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Panther Fusion® Respiratory Virus Assays for the detection of influenza and other respiratory viruses

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A R T I C L E   I N F O

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A B S T R A C T

Background: Nucleic acid amplification tests (NAATs), such as PCR, are preferred for respiratory virus testing, due to superior diagnostic accuracy and faster turnaround time. Panther Fusion® Respiratory Assays (Fusion), which includes FluA/B/RSV (FFABR), Paraflu and AdV/hMPV/RV, offers a modular approach to syndromic testing on a fully automated platform while improving gene targets and expanding the test menu.

Objectives and study design: We evaluated Fusion using 275 consecutive nasopharyngeal specimens previously used in an analysis of five PCRs, as well as 225 archived specimens.

Results: Of the combined 500 specimens, 134 were positive for influenza A (FluA), 54 for FluB, 65 for RSV, 64 for parainfluenza (PIV), 24 for adenovirus (AdV), 21 for human metapneumovirus (hMPV), and 40 for rhinovirus (RV) with Fusion. Of the positive samples Fusion correlated with historical results for all but one, despite multiple freeze-thaw cycles of this collection. Fusion was positive for an additional 33 samples, including 11 FluAs, 7 RSVs, 3 PIV3s, 3 AdV, 6 hMPV and 3 RVs. These samples were retested with corresponding Prodesse (Pro) assays using quadruple sample volume. This resolver test confirmed Fusion results for an additional 4 FluAs, 4 RSVs, 1 PIV3 and 3 AdVs. The sensitivity and specificity ranges of Fusion were 99–100% and 98–100%.

Limit of detection (LOD) analyses were performed on a variety of Flu isolates. The LODs ranged from 2.69 to 2.99 log copies/ml and demonstrated superior LOD as compared to previously published data for some assays or to concurrent analyses with two new commercial tests.

1. Background

Respiratory tract infections (RTI) are common and are associated with significant health burden. The major viral agents of RTI include FluA/B, RSV, hMPV, PIV1-4, AdV, and RV. The spectrum of diseases associated with viral infection of the upper and lower respiratory tract include the common cold, otitis media, influenza-like illness, croup, bronchiolitis and pneumonia; all of which can be caused by any one of these viruses, leading to diagnostic limitations based on symptoms alone.

Rapid identification is important for both therapeutic and infection control purposes. Traditional rapid diagnostics, such as immunoassays, produce quick results and are simple to perform but have sub-optimal sensitivity (Reviewed in [1]). NAATs, which are rapid and have enhanced sensitivity, are considered the method of choice by many and are recommended by IDSA Guidelines [2–4]. However, performance differences have been observed among commercial NAATs, particularly after 2014 when sequence divergence in the matrix gene of A(H3N2) viruses emerged [5–7]. Especially problematic was a C163 T mutation that was first observed among 3C.2a clades of A(H3N2) [8–10]. Commercial assays with significantly reduced sensitivities after the C163 T mutation emerged, included Prodesse ProFlu+ (PFlu) and Xpert® Flu (Xpt).

The Panther Fusion® Respiratory Virus assays on the fully-automated Panther Fusion® system include the Flu A/B/RSV, Paraflu, and AdV/hMPV/RV (Table 1). This new system from Hologic has redesigned amplification reactions as compared to Pro. The FluA component still targets the matrix gene, but it uses a dual target approach with multiple probes for added redundancy to help safeguard against genetic drift. Both FluB and RSV now target the matrix gene and the AdV hexon gene target is designed to detect all AdV genotypes. The gene targets for hMPV and PIV 4 are the nucleocapsid genes, while those for PIV 1–3
and RV are the hemagglutinin-neuraminidase region and the 5' UTR, respectively. This test system also expands the menu of virus detected with the inclusion of a RV and PIV4.

2. Objectives

This study looks at the performance of the Panther Fusion® Respiratory Virus panels on a collection of samples that were previously analyzed with five other respiratory virus assays [7], to effectively enable a comparative analysis. This population set was also highly representative of the A(H3N2) clade (3C.2a), truly challenging any FluA assay.

3. Study design

3.1. Specimens

Clinical specimens included 275 consecutive nasopharyngeal swab specimens, in 3 ml of viral transport medium, received into the laboratory for the detection of respiratory viruses during a 2-week period in the winter of 2015 (age range 22 d to 93 yr., median 25 yr., 45% pediatric cases, Table S1). These specimens were previously used in a prospective analysis of PFlu and PAST (Hologic, San Diego, CA), FilmArray Respiratory Panel 1.7 (RP, BioFire, Salt Lake City, UT), and cobas® Influenza A/B test (cobas, Roche Diagnostics, Indianapolis, IN) specifically for the detection of FluA. Subsequently, Xpt (Cepheid, Sarl, Switzerland) was analyzed retrospectively. Specimens were stored at -80 °C, after original testing with PFlu/PAST (49%) or Pro (51%), thawed for clAB and RP or PAST testing, frozen at -80 °C, thawed and frozen for Xpt testing. Some were frozen and thawed additional times for previous discrepancy analysis. They were again thawed for testing by fusion. Selected archived samples positive for respiratory viruses (n = 225), previously tested by various combinations of NAATs, were analyzed.

Clinical specimens containing low Ct values on Fusion (presumably high titers) of RSV, PIV1, PIV3, hMPV, AdV, and RV were serially diluted 1:10 in VTM and tested in triplicate. Viral stocks were serially diluted 1:10 in VTM and tested in quadruplicate for LOD analyses. Viral nucleic acid concentration determinations were based on quantified control viral RNA (Hologic) using either PFlu or PAST, depending on strain-based amplification efficiency.

3.2. Viruses

FluA isolates obtained through the NYS DOH Proficiency Testing program were classified based on HA sequences and included A/California/7/2009(H1N1)pdm09-like (09H1N1), A/Perth/16/2009(H3N2)-like (Perth), A/Texas/50/2012(H3N2)-like (Texas) HA gene, and B/Massachusetts/2/2012-like (Flub). Texas was later shown to be a chimeric virus with an A/Hong Kong/5738/2014-like M1 gene [7]. Texas is also A/New_York/04/2014 (EPI_ISL_157766) in the GI-SAI database (personal communication with Jennifer LaPlante, NYS DOH Wadsworth Center). A/Switzerland/9712593/2013(H3N2)-like (Swiss) and A/Indiana/09/2012(H3N2v)-like were gifts from Jennifer LaPlante and Judith Lovchik, Indiana State Department of Health, respectively. Viral stocks were serially diluted 1:10 in VTM and tested in quadruplicate for LOD analyses. Viral nucleic acid concentration determinations were based on quantified control viral RNA (Hologic) using either PFlu or PAST, depending on strain-based amplification efficiency.

3.3. Nucleic acid extraction and amplification

Fusion Assays (Hologic) were performed on the fully automated Panther Fusion® with continuous, random access. This instrument utilizes universal nucleic acid extraction and PCR chemistry. The assay specific reagents are available in ready to use reagent cartridges. Initially, 500 μL of specimen was added to a Panther Fusion Specimen Lysis Tube containing 750 μL buffer and 360 μL of the mixture is used for an extraction. The nucleic acid was subsequently eluted into 50 μL and 5 μL were amplified for an effective sample volume tested of 14.4 μL.

LOD studies were expanded to newer tests kits, RP2 and Cepheid Xpert® Xpress Flu (Xpress), both of which have been marketed as having improved sensitivities among currently circulating strains of influenza. Testing was performed in accordance with the manufacturer’s package insert.

3.4. Statistical analysis

Specimens were considered true positive (TP) using a composite reference standard (CRS) defined as positive with previously published results [11]. Samples equivocal for FluA with RP were considered positive by that test method. The resolver test involved a modification of Pro assays to enhance the analytical sensitivity. Specifically, viral RNA was extracted from 0.4 μl of specimen (twice the normal volume) using the easyMAG extractor (bioMerieux, Durham, NC) and eluted to a volume of 25 μL. RNA extracts, 5 μL (effective sample volume tested of 80 μL), were amplified with the appropriate Pro assay on SmartCyclers (Cepheid). Sensitivities, specificities, and confidence intervals (CI) were determined using Microsoft Excel 2016 (Redmond, WA) [11]. Probit analyses for the limit of detection with a 95% probability of detection were performed using SPSS version 8.0 (IBM, Armonk, NY).
4. Results

4.1. Performance with consecutive clinical samples

The performance of Fusion was first evaluated using 275 consecutive nasopharyngeal specimens collected during the peak of the influenza season in January-February 2015. This sample set was previously used in a prospective analysis for cIAB, PFlu/PFAST, RP and Xpt. The incidence of FluA in this population was previously considered to be 24%, exclusively A(H3N2), with 66 true positive cases. Even though this collection of specimens has been used in multiple studies and has gone through multiple freeze-thaws cycles, FFABR was positive for 65 of the TP cases (Table 2). The one false negative sample was previously positive by RP only. FFABR was positive in an additional 4 T P specimens. As a result of reclassification after resolver testing, the incidence of FluA in the sample set was now 25%. The sensitivity and specificity of FFABR for the detection of A(H3N2) circulating in 2015 were 98.7% and 97.1%.

This sample set was also positive for multiple other viruses, including RSV (55), hMPV (8), PIV2 (1), PIV3 (10), Adv (7) and RV (18). Total co-infections include 3 triple infections (2 H3N2, RSV & Adv, 1 RSV, Adv and RV) and 13 dual infections (1 H3N2 & RSV, 3 H3N2 & RV, 1 H3N2 & hMPV, 1 RSV & PIV3, 2 RSV & Adv, 4 RSV & RV, 1 PIV3 & RV).

4.2. Performance with additional respiratory viruses

To expand the analysis of Fusion with other respiratory viruses, 225 archived, respiratory virus positive samples were evaluated. The viruses included in this sample set were A(H1N1)pdm09 (49), A(H3N2) from 2009 (5), seasonal A(H1N1) from 2009 (4), FluB (54), RSV (7), PIV1 (15), PIV2 (3), PIV3 (16), PIV4 (17), Adv (17), hMPV (7), and RV/EV (20), as well as 25 samples negative for all Fusion detectable viruses but positive for either coronaviruses or atypical bacteria (Table 3). Total co-infections in this set included 3 triple infections (2 H3N2 & RSV & Adv, 1 RSV, Adv and RV, 1 H3N2 & hMPV, 1 RSV & PIV3, 2 RSV & Adv, 4 RSV & RV, 1 PIV3 & RV).

Table 2

| n   | TP | FFABR | cIAB | PFAST | RP | Xpt | Co-Infections or other viruses |
|-----|----|-------|------|-------|----|-----|--------------------------------|
| 51  | +  | +     | +    | +     | +  | 1 RSV & 3 RV |
| 5   | +  | +     | +    | +     | -  |      |                                 |
| 4   | +  | +     | -    | +     | +  | 1 RSV & Adv |
| 1   | +  | +     | -    | +     | -  |      |                                 |
| 2   | +  | +     | -    | +     | b | 1 RSV & Adv |
| 2   | +  | +     | +    | -     | -  |      |                                 |
| 1   | +  | -     | -    | +     | -  |      |                                 |
| 4   | +  | +     | -    | +     | -  |      |                                 |
| 6   | +  | -     | -    | +     | -  |      |                                 |
| 199 | -  | -     | -    | -     | -  |      | multiple other viruses |

* True positive.
* 2 RP positive FluA, but not typed, and 1 RP FluA equivocal.
* Cells with yellow highlight were previously considered to be true negative (TN) in previous study (positive by one test only) [1].
* True positive after discrepancy analysis.
* Positive for multiple other viruses, including RSV (55), hMPV (8), PIV2 (1), PIV3 (10), Adv (7) & RV (18). Total co-infections include 3 triple infections (2 H3N2, RSV & Adv, 1 RSV, Adv and RV) and 13 dual infections (1 H3N2 & RSV, 3 H3N2 & RV, 1 H3N2 & hMPV, 1 RSV & PIV3, 2 RSV & Adv, 4 RSV & RV, 1 PIV3 & RV).

Table 3

| True Pos | n | FFABR | Pro | RP | cIAB | Xpt | Co-Infections |
|----------|---|-------|-----|----|------|-----|--------------|
| H1N1pdm09 | 46 | +     | +   | +  | +   | +   | 2 RSV        |
| H1N1pdm09 | 1  | +     | +   | +  | +   | +   |              |
| H1N1pdm09 | 2  | +     | +   | -  | +   | +   |              |
| H3N2     | 5  | +     | +   | +  | +   | +   |              |
| sH1N1f   | 4  | +     | +   | +  | +   | +   |              |
| FluB     | 25 | +     | +   | +  | +   | +   | 2 RSV        |
| FluB     | 1  | +     | +   | +  | +   | +   |              |
| FluB     | 2  | +     | +   | +  | +   | +   |              |
| FluB     | 13 | +     | na  | na | na  | na  |              |
| FluB     | 3  | na    | na  | na | na  | na  |              |
| True Neg | 1  | –     | –   | PIV1| na  | na  |               |
| True Neg | 1  | –     | –   | na  | na  | na  |               |
| True Neg | 21 | –     | –   | na  | na  | na  |               |
| Unknown  | 3  | –     | –   | RVEV| na  | na  |               |
| Total    | 225|       |     |     |     |     |               |

* Virus specific Prodesse test.
* A(H1N1)pdm09.
* 6 were equivocal for FluA with RP.
* 1 repeatedly produced an error with Xpt.
* 1 positive for FluA with RP but not typed.
* Seasonal A(H1N1) circulating in 2009 prior to the pandemic not analyzed.
* True negative for organisms tested for with Fusion. Other organisms detected by RP were 11 coronaviruses and 8 atypical bacteria.
* True status unknown, discrepant between only two methods for detecting RV. Negative for EV with lab developed test.

For FluB, 69 for RSV, 65 for PIV, 27 for Adv, 21 for hMPV, and 41 for RV. Fusion correlated with all historical positive results except 6 samples negative with Fusion RV but positive for EV/RV by RP. These six samples were tested by our lab developed assay for EV and were positive, excluding them as false negative cases. Fusion had 29 positive test results not detected by another method, including 1 more FluA, 7 RSV, 3 PIV3, 3 Adv, 6 hMPV and 3 RV. These samples, except the 3 positive for RV, were analyzed by the appropriate resolver tests, which confirmed Fusion results for 4 RSV, 1 PIV3 and 3 Adv. The sensitivity of Fusion ranged from 99 to 100% for the various viruses and the specificity ranged from 98% to 100% (Table 4).

4.3. Limit of detection

Because previous studies demonstrated FluA assay performance variations can be strain associated, we performed LOD analyses with six isolates of Flu. We also included RP2 and Xpress in this analysis as these assays were new to market and considered to have improved viral strain coverage. Fusion demonstrated excellent analytical sensitivity with low LODs ranging from 2.69 to 2.99 log copies/ml (Table 5). The LODs were highly consistent across the strains and clades of FluA. The assay was highly reproducible with coefficients of variances ranging from 0.5 to 4.2% across the dilutions (data not shown). RP2 and Xpress demonstrated improved analytical sensitivity and consistency as compared to the manufacturer’s previous test systems. However, the LODs were still relatively higher, particularly with newly circulating A(H3N2) subclades.

To assess differences in analytical sensitivity for the other Fusion targets versus Pro or RP, clinical specimens containing RSV, PIV1, PIV3,
Table 4
Fusion performance against historical data for respiratory virus detection in total collection of 500 samples.

| Virus              | TP         | Fusion TP | Fusion FP | TN         | Sens | Spec   |
|--------------------|------------|-----------|-----------|------------|------|--------|
| H1N1pdm09          | 49         | 49        | 451       | 451        | 100% | 100%   |
| H3N2               | 75         | 79        | 418       | 418        | 99%  | 98%    |
| sH1N1              | 4          | 4         | 496       | 496        | 100% | 100%   |
| FluB               | 54         | 54        | 446       | 446        | 100% | 100%   |
| RSV                | 66         | 66        | 435       | 435        | 100% | 99%    |
| hMPV               | 15         | 15        | 479       | 479        | 100% | 99%    |
| PIV1               | 15         | 15        | 485       | 485        | 100% | 100%   |
| PIV2               | 4          | 4         | 496       | 496        | 100% | 100%   |
| PIV3               | 27         | 27        | 472       | 472        | 100% | 100%   |
| PIV4               | 17         | 17        | 483       | 483        | 100% | 100%   |
| Adv                | 24         | 24        | 476       | 476        | 100% | 100%   |
| RV                 | 38         | 38        | 459       | 459        | 100% | 99%    |
| All Viruses        | 391        | 390       | 146       | 135        | 100% | 87%    |

* Samples with no virus detected (total true results among 500 samples was 525).

hMPV, Adv, and RV were serially diluted for endpoint comparison. Fusion was positive for an additional 10-fold dilution for RSV, PIV3, and Adv and two 10-fold dilutions for hMPV, while the endpoint sensitivities were similar between Fusion and Pro or RP for PIV1 and RV (data not shown).

Table 5
Limit of Detection (estimated log copies/ml) for Fusion, RP2 and Xpress.

| Virus              | Strain (source)                  | H3N2 Clade | Fusion | RP2 | Xpress |
|--------------------|----------------------------------|------------|--------|-----|--------|
| H1N1pdm09          | A/California/07/2009-Like (NYS-PT)| na         | 2.77   | 2.85| 3.08   |
| sH3N2              | A/Perth/16/2009-Like (NYS-PT)    | 1          | 2.69   | 3.37| 2.69   |
| sH3N2              | A/Switzerland/9715291/2013-Like (NYS-Cell) | 3C.3a       | 2.75   | 4.57| 3.58   |
| sH3N2              | A/Texas/50/2012-Like (NYS-PT)*   | 3C.2a       | 2.96   | 3.87| 3.48   |
| H1N2v              | A/Indiana/09/2012-Like (IS)      | vH3E3      | 2.82   | 2.83| 2.84   |
| FluB               | B/Massachusetts/02/2012-Like (NYS-PT) | na         | 2.99   | 3.86| 3.64   |

* Chimeric isolate with A/Texas/50/2012-Like HA gene and A/Hong Kong/5738/2014-like M1 gene.
In summary, Fusion offers exquisite sensitivity for the detection of respiratory viruses on a fully automated platform. There are many options for respiratory virus testing, each with their own niche. Fusion appears to be the leader with regards to sensitivity, protections against genomic drift, while maintaining high throughput and minimal hands on time.

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Ethical approval

Studies were performed in accordance with IRB requirements at Albany Medical Center.

CRedit authorship contribution statement

Kathleen A. Stellrecht: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization. Jesse L. Climo: Data curation, Formal analysis, Investigation. Lisa I. Wilson: Data curation, Investigation. Vincente P. Macea: Investigation. Shafiq A. Butt: Project administration, Resources, Supervision.

Declaration of Competing Interest

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jcv.2019.104204.

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