbrough and she was joined by Dr. Neil Anderson. Both of our guests in this podcast are from

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the Department of Pathology and Immunology at the School of Medicine of Washington University in St. Louis. Their question and answer feature on the Influence of Molecular Testing on Influenza Diagnosis appears in the November 2018 issue of *Clinical Chemistry*. I'm Bob Barrett. Thanks for listening.

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