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# The FilmArray<sup>®</sup> respiratory panel: an automated, broadly multiplexed molecular test for the rapid and accurate detection of respiratory pathogens

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The FilmArray Respiratory Panel (RP) (BioFire Diagnostics, Inc., Salt Lake City, UT, USA) is the first multiplex molecular panel cleared by the US FDA for the detection of both bacterial and viral respiratory pathogens in nasopharyngeal swabs. The FilmArray RP targets 20 pathogens including 17 viruses and subtypes and three bacteria, and is performed with minimal sample manipulation. The FilmArray RP has a fully automated sample-to-answer workflow with a turn-around-time of approximately 1 h. The reported sensitivity and specificity of the assay ranges from 80 to 100 and 100%, respectively, with the sensitivity for the adenovirus as low as 46%. A new version of the FilmArray RP assay (version 1.7) with improved sensitivity for the adenovirus was released in 2013. The performance characteristics and simplified workflow have allowed its implementation in a wide range of laboratories. The FilmArray RP has changed the diagnostic landscape and will have a significant impact on the care of patients with respiratory tract infection.

**KEYWORDS:** automation • multiplex PCR • rapid diagnosis • respiratory tract infection

Community-acquired respiratory tract infections occur with varied frequency throughout the year. These infections are among the most common reasons for healthcare visits and can be caused by both viral and bacterial pathogens [1]. Symptoms caused by viruses are non-specific and include sore throat, runny nose, watery eyes, cough, wheezing, shortness of breath, sputum production and nasal congestion. Additionally, these symptoms are indistinguishable from those caused by bacterial pathogens [2]. Mixed infections with two or more respiratory pathogens are not uncommon and might be underreported due to the limited sensitivity of methods currently used for diagnosis [3–5]. The identity of the pathogen causing symptoms is critical for rapid institution of adequate antiviral or antibiotic therapy as well as proper isolation of

infected patients to prevent health-care associated infection, which can have devastating effects in an immunocompromised population [6,7]. Empirical, broad-spectrum therapy is often administered due to limitations of conventional diagnostic methods to provide timely results to guide clinician's decision. A great illustration of the importance of specific diagnosis came with the emergence of the novel H1N1 influenza virus in 2009. Unlike the seasonal H1N1 influenza virus, the novel virus was sensitive to the antiviral drug oseltamivir (Tamiflu<sup>®</sup>), but resistant to amantadine and rimantadine (Symadine<sup>®</sup> and Flumadine<sup>®</sup>). Since respiratory symptoms of these two influenza viruses are similar, accurate and timely identification of the correct virus was critical for the administration of appropriate therapy [8].

In normal hosts, most respiratory viral infections are self-limited, although complications can occur. In the last two decades, respiratory viruses have become increasingly recognized as a serious cause of morbidity and mortality in hematopoietic stem cell transplant (HSCT) and solid organ transplant (SOT) recipients [9–13]. As part of their treatment, patients undergoing HSCT and SOT become severely immunosuppressed, rendering them highly susceptible to infectious pathogens. Serious complications, which can be fatal, include viral pneumonia, lateral airflow obstruction syndrome, graft rejection and superinfection with bacterial and fungal pathogens [9,12]. Similarly, respiratory viruses can have a significant impact in young children and elderly patients resulting in frequent hospitalization and significant health costs [14,15].

The most common viruses causing respiratory illness include influenza virus type A, influenza virus type B, respiratory syncytial virus (RSV), parainfluenza viruses (PIV) 1, 2 and 3, human metapneumovirus (hMPV) and picornaviruses (rhinoviruses and enteroviruses) [7]. In children undergoing treatment for hematologic malignancies, infections due to influenza, parainfluenza, parainfluenza viruses, and RSV are particularly common and have significant impact on oncologic care [16,17]. The clinical significance of other viruses such as bocavirus, human coronaviruses NL63, human coronaviruses HKU1, parainfluenza virus 4 and rhinovirus is less clear [18]. Respiratory tract infections caused by bacterial pathogens includes *Streptococcus pneumoniae*, *Haemophilus influenzae*, as well as atypical bacterial that are often difficult to culture in the laboratory including *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* [19].

## Respiratory tract pathogens

### Influenza

Influenza viruses are enveloped, negative sense, single-stranded RNA (ssRNA) viruses belonging to the *Orthomyxoviridae* family. There are three types of influenza viruses: influenza virus type A, influenza virus type B and influenza virus type C. Types A and B are the most commonly isolated while type C is rare and often not included in routine diagnostic test. Influenza viruses type A are further sub-typed based on the sequence of two glycoproteins: hemagglutinin (H) and neuraminidase (N) [20]. Influenza viruses cause annual, seasonal epidemic characterized by an increase in the frequency of upper respiratory symptoms seen in the community between December and May in the northern hemisphere [21]. Although the infection usually remains limited to the upper respiratory tract in most patients, complications due to influenza viruses have been reported in HSCT and SOT patients, especially lung transplant recipients [18,22,23]. In one study, the frequency of pneumonia caused by influenza viruses was 30% with a fatality rate of 15% in HSCT recipients [12]. However, reports on frequency of complications has varied (7–44%) with fatality ranging from 15 to 28% in HSCT recipients [18]. In SOT, the complication rate varies based on the organ transplanted with lung transplants recipients being particularly at increased risk [22,23].

### RSV

RSV is an enveloped, non-segmented, ssRNA virus belonging to the *Paramyxoviridae* family. The seasonality of RSV follows closely that of influenza viruses with increased incidence in the winter months in the northern hemisphere [24]. In transplant patients and young children, infection with RSV can result in serious complications [25,26]. As such, in most centers, detection of RSV pre-transplant results in a delay of SCT until patient clears the infection. In one study of HSCT recipients, 80–90% of patients with upper respiratory RSV infection developed pneumonia with 30–40% exhibiting symptoms within 7 days following upper respiratory tract symptoms [26]. In a large study of children under 5 years of age, the incidence of RSV infection was 18%. RSV infections occurred in previously healthy children with no pre-existing conditions. Risk factors were identified only for those under 2 year of age [25].

### PIV

PIV are non-segmented, negative sense RNA viruses, structurally related to RSV and belong to the *Paraxmyxoviridae* family. There are four predominant PIV serotypes including: PIV-1, PIV-2, PIV-3 and PIV-4 [27]. Until recently, PIV-4 was rarely isolated since most diagnostic assays available did not include reagents for the detection of PIV-4 and so less information is available on this PIV subtype. In the northern hemisphere, PIV occurs year-round with PIV-1 occurring most frequently in the fall, PIV-2 occurring in the fall to early winter and PIV-3 occurring in the spring and summer months [24,27]. Infections caused by PIV are usually mild, ranging from asymptomatic shedding to the common cold, croup and bronchiolitis. Similar to RSV, PIV infection occurs frequently in children, with most children exposed to PIV-3 by the age of two and PIV-1 by the age of 5 [24]. The reported incidence of PIV in HSTC populations ranges from 0.2 to 18% with 13 to 43% progressing to lower respiratory tract infections (LRTIs) and 12 to 50% of these LRTI resulting in death with most infections caused by PIV-3 [18,28]. In lung transplant recipients, PIV LRTI have been associated with high rate of allograft rejection [29].

### hMPV

hMPV is another member of the *Paraxmyxoviridae* family and is structurally related to RSV and PIV. It is a relatively newly described virus and has become increasingly recognized as a cause of significant respiratory illness in young children, older adults and immunocompromised patients [30,31]. The incidence of hMPV in HSCT patients ranges from 3 to 7% with complications and fatality rate similar to those of RSV [18,32]. Similar to other *Paramyxoviridae* viruses, hMPV can result in graft dysfunction and/or rejection in lung transplant recipients [33,34].

### Adenoviruses

Adenoviruses are non-enveloped, double stranded DNA viruses belonging to the *Adenoviridae* family. Adenoviruses are divided into seven types (A–G) and 52 serotypes, with type B/C most

commonly associated with respiratory illnesses [35]. Adenoviruses can remain dormant in lymphoid cells and may reactivate following immunosuppression [36]. Adenoviruses are present year-round and common in pediatric populations where they generally cause self-limited, mild infections [37]. The incidence of adenovirus in HSCT and SOT patients ranges from 3 to 29% and 5 to 10%, respectively and varies with patient age, type of transplant, the degree of immunosuppression, and the organ being transplanted [13,18,38].

### Rhinoviruses

Rhinoviruses are small, ssRNA viruses of the *Picornaviridae* family. Rhinoviruses are a diverse group of viruses with more than 100 serotypes identified to date [39]. Rhinoviruses are the most common cause of the 'common cold' and can be isolated throughout the year with a peak incidence in September [40]. In healthy individuals, rhinovirus infections are usually self-limited with symptoms lasting between 7–14 days [41]. Several reports have linked rhinoviruses with more severe presentations including otitis media, bronchiolitis and exacerbation of asthma in children [41]. In immunocompromised hosts, severe complications including pneumonia, can occur. In one recent study, the severity of rhinovirus infection in immunocompromised patients was similar to that of the 2009 H1N1 pandemic influenza A [42]. With the use of current diagnostic molecular methods, information of the frequency and severity of infections caused by rhinoviruses will become available.

### Coronaviruses

Coronaviruses (CoV) are the largest RNA viruses and belong to the *Coronaviridae* family along with toroviruses [43]. CoV are divided into three groups based on sequence homology with group 1 including CoV-229E and CoV-NL63, group 2 including CoV-OC43 and CoV-HKU1 and group 3 which does not include any human CoVs. CoV are responsible for a wide range of upper respiratory tract infections (URTI) but are associated mainly with the 'common cold' [43]. Only a limited number of reports on CoV infections in immunocompromised hosts are available. In one study, asymptomatic shedding of CoV was detected in the first 100 days following allogeneic HSCT [44]. In other reports, LIRTs, with fatal outcomes have been reported in patients following SCT [45,46].

### Bacterial pathogens

Bacterial pathogens included in the respiratory panel (RP) include *Bordetella pertussis*, *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*. All three organisms can cause both upper and lower respiratory tract infections including acute sinusitis, bronchitis and pneumonia [47]. *B. pertussis* causes pertussis or whooping cough primarily in non-vaccinated children and in adults, the infection is associated with a persistent cough of up to 2 weeks [48]. Atypical organisms, including *M. pneumoniae* and *C. pneumoniae*, account for about one third of cases of bacterial pneumonia [19,49]. Unlike other common bacteria associated with these symptoms, *B. pertussis*,

*M. pneumoniae* and *C. pneumoniae* do not grow readily on media used for routine bacterial culture and therefore require a high level of suspicion from the clinician to inform the laboratory and request specific diagnostic tests. In one study, persistent cough of at least 2 weeks was observed in children infected with one or more of these three organisms underscoring the need for sensitive and specific diagnosis to guide therapy [50].

### Diagnostic assays for respiratory pathogens

Conventional methods used to diagnose respiratory viral infections include rapid antigen tests, direct fluorescent antibody assays, shell vials and viral culture [51]. Each of these methods has advantages and disadvantages with sensitivities and specificities ranging from 44 to 99% and 74 to 100%, respectively requiring additional testing of negative specimens. In addition, these assays can be subjective, require expertise for interpretation of cytopathic effect, have a limited range of detection and a turn-around-time as long as 14 days [51].

Molecular assays, based on PCR, are rapid and sensitive compared to conventional methods. Until recently, individual laboratories with the appropriate expertise, developed and implemented their own real-time PCR assays for each of the most common respiratory viruses [31,52–54]. Several commercial assays, for both research-use only (RUO) and those cleared by the FDA (TABLE 1) are now widely available, facilitating the implementation of these technologies in diagnostic microbiology laboratory.

Until recently, most FDA-approved molecular assays targeted only the most commonly isolated viruses, including influenza A and B viruses and RSV, either as singleplex or duplex assay. Although this method has the benefit of targeted approach to diagnosis of respiratory infections, it is limited to only the most common viruses, requires clinicians to order multiple tests and does not always permit the detection of co-infecting pathogens. An alternative approach was the development of broadly multiplexed assay that allow simultaneous detection of a wider range of possible pathogens (5 or greater) in one single tube [4,55–59].

In 2008, the FDA cleared the first broadly multiplexed molecular assay, the xTAG® respiratory viral panel (RVP) (Luminex Molecular Diagnostics, Toronto, ON, Canada). The xTAG RVP detects 12 viruses and subtypes including: RSV A, RSV B, influenza virus A, influenza virus A H1 subtype, influenza virus A H3 subtype, influenza virus B, PIV 1, 2, 3, MPV, adenovirus and enterovirus/rhinovirus. The xTAG RVP includes five steps: nucleic acid extraction, multiplex RT-PCR, multiplex target-specific primer extension, hybridization; and detection of the amplified target on a Luminex 100/200 platform [60].

A second version of the assay, the xTAG® Respiratory Viral Panel Fast (RVP FAST), was approved in 2011 and detects RSV, influenza virus A (H1 subtype, H3 subtype and untypeable), influenza virus B, MPV, adenovirus and rhinovirus. The assay was simplified to reduce hands on time, workflow and turn-around-time from approximately 8 to 6 h. A study

**Table 1. FDA cleared molecular diagnostic assays for respiratory pathogens<sup>†</sup>.**

Name	Technology	Tests	Targets	Run time (min)	Maximum run size	Random access?	Specimen types
Focus Diagnostics	Real-time PCR	Simplexa Flu A/B & RSV Direct	FluA, FluB and RSV	50	8	No	NPS
IQuum	Real-time PCR	Liat Influenza A, B	FluA and FluB	20	1	Yes	NPS
Cepheid	Real-time PCR	Xpert Flu	FluA, FluA H1 2009 and FluB	~65	1	Yes	NPS, NW, NA
BioFire Diagnostics, Inc.	Real-time PCR	Respiratory Panel	FluA, FluA H1, H1 2009, H3, FluB, RSV, PIV 1-4, CoV OC43, HKU1, NL63 and 229E, hMPV, AdV, rhinovirus/enterovirus, <i>B. pertussis</i> , <i>M. pneumoniae</i> , <i>C. chlamydophila</i>	60	1	Yes	NPS
Nanosphere Verigene, Inc.	RT-PCR, multiplex gold nanoparticle probes	Respiratory virus plus test	FluA, FluA H1, H1 2009, H3, FluB, RSV A, RSV B	<2.5 h	1	Yes	NPS
Gen-Probe Prodesse, Inc.	Real-time PCR	ProFlu+ ProFAST+ ProParaflu+ Pro hMPV+ ProAdeno+	FluA, FluB, RSV FluA H1, H3, 2009 H1 PIV 1-3 hMPV adenovirus	4-5 h	Varies <sup>‡</sup>	No	NPS
Focus Diagnostics	Real-time PCR	Simplexa Flu A/B & RSV	FluA, FluB, RSV	4-5 h	Up to 96	No	NPS
Quidel Corporation	Real-time PCR	Influenza A + B hMPV and RSV	FluA, FluB hMPV and RSV	4-5 h	Varies <sup>‡</sup>	No	NS, NPS
Luminex Molecular Diagnostics, Inc.	PCR, beads hybridization and flow cytometry	xTAG RVP	FluA, FluA H1, H3, FluB, RSV A, RSV B, PIV 1-3, hMPV, AdV, rhinovirus	6-8 h	Up to 96	No	NPS
Luminex Molecular Diagnostics, Inc.	PCR, beads hybridization and flow cytometry	xTAG RVP Fast	FluA, FluA H1, H3, FluB, RSV, hMPV, AdV, rhinovirus	5-6 h	Up to 96	No	NPS
GenMark Diagnostic	PCR, hybridization, electric current	eSensor RVP	FluA, FluA H1, H3, FluB, RSV A, RSV B, PIV 1-3, hMPV, AdV C, AdV B/E, rhinovirus	~6 h	Varies <sup>‡</sup>	No	NPS

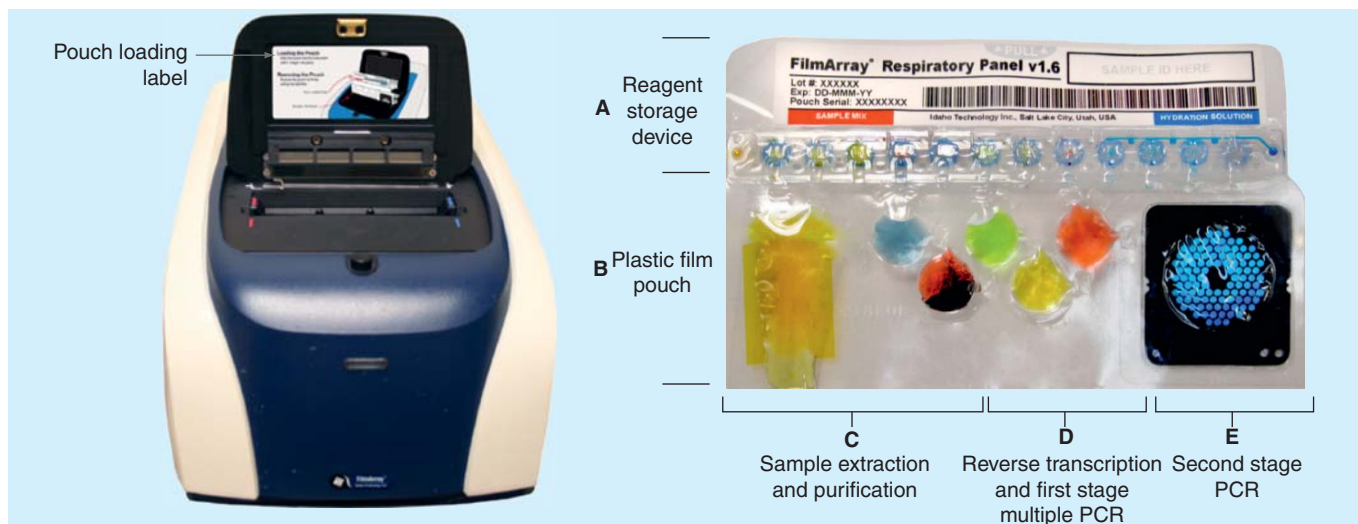
<sup>†</sup>As of 24 June 2013.

<sup>‡</sup>Depends on size of instrument available: Smartcycler/ABI Fast Dx (up to 96); GenMark Dx: 1 tower/8 tests, up to three towers/PC.

Adv: Adenovirus; Co: Coronavirus; Flu: Influenza; hMPV: Human metapneumovirus; NPS: Nasopharyngeal swabs; NS: Nasal swabs; NW: Nasal washes; RSV: Respiratory syncytial virus.

comparing the xTAG RVP to a pre-market, RUO version of the xTAG RVP FAST reported a reduced sensitivity of the xTAG RVP FAST (88.6 and 77.5%), especially for influenza B

virus, parainfluenza virus Type 2 and HCoV 229E, with the last two targets not included in the FDA cleared version of the assay [61].



**Figure 1. The FilmArray instrument and pouch.**

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Another recently cleared multiplexed RVP is the eSensor RVP (GenMark Diagnostics Inc., Carlsbad, CA, USA). The eSensor RVP can detect influenza virus A H1, influenza virus A H3, influenza virus A 2009 H1N1 influenza B, RSV subtype A, RSV subtype B, PIV 1, PIV 2, PIV 3, HMPV, human rhinovirus, adenovirus species B/E and adenovirus species C.

Two studies have evaluated the performance of the eSensor RVP compared to other multiplex respiratory panels including the FilmArray RP, the xTAG RVP and the xTAG RVP FAST and to laboratory developed tests [58,59]. The sensitivity and specificity of the eSensor RVP varied from 90 to 100% and 99 to 100% depending on the viral target.

### The FilmArray RP

The FilmArray RP assay is the first and only FDA-cleared assay for the qualitative detection of nucleic acid targets from both viruses and bacteria in nasopharyngeal swab specimens. The FilmArray RP was initially FDA-cleared for the detection of 15 viruses including the same viruses as the xTAG RVP plus CoV NL63 and HKU1 and PIV-4. In 2012, five more targets were cleared including CoV 229E and OC43, and three bacterial targets *B. pertussis*, *C. pneumoniae* and *M. pneumoniae* (version 1.6). To increase the detection rate for adenovirus, a second assay for the virus was added to the RP and this was FDA cleared in 2013 (version 1.7). The assay is performed on the FilmArray instrument and can be completed in approximately 1 h.

### The FilmArray instrument

The FilmArray is an integrated platform that combines automated sample preparation, total nucleic acid extraction with nested, multiplex PCR and reverse transcriptase PCR and automated detection of amplified targets [62]. The instrument has a small footprint (39.1 × 25.4 × 16.3 cm) and contains

pneumatic and electrical components to move reagents through the pouch and perform the functions described. Nested PCR is effected using two Peltier devices, and melt curves are detected using a blue LED light source and a charge couple device (CCD) camera (FIGURE 1) [62,63].

Nucleic acids are released from cells by the combined action of denaturing buffers, ceramic beads and a bead beater. Once lysed, cells are transferred to a blister containing magnetic beads which binds the released nucleic acids. Following application of a magnet and several washes, the nucleic acids are eluted and moved to PCR sites for amplification.

Once purified, the DNA/RNA extract is mixed with the first stage multiplexed PCR reagents, including a set of outer primers, and temperature cycling occurs on the first Peltier device. A reverse transcription PCR step is performed prior to the first PCR cycle. Amplification of target nucleic acids is then accomplished using the principle of nested PCR which uses a two stages approach to increase the sensitivity and specificity of the PCR reaction [64].

The resulting mixture is diluted and moved to the second stage PCR where the amplified products from the first stage PCR are used as templates and further amplified using a second set of inner primers with cycling occurring on the second Peltier device. During the second stage PCR, LCGreen Plus, a fluorescent, DNA intercalating dye, is incorporated into the DNA as it is amplified.

Positive reactions are determined based on DNA melting curve analysis of amplified product. Each target is run in triplicate, in three separate wells of the microarray. The melt curve of each individual replicate for each target is measured following amplification and a positive reaction is determined if the melt curve shape and peak falls within pre-established ranges.

Control of the instrument and interpretation of the results are done automatically by the FilmArray software [62,63].

**Table 2. Clinical sensitivity and specificity of the biofire filmarray respiratory panel.**

Study (year)	FA RP version	n	Patient population	Comparator assay	Discordant analysis	Sensitivity (%)	Specificity (%)	Ref.
Rand <i>et al.</i> (2011)	Premarket RUO	200	Adult and pediatrics	xTAG RVP	LDT	90–100	100	[67]
Babady <i>et al.</i> (2012)	Premarket RUO	358	Pediatrics	xTAG RVP Fast	ResPlex II v2.0	91.6–100	98.2–100	[65]
Popowitch <i>et al.</i> (2013)	FDA cleared version 1	300	Adult and pediatrics	xTAG RVP xTAG RVP Fast eSensor GenMark	LDT	57.1–100	100	[59]
Loeffelholz <i>et al.</i> (2011)	Premarket RUO	192	Pediatrics	Prodesse assays	LDT	54.5–100	98.4–100	[66]
Hayden <i>et al.</i> (2012)	Premarket RUO	176	Pediatrics	ResPlex II v2.0	ND <sup>†</sup>	ND <sup>†</sup>	ND <sup>†</sup>	[57]
Pierce <i>et al.</i> (2012)	Premarket RUO	215	Pediatrics	LDT	Repeat testing	46–100	50–100	[68]
Hammond <i>et al.</i> (2012)	Premarket RUO	90	Adults	Conventional methods	BioFire in-house singleplex assay	100	94	[70]

<sup>†</sup>LDT: Laboratory-Developed tests.

<sup>†</sup>ND: Not done or not determined (discordant results were not further analyzed).

FA RP: FilmArray respiratory panel; RUO: Research use only.

### The pouch

All reagents necessary to perform the assay are contained in the vacuum sealed FilmArray pouch. The lyophilized reagents, which are distributed in 12 separate reservoirs, are rehydrated with a buffer solution just prior to adding the specimen. Additional reagents are contained in three of the pouch's six blisters, including ceramic beads for lysis, magnetic beads for DNA/RNA purification and the oligonucleotides for the first stage PCR. The blisters are connected to channels which are used to move the liquid reaction from one blister to another. The last section of the pouch is the 'solid-phase array', a set of 102 wells with each well containing primers for the second stage PCR (FIGURE 1) [62,63].

### The FilmArray RP

The FilmArray RP targets 20 viruses and bacteria including Influenza virus type A (including subtypes H1N1, H3N2 and the 2009-H1N1), influenza virus type B, RSV, adenovirus, hMPV, rhinoviruses/enteroviruses, CoV HKU1, NL63, 229E, OC43, PIV-1, PIV-2, PIV-3, PIV-4, *B. pertussis*, *C. pneumoniae* and *M. pneumoniae*. In addition, the assay contains two target controls, a RNA target from *Schizosaccharomyces pombe*, which controls the entire process from extraction to DNA melt analysis, and a DNA target control, which is included in the array well and controls for the second stage PCR. Each target has at least three replicate assays and the final interpretation is determined from the number of replicates that are positive. The FilmArray RP has multiple targets for some of the pathogens detected (e.g., influenza virus type A has two pan-influenza targets and one HA specific target).

### Diagnostic performance characteristics

Published reports on the performance of the FilmArray RP are summarized in TABLE 2. The FilmArray RP has been evaluated against other FDA cleared molecular assays [59,65–67]. Most of the published reports evaluated the pre-market version of the FilmArray RP on samples from pediatric patients where the prevalence of respiratory viruses is expected to be higher. Overall, the FilmArray RP has a sensitivity and specificity >80%. However, the reported sensitivity of the first version of FilmArray RP for adenovirus is around 50%. As noted above, the manufacturer has released a new version of the FilmArray RP with improved adenovirus detection.

Rand *et al.* compared the performance of the FilmArray RP and xTAG RVP on 200 specimens from both adult and pediatric patients, previously tested by viral culture and antigen testing [67]. The complete agreement between the two tests was excellent at 91.5% with more viruses detected by the FilmArray RP (160 viruses by FilmArray RP versus 149 viruses by xTAG RVP). Notably, the FilmArray RP had greater sensitivity for RSV than the xTAG RVP (100 vs 82.2%). Loeffelholz and colleagues compared the FilmArray RP to the series of FDA cleared Prodesse (GenProbe) Real-time PCR assays including the ProFlu+, ProFAST+, ProParaflu+, ProhMPV+ and ProAdeno+ [66]. The FilmArray RP and Prodesse assays showed good overall agreement (94.3%) when tested on 192 specimens from pediatric patients, with the FilmArray RP being more sensitive for PIV-1 and -3, detecting an additional two PIV-1 and three PIV-3 not detected by the ProParaflu+ assay. The ProAdeno+ was more sensitive for adenoviruses than the FilmArray RP, detecting a total of 11 adenoviruses compared to five adenovirus detected by the

FilmArray RP. Additionally, the authors compared the FilmArray RP to LDT for targets not included in the Prodesse assays with the sensitivity ranging from 50 to 100% although the number of positive specimens tested was small (n = 1 to 8), except for rhinovirus/enterovirus (n = 118) targets. We compared the performance of the FilmArray RP to the pre-market version of the xTAG RVP FAST on 358 respiratory specimens from pediatric patients [65]. In our report, the FilmArray RP was overall more sensitive than the xTAG RVP FAST for most viruses common to both assays, especially for RSV (100 vs 60%) and FluB (100 vs 50%). However, the xTAG RVP FAST was more sensitive than the FilmArray RP for PIV-4 (100 vs 33.3%) and rhinoviruses (97.6 vs 91.6%).

In a recent study, the FilmArray RP was evaluated along other multiplexed FDA-cleared molecular assays including the xTAG RVP, the xTAG RVP FAST and the GenMark eSensor [59]. The FilmArray RP had an overall sensitivity of 84.5% with sensitivity varying from 92–100% for influenza virus A/H3, MPV, PIV-1, PIV-2, PIV-3 and RSV B and sensitivity varying from 73–83% for influenza virus A H1/2009, influenza virus, RSV A and rhinoviruses/enteroviruses. Of note, the sensitivity of the FilmArray RP and the xTAG RVP for RSV was similar [59]. The sensitivity of the FilmArray RP for adenoviruses was especially low at 57% as reported in other studies [66,68].

Other studies have evaluated the FilmArray RP against conventional methods, laboratory-developed assays and RUO assays [57,68–70]. In one study done using mock specimens prepared by combining previously positive nasal washes, nasal swabs, bronchoalveolar lavage fluids, sputum and tracheal aspirates, the FilmArray RP detected 90% of viruses identified by the LDT assays with discordant results mainly occurring at low viral loads [69]. The FilmArray RP was also evaluated against the Resplex II Panel v2.0 (Qiagen) and the two tests had an overall agreement of 83.8% with the FilmArray RP detecting about 10% more positive specimens and 21% more viruses than the Resplex assays [57]. Pierce *et al.* reported an overall agreement between the FilmArray RP and their LDT real-time PCRs of 98.6% with the FilmArray RP adenovirus assay being less sensitive than the LDT adenovirus real-time PCR, missing 13/24 adenovirus positive specimens. The FilmArray RP was unable to specifically detect adenovirus serotypes 6 and 41 at any viral concentrations and serotypes 2, 20, 35 and 37 at low viral concentrations [68].

According to the manufacturer's product insert, the low sensitivity of the FilmArray RP for adenovirus specifically relates to adenovirus C, serotypes 2 and 6 as confirmed in Pierce *et al.* study, and recommended testing of negative specimens using alternative methods to detect adenoviruses when suspected (FilmArray RP PI v1.6). In April 2013, a new version of the FilmArray RP assay (version 1.7) was released. The FilmArray RP v1.7 was designed to enhance the detection of adenoviruses by adding a second adenovirus assay to the panel. No peer-reviewed published reports are yet available on the performance of the improved assay for adenovirus. Abstracts presented at the 29th clinical virology symposium showed increased sensitivity of the FilmArray RP v1.7 when compared

to FilmArray RP v1.6 (81.6 vs 23.8%) but still missed adenoviruses detected by the xTAG RVP or Prodesse ProAdeno+ Assay and LDT adenovirus singleplex [71,72].

## Conclusions

Respiratory tract infections can be caused by a wide range of pathogens including viruses and bacteria. In addition, novel viruses, including bocavirus and novel CoVs, are increasingly being recognized as causes of respiratory tract illness. Given the non-specific nature of the respiratory symptoms, the ability to detect these novel viruses as well as other significant pathogens is paramount for optimal patient care. The FilmArray RP is the most extensive panel that is currently FDA cleared for rapid detection of respiratory tract pathogens. Although its adenovirus assays still require improvement, the overall clinical sensitivity and specificity of the FilmArray RP assay is better than conventional methods and comparable to other high complexity multiplexed molecular assays on the market.

## Expert commentary

Multiplex molecular diagnostic assays are ideal for infections with a wide differential diagnosis. However, the design of broadly multiplexed assays is challenging as multiplex PCR assays are subject to decreased sensitivity due in part to, targets' competition and primer dimers formation [64]. The overall sensitivity and specificity of the FilmArray RP in published reports varied between 85–100% and 100%, respectively with the sensitivity of the adenovirus assays remaining a challenge even in the new version of the assay. However, even with the lower sensitivity of the adenovirus, the FilmArray RP has drastically changed the diagnostic landscape and allowed implementation of a sensitive and rapid molecular assay in a wide range of diagnostic settings [73,74].

The FilmArray RP was the second highly multiplexed molecular assay to be cleared by the FDA and the first one to include bacterial pathogens in the panel. It is important to note however that as extensive as the FilmArray RP panel is, other important bacterial causes of pneumonia including *S. pneumoniae* and *H. influenzae*, are not included on the panel. When compared to other FDA cleared multiplexed assay (TABLE 1), the FilmArray RP has the greatest number of targets in its panel, the simplest workflow, the shortest turn-around-time and the highest reagent cost [59,65]. The true value of the FilmArray RP assay lies in its ability to provide actionable results to clinicians and to facilitate the flow of patients in the hospital by providing infection control staff with real-time information.

The only specimen type that is currently cleared by the FDA for testing is naso-pharyngeal swabs. However, other respiratory tract specimens are routinely submitted to the laboratory for testing including nasal swabs, nasal washes, throat swabs, bronchoalveolar lavage fluids and sputum. All studies included in this article evaluated the off-label use of FilmArray RP on other specimen types with sensitivity and specificity similar to that of NP swabs suggesting that RP would be useful for diagnosing both upper and lower respiratory tract infections.

### Five-year view

Five years ago, the FDA cleared the xTAG RVP as the first broadly multiplexed molecular assay for the detection of respiratory viruses in nasopharyngeal swabs. Today there are four FDA-cleared broadly multiplexed assays, the xTAG RVP and the xTAG RVP FAST (Luminex Corp.), the eSensor RVP (GenMark inc.) and the FilmArray respiratory panel (RP) (BioFire Diagnostics). The FilmArray RP tests for a wide range of pathogens with high sensitivity and specificity and in a timely manner. As such, the FilmArray RP has raised the expectations of both the clinical laboratories and clinicians as to what is possible for the rapid and sensitive diagnosis of infectious diseases in general. The next 5 years should see the continued increase in the options for rapid, sensitive and simple to perform molecular assays for infectious disease diagnosis.

One of the limitations of the FilmArray RP is still its cost compared to traditional methods and other commercially available molecular diagnostic tools, although when considering workflow and labor costs, the overall cost of the FilmArray RP is comparable to other highly multiplexed assays (i.e., xTAG RVP and the eSensor RVP) [59]. In this era of health care reform, clinical laboratories and hospitals are constantly faced with the challenge of delivering the best patient care possible in the most cost-effective way. For the FilmArray RP to fully realize its potential, the cost of the assay will have to decrease so to be available to a wider range of patients.

The FilmArray RP is currently classified as a moderate complexity test and as such is subject to the requirements associated with performing moderate/high complexity tests including quality control and assessment and performance of the test in accredited laboratory settings [75]. It is possible that the

FilmArray RP might eventually obtain a waived complexity category, which will allow its use in point of care settings like an emergency room or doctor's office.

As antiviral drugs become available to treat viruses other than influenza and RSV, the ability of any molecular platform to rapidly diagnose the specific virus responsible for a respiratory syndrome will become even more important. Furthermore, quantitative or semi-quantitative assays that provide information on viral loads will be useful for monitoring of patient response to treatment or to gain a better understanding of the infectious doses for each of the viruses included in multiplexed panels. The next five years will see an emergence of outcome studies on the real impact and benefit of these assays on patient care and public health in general.

Finally, the impact of new and emerging infections cannot be denied. In the last year, the avian H7N9 influenza A virus and the Middle Eastern Syndrome Coronaviruses have reminded us of how quickly new and emerging viruses can appear and spread. The challenge for manufacturers of these molecular assays will be to design the assays to be sensitive and specific and yet broad enough to accommodate potential emerging pathogens.

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*The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.*

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### Key issues

- Respiratory tract infections occur all year long with different pathogens peaking at different times but overlapping in their seasonal distributions.
- Clinical symptoms caused by respiratory pathogens, including bacteria and viruses are non-specific.
- There are currently four highly multiplexed respiratory panels that are US FDA approved for diagnosis of respiratory infections.
- The FilmArray Respiratory Panel is sensitive and specific, has the simplest workflow and fastest turn-around-time of all assays.
- The FilmArray Respiratory Panel is the only panel that includes both viral and bacterial causes of upper respiratory tract infections/lower respiratory tract infections .

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