Commentary

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COMMENTARY ON: PERFORMANCE OF THE COBAS® INFLUENZA A/B ASSAY FOR RAPID PCR-BASED DETECTION OF INFLUENZA COMPARED TO PRODESSE ProFlu+ AND VIRAL CULTURE

Molecular Technology Poised to Change Testing for Influenza at the Point-of-Care

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Clinicians are continuously looking for ways to improve the care they deliver, with the goals of optimizing patient outcomes, improving efficiency of health care delivery, and ultimately advancing the health of population. Optimization of clinical care can be particularly challenging for front-line providers (e.g. emergency, urgent care, family and primary care clinicians) who work in high volume, busy episodic care settings, where decisions must be made rapidly, patient throughput is critical, and follow-up is often not possible. One fundamental strategy which can aid in improving patient care is to arm clinicians with reliable diagnostics, which are adapted and customized for both the clinical need, and the setting in which they are intended to be utilized.

Broadly speaking, tests that provide the greatest benefit are those with well-defined indications for use, which can provide accurate, reliable, and real-time results (actionable during the patient stay), and can contribute to critical clinical decisions – either therapeutic or disposition-related. Notably, from the front-line physician perspective, current diagnostic tools available for critical infectious disease conditions have lagged significantly behind those that have been advanced for other high impact clinical conditions (e.g. troponin testing for acute cardiac conditions). Although highly advanced high-throughput solutions have been developed for centralized laboratories, lesser focus has been put on the development of point-of-care solutions for bedside or satellite laboratory use. The study by Chen et al., published in this issue, represents another important and welcome advance in the developmental pipeline for infectious disease diagnostics, among front-line clinicians with an important new PCR-based diagnostic tool [1].

Influenza remains an important clinical condition, with regard to burden of disease and morbidity/mortality. Annual global attack rates are estimated at up to 10% for adults and 30% for children [2]. This translates to dramatic seasonal rises in outpatient visits, stressing already overcrowded episodic care sites such as emergency departments [3], producing even greater surges and associated challenges in rendering care during pandemics [4, 5]. In those circumstances, safe and appropriate clinical decision-making for patients with respiratory illnesses (e.g. regarding focused use of anti-virals, antibiotics, and inpatient admission) can be life-saving for some patients. Historically, appropriate treatment and patient disposition has been challenged by relying on either a clinical diagnosis (i.e. influenza-like illness), or traditional antigen based rapid influenza tests (RIDT), each of which suffer from poor to moderate sensitivity [6–7]. The adverse impact of these diagnostic shortfalls is evidenced by several recent emergency department-based studies which demonstrate remarkably low (less than 50%) [8] rates of antiviral treatment for those ultimately confirmed as having influenza, even for those with 'high risk' clinical characteristics and/or co-morbidities, where recommendation to treat are definitive [9].

The early revolutionary innovations in molecular diagnostics have focused on the requirement of the centralized laboratory to provide such new assays. PCR was invented in the early 1980s, and by the late 1980s the first automated thermocyclers became available. While the first FDA-approved PCR-based test was approved in 1991 for *Chlamydia trachomatis* [10], it was not until the mid-2000s that the first fully automated PCR-instruments were introduced

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incorporating all steps from sample preparation to amplification and result generation [11, 12]. These developments reflected the move from individual instruments to total laboratory automation, which has now been achieved in centralized laboratories for clinical chemistry and immunoassays [13]. However, these dramatic advancements fall short of guiding front-line clinicians to make rapid decisions about infectious diseases for their patients. More intense recent focus on aligning technical advances with clinical needs has given way to significant new advancement, now opening the door for true practice change.

Notable developments in the influenza diagnostic arena, which the report by Chen et al. builds upon, include optimization of assay performance, high sensitivity, speed of 20 minutes, and a small platform footprint. These advances, as well as innovations achieved by other rapid molecular platforms (such as the Cepheid GeneXpert) which permit random access loading and integration of rapid results with the electronic medical record, facilitate real-time resulting to clinicians [14]. The isothermal amplification-based assay (Alere i Influenza A and B) received CLIA waiver status by the FDA this past year, permitting true point of care use with improved turn-around-times (TAT) (15 min) [15]. In this report by Chen et al., another PCR-based molecular assay is introduced that delivers an influenza assay for clinicians combining short TAT (15 min), minimal sample handling (<1 min) as well as a CLIA waiver status. The cobas test cartridge also includes a barcode, permitting future EMR integration, though that component remains to be developed and tested. The methodological advances of the 'Lab in a tube' (LIAT) System were achieved through a number of inventions. First, a technology characterized by "flow cycling" uses a flexible reaction vessel and modular sample processors that move the sample to the required temperature [16]. This, together with the low reaction volume and containment of all reagents in the lab-in-a-tube permit the shortened PCR assay time.

Several new POC diagnostic technologies for infectious diseases are now being introduced to better align with the clinical need; the next critical step will be to design and conduct studies which systematically address questions of implementation and uptake into the real-world (i.e. doctor's offices, urgent care settings and emergency departments) where the greatest need exists. Important areas to address include defining exactly which patients will benefit from testing and in what setting, as well as who will perform the test, how quality assurance and quality control activities can be performed and most importantly, the impact of these new generation assays on clinical, health care operations, and the public health, relative to current practice.

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