

# Point-of-care diagnosis of invasive aspergillosis in non-neutropenic patients: *Aspergillus* Galactomannan Lateral Flow Assay versus *Aspergillus*-specific Lateral Flow Device test in bronchoalveolar lavage

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## Summary

**Background:** We compared new *Aspergillus* Galactomannan Lateral Flow Assay with the newly formatted *Aspergillus*-specific Lateral Flow device tests for the diagnosis of invasive pulmonary aspergillosis (IPA) in non-neutropenic patients.

**Methods:** We performed both tests in 82 bronchoalveolar lavage fluid samples from 82 patients at risk for IPA but without underlying haematologic malignancy. Samples were collected between September 2016 and September 2018 at the University of California San Diego, United States. IPA was classified following two published consensus criteria.

**Results:** Classification of cases varied widely between the two consensus criteria. When using criteria established for the intensive care unit, 26/82 patients (32%) met criteria for proven or putative IPA. Both point-of-care assays showed sensitivities ranging between 58% and 69%, with specificities between 68% and 75%. Sensitivity increased up to 81% when both tests were combined.

**Conclusion:** The study outlines the need for updated, unified and more broadly applicable consensus definitions for classifying IPA in non-neutropenic patients, a work that is currently in progress. Both point-of-care tests showed comparable performance, with sensitivities and specificities in the 60%-70% range when used alone and increasing to 80% when used in combination. The new point-of-care tests may serve a role at the bedside in those with clinical suspicion of IPA.

## KEYWORDS

*Aspergillus* Galactomannan Lateral Flow Assay (LFA), *Aspergillus*-specific Lateral Flow Device tests (LFD), autoimmune diseases, BAL, galactomannan, HIV, intensive care, respiratory diseases, solid organ transplantation

## 1 | INTRODUCTION

Invasive pulmonary aspergillosis (IPA) is a serious opportunistic infection with high mortality rates of 30%-60%.<sup>1-3</sup> Early diagnosis of

IPA and treatment initiation is the single most important factor in reducing morbidity and mortality from IPA,<sup>1,4,5</sup> but diagnosis can be difficult to establish. In patients with traditional risk factors for IPA, such as those with haematological malignancies and prolonged neutropaenia, the use of mould-active prophylaxis has been associated with a decrease in the prevalence of IPA.<sup>6,7</sup> Conversely, the

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prevalence of IPA continues to increase in non-neutropenic patients with other severe underlying diseases, including patients in the intensive care unit (ICU) where prevalence rates vary between 0.33% and 19%,<sup>8–11</sup> solid organ transplant (SOT) recipients,<sup>12</sup> patients receiving systemic glucocorticoids,<sup>13</sup> patients with underlying respiratory conditions,<sup>3,8,14</sup> patients with solid cancers<sup>8,15</sup> and other patient groups.<sup>8,16</sup> Given this increase and the importance of early treatment to improve survival, there is an unmet need for better tests for early diagnosis IPA in non-neutropenic patients, including those critically ill in the ICU.

Diagnosis of IPA is based on compatible signs and symptoms of infection in an appropriate host with supportive radiological and mycological findings.<sup>17</sup> Importantly, the pathogenesis of IPA differs between neutropenic and non-neutropenic patients,<sup>18</sup> impacting clinical presentation, radiological findings and diagnostic test results in the mycology laboratory. For example, serum galactomannan (GM) testing is the gold standard test that is used in consensus definitions for diagnosing IPA in neutropenic patients with angioinvasive disease, but sensitivities decrease to 30% and less in non-neutropenic patients. As a result, GM testing of bronchoalveolar lavage fluid (BALF) is preferable.<sup>19–21</sup> In addition, “typical” signs of IPA on computerised tomography (CT) in neutropenic patients, such as the “halo sign” or “air crescent sign,” are atypical in non-neutropenic patients and rarely occur.<sup>8,22,23</sup> Despite these important differences, revised European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) definitions focus primarily on neutropenic patients with underlying haematological malignancies and “typical” presentation of IPA and have been shown to have limited applicability in non-neutropenic patients who frequently do not fulfil radiological and host criteria.<sup>17</sup> While an alternative clinical algorithm for diagnosing IPA in the ICU setting seems to overcome some of those limitations including attempting to distinguish colonisation from true infection/disease,<sup>22</sup> that algorithm relies on clinical signs that typically occur during later stages of IPA in non-neutropenic patients,<sup>8</sup> and is applicable only to those with a positive BALF culture for *Aspergillus* spp., which is an entry criteria in this algorithm.<sup>20,24</sup>

Given the absence of widely accepted criteria for defining IPA in non-neutropenic patients, studies on new diagnostic tests for IPA focus mostly on patients with underlying haematological malignancies,<sup>21,25–27</sup> where broadly accepted classification criteria exist, while diagnostic studies in non-neutropenic patients are scarce. Importantly, two novel point-of-care diagnostic tests, both European conformity (CE) marked for diagnosis of IPA in BALF, have recently become commercially available, but to date have been only validated in patients with underlying haematological malignancies.<sup>25,28</sup> These POC tests may allow earlier diagnosis and initiation of anti-mould treatment compared to GM testing, given the longer and variable turnaround time of GM, and may thereby improve survival.

The objective of this study was to evaluate the new *Aspergillus* Galactomannan Lateral Flow Assay (LFA) and compare performance with the newly formatted *Aspergillus*-specific Lateral Flow Device

tests (LFD) for the diagnosis of IPA in patients at risk for IPA but without neutropaenia or underlying haematologic malignancy.

## 2 | METHODS

A total of 82 BALF samples obtained from 82 patients without underlying haematological malignancies, but with clinical suspicion of IPA, who had bronchoscopy performed and BALF GM ordered between September 2016 and September 2018 at the University of California San Diego, United States were included in this analysis.

Invasive pulmonary aspergillosis was classified according to two criteria: (i) the revised EORTC/MSG criteria<sup>17</sup> and (ii) a slightly modified version of the clinical algorithm described by Blot and colleagues.<sup>22,29</sup> The Blot algorithm was broadened by adding BALF GM >1.0 ODI as entry criterion, given that BALF culture was previously shown to have a sensitivity of only 58% for proven IPA in ICU patients, while BALF GM >1.0 ODI had a sensitivity of 85% (with a specificity of >90%).<sup>19</sup>

Galactomannan (Platelia *Aspergillus* Ag ELISA; Bio-Rad Laboratories, Munich, Germany) and culture were performed prospectively in all BALF samples. GM-positive and randomly selected GM-negative samples were stored at –20°C and tested between August and September 2018 for the *Aspergillus*-specific LFD (OLM Diagnostics, Newcastle upon Tyne, UK) and the *Aspergillus* galactomannan LFA (IMMY, Norman, OK, USA). Stored BALF samples were thawed, vortexed and tested according to the manufacturer's instructions. For the *Aspergillus*-specific LFD, clear BALF was centrifuged only, while milky, or turbid BALF was pretreated according to the manufacturer's instructions, and 70 µL of supernatant was added to the test. Results were read 15 and 25 minutes later and scored as either –, +, ++ or +++. For the *Aspergillus* galactomannan LFA, BALF samples were pretreated, heated and centrifuged. Test strips were then inserted into 80 µL of sample following the manufacturer's instructions. Results were read after 30 minutes and scores given ranging from 0 (i.e. negative) to 4 (highly positive). Results of both the LFD and LFA were each read by two interpreters who were blinded to IPA status, GM ELISA and culture results.

Statistical analyses were performed using SPSS 25 (SPSS Inc., Chicago, IL, USA). A two-sided *P*-value of less than 0.05 was considered statistically significant. The Human Research Protections Program at the University of California, San Diego approved the study protocol and all study-related procedures.

## 3 | RESULTS

A total of 82 samples from unique patients were included in the analysis. Demographic characteristics and underlying diseases of the study population are displayed in Table 1.

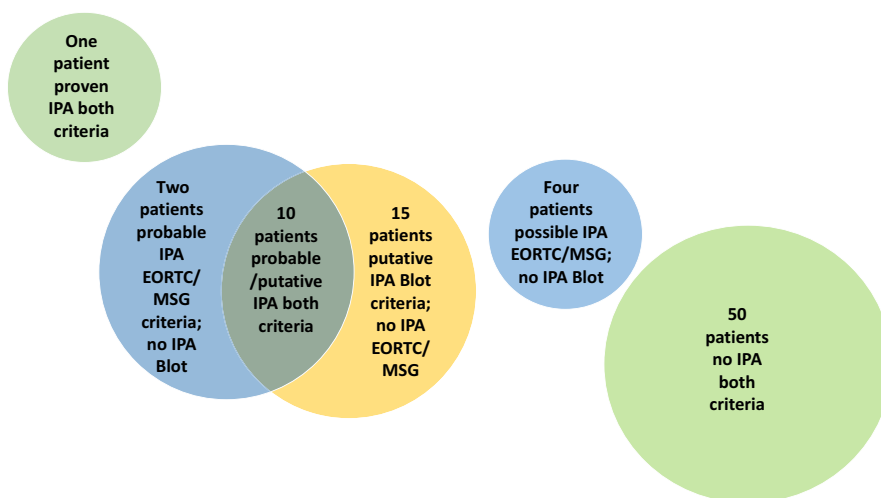
Classification of IPA using the two criteria is displayed in Figure 1. One patient was classified as proven IPA by EORTC/MSG criteria, while the remaining patients were classified as probable IPA (*n* = 12),

**TABLE 1** Demographic data and underlying diseases of the study population

	Classification according to revised EORTC/MSG criteria			Classification according to Blot criteria
	Probable or proven IPA (n = 13)	No evidence for IPA (n = 65)	Possible IPA (n = 4)	Putative/Proven IPA (n = 26)
Female (n, %)	5 (38%)	26 (40%)	1 (25%)	8 (31%)
Age, years (median, range)	58 (41-79)	56 (19-80)	66 (49-67)	57 (19-79)
Primary underlying diseases/conditions (n, %)				
Lung transplant	2 (15%)	19 (29%)	3 (75%)	7 (27%)
Other transplant	1 (8%)	2 (3%)	-	1 (4%)
Oncological malignancy	1 (8%)	5 (8%)	1 (25%)	2 (8%)
Liver cirrhosis	-	5 (8%)	-	3 (12%)
Interstitial lung disease	1 (8%)	5 (8%)	-	2 (8%)
Rheumatoid/autoimmune diseases with lung involvement	1 (8%)	4 (6%)	-	1 (4%)
HIV/AIDS	1 (8%)	3 (5%)	-	2 (8%)
Tuberculosis	1 (8%)	1 (2%)	-	-
Asthma	-	3 (5%)	-	1 (4%)
Cystic fibrosis	-	3 (5%)	-	-
Others	1 (8%)	4 (6%)	-	2 (8%)
ICU COPD	1 (8%)	3 (5%)	-	1 (4%)
ICU septic shock	3 (23%)	1 (2%)	-	3 (12%)
ICU others	-	7 (11%)	-	1 (4%)
Overall mortality 30-days	2 (15%)	14 (22%)	1 (25%)	8 (31%)
Overall mortality 90-days	3/12 (25%)	14/63 (22%)	1 (25%)	9/25 (36%)

BALF, Bronchoalveolar lavage fluid; CT, Computerised tomography; ELISA, Enzyme-linked immunosorbent assay; EORTC/MSG, European Organization for Research and Treatment of Cancer/Mycoses Study Group; GM, Galactomannan; IPA, Invasive pulmonary aspergillosis; LFA, Galactomannan Lateral Flow Assay; LFD, *Aspergillus*-specific Lateral Flow Device tests; SOT, Solid organ transplant.

In one case of probable IPA and putative IPA, an additional BALF sample drawn 14 days earlier was available (only the later sample was included in the analysis). The patient fulfilled probable IPA criteria throughout the 14 days. Patients first BALF sample (not included in this analysis) resulted positive for GM (2.38 ODI), grew *Aspergillus terreus* in culture and gave positive results with both the LFA and LFD, but the patient did not fulfil criteria of putative IPA according to Blot because of lack of typical symptoms. Two weeks later, at the time of the second BALF sample, this patient had still positive GM, positive LFD and positive LFA, negative culture, but symptoms as defined by Blot criteria and therefore fulfilled putative IPA criteria.

**FIGURE 1** Categorisation of IPA based on revised EORTC/MSG criteria and modified Blot Criteria. Green bubbles indicate classification agreement of both criteria, while yellow and blue bubbles outline cases where classification differed between criteria

**TABLE 2** Performance of the *Aspergillus*-specific Lateral Flow Device test (LFD), the *Aspergillus* Galactomannan Lateral Flow Assay (LFA), galactomannan (GM) and fungal culture in bronchoalveolar lavage (BALF) for diagnosis of invasive pulmonary aspergillosis (IPA) in patients without haematological malignancies. Sensitivity and specificity for probable/proven IPA versus no IPA, putative/proven IPA versus no IPA as well as test positivity in cases of possible IPA and those who fulfilled Blot entry criteria but not symptom or host criteria, as well as those with BALF GM levels between 0.5 and 1.0 are displayed

Biomarkers/tests and combinations	Revised EORTC/MSG criteria			BLot criteria			
	Sensitivity probable/ proven IPA versus no IPA	Specificity probable/ proven IPA versus no IPA	Positivity in possible IPA (n = 4)	Sensitivity putative/ proven IPA versus no IPA	Specificity putative/ proven IPA versus no IPA	Positivity in those fulfilling Entry criteria but not symptoms or host criteria (n = 10)	Positivity in those with BALF GM >0.5 and <1 ODI (n = 7)
<i>Aspergillus</i> -specific LFD 15 minutes	46% (6/13)	66% (43/65)	25% (1/4)	58% (15/26)	75% (42/56)	60% (6/10)	43% (3/7)
<i>Aspergillus</i> -specific LFD 25 minutes	62% (8/13)	63% (41/65)	50% (2/4)	69% (18/26)	71% (40/56)	60% (6/10)	43% (3/7)
<i>Aspergillus</i> galactomannan LFA 30 minutes	69% (9/13)	62% (40/65)	25% (1/4)	65% (17/26)	68% (38/56)	50% (5/5)	43% (3/7)
BALF GM 0.5 ODI cut-off <sup>a</sup>	85% (11/13)	66% (37/65)	0% (0/4)	92% (24/26)	73% (41/56)	80% (8/10)	100% (7/7)
BALF GM 1.0 ODI cut-off <sup>a</sup>	77% (10/13)	71% (46/65)	0% (0/4)	85% (22/26)	88% (49/56)	70% (7/10)	0% (0/7)
BAL culture <sup>a</sup>	31% (4/13)	88% (57/65)	0% (0/4)	35% (9/26)	95% (53/56)	30% (3/10)	0% (0/7)
<i>Aspergillus</i> -specific LFD 15 minutes AND/OR <i>Aspergillus</i> galactomannan LFA 30 minutes	69% (9/13)	54% (35/65)	25% (1/4)	77% (20/26)	64% (36/56)	60% (6/10)	57% (4/7)
<i>Aspergillus</i> -specific LFD 25 minutes AND/OR <i>Aspergillus</i> galactomannan LFA 30 minutes	77% (10/13)	52% (34/65)	50% (2/4)	81% (21/26)	61% (34/56)	60% (6/10)	57% (4/7)

<sup>a</sup>The study could not evaluate performance of GM and culture as test results used as mycological standard for defining probable and putative IPA.

possible IPA (n = 4) and no evidence for IPA (n = 65). When using modified Blot criteria, one fulfilled proven IPA, 25 patients fulfilled criteria of putative IPA, while the remaining 56 patients (including 2 who fulfilled probable IPA and 4 who fulfilled possible IPA according to EORTC/MSG definitions) did not fulfil Blot IPA criteria. Overall 10 of those 56 patients fulfilled Blot entry criteria (i.e. BALF GM >1.0 ODI and/or positive BALF culture with *Aspergillus* spp. growth; median BALF GM 1.91, range 0-6.55 ODI), but did not fulfil other criteria for putative IPA. Of those 10, eight did not have at least one of the seven predefined compatible signs and symptoms, while two did not fulfil predefined host risk factors or additional mycology criteria. In addition, a total of 7 patients had BALF GM levels between 0.5 and 1 ODI but negative culture and therefore did not fulfil modified Blot entry criteria.

Performance of the *Aspergillus*-specific LFD, *Aspergillus* galactomannan LFA, BALF culture, GM ELISA, as well as combinations of the point-of-care assays for probable/proven versus no IPA and putative/proven versus no IPA are depicted in Table 1. In addition, positivity rates in patients with possible IPA according to EORTC/MSG, patients who fulfilled Blot entry criteria but not clinical or host criteria, and those with BALF GM levels <1 ODI but above 0.5 ODI are displayed in Table 2. BALF GM and culture were used as criteria for probable and putative IPA, and actual performance could therefore not be evaluated. Overall 9 cases with probable and/or putative IPA had *Aspergillus* spp. growth in BALF culture; among those the LFD resulted positive in 4/9 after 15 minutes and in 6/9 after 25 minutes, the LFA resulted positive in 5/9, GM>1.0ODI in 5/9 and GM>0.5ODI in 7/9. The single case with proven IPA (tissue invasion in lung biopsy) had negative BALF GM but *Aspergillus fumigatus* growth in BALF culture and positive *Aspergillus* galactomannan LFA and *Aspergillus*-specific LFD test results.

No difference in mortality was seen between EORTC/MSG categories of IPA (Table 1). Patients with putative or proven IPA according to Blot criteria had a trend towards higher 90-day overall mortality than those without IPA (9/25 versus 9/54;  $P = 0.057$ ), with

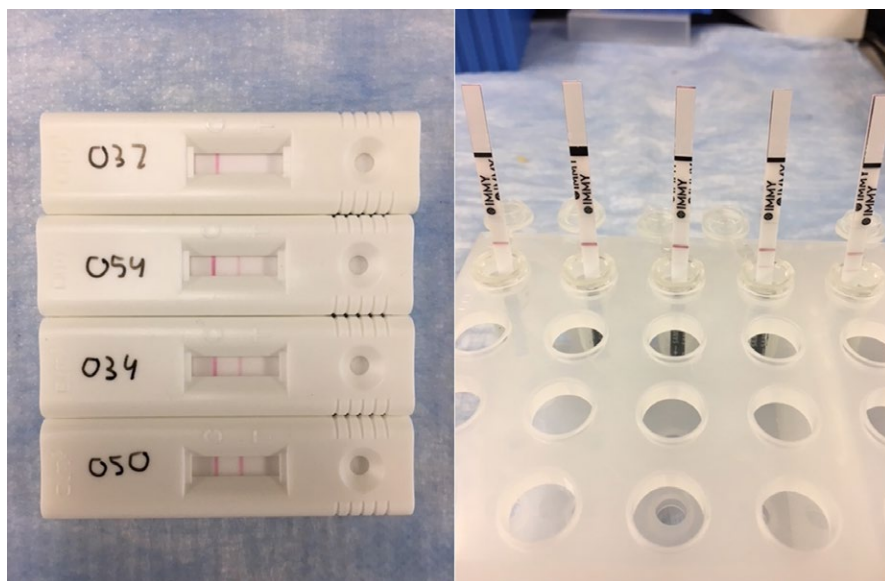
a weaker trend observed for 30-day overall mortality (8/26 versus 9/56;  $P = 0.127$ ).

For both the LFD and LFA, the strength of the positive result (Figure 2) correlated with BALF GM levels. BALF GM levels were significantly higher in those with at least a ++ positive test result (n = 14) versus + positive test results (n = 15) with the *Aspergillus*-specific LFD 15 minutes (median 5.51 ODI, IQR 1.19-6.15 ODI versus median 1.59 ODI, IQR 0.6-2.2 ODI;  $P = 0.029$ ; BALF GM levels for those with negative LFD results were median <0.5 ODI; IQR <0.5-0.64 ODI). There was a similar trend observed for the *Aspergillus* galactomannan LFA, with a tendency towards higher results in those with scores of 2 or higher (n = 11) versus those with a score of 1 (n = 24) (median 5.62 ODI, IQR 0.61-6.09 ODI versus median 1.14 ODI, IQR <0.5-2.39 ODI;  $P = 0.068$ ; BALF GM levels for those with negative LFD results were median <0.5 ODI; IQR <0.5-0.6 ODI).

## 4 | DISCUSSION

We evaluated the diagnostic performance of two new BALF point-of-care diagnostic tests for patients at risk for IPA but without neutropaenia or underlying haematologic malignancy. Our study reports two major findings. First, classification of IPA differed substantially when utilising revised EORTC/MSG or Blot criteria, outlining the need for broader and improved consensus definitions for classifying IPA in non-neutropenic patients. Second, both point-of-care tests for IPA showed comparable performance, with sensitivities and specificities in the 60-70% range when used alone, increasing to 80% when used in combination.

Non-neutropenic patients who develop IPA continue to suffer from poor diagnostic algorithms and delayed access to novel diagnostics. A critical reason is the missing gold standard for defining IPA in non-neutropenic patients, where different pathogenesis (i.e. airway invasive growth of *Aspergillus* spp. versus angioinvasive growth in neutropenic patients)<sup>18</sup> results in "atypical" clinical and



**FIGURE 2** Left: Results with the CE-marked *Aspergillus*-specific Lateral Flow Device test ranging from negative (-) to strong positive (+++). Right: Results with the CE-marked *Aspergillus* Galactomannan Lateral Flow Assay, ranging from negative (0) to strong positive (4)

radiological presentations of IPA, deviating significantly from what has been defined as “typical presentation” in neutropenic patients.<sup>17</sup> For example, fever is only present in 70% of non-neutropenic patients compared to over 95% of neutropenic patients, and cough and chest pain are significantly less commonly observed in non-neutropenic patients.<sup>8</sup> “Typical” signs of IPA on CT such as the “halo sign” or “air crescent sign” are atypical in non-neutropenic patients and occur in only 30%-50% of cases.<sup>8,22,23</sup>

In our study, 17 patients fulfilled either criteria of putative IPA according to Blot or probable IPA according to EORTC/MSG but not both, while 10 patients fulfilled both criteria. Overall, putative IPA classification according to Blot criteria showed some correlation with higher mortality, while probable IPA classification according to EORTC/MSG did not. While Blot criteria seem to be preferable to revised EORTC/MSG criteria in non-neutropenic patients, there are two important limitations to note. First, the original Blot criteria are applicable only to a small proportion of non-neutropenic patients with IPA, namely those with *Aspergillus* spp. detection in BALF culture. Sensitivity of BALF culture for IPA, however, only ranges from 29% to 58% in previous studies of proven IPA.<sup>3,19</sup> BALF culture was only 31% sensitive in our study. To overcome this limitation, we tried to broaden applicability of Blot definitions by including BALF GM >1.0 ODI as entry criterion in this study. However, future studies are needed to evaluate this approach, as well as evaluate whether introduction of GM with a lower cut-off of 0.5 ODI may yield superior performance. Second, symptoms as defined by Blot criteria may occur late in the course of disease, making them less applicable for earlier stages of IPA in non-neutropenic patients, where 31% do not have fever and 72% lack cough.<sup>8</sup> This is outlined by one of our cases, who fulfilled probable IPA criteria first (plus had positive results with both the LFD and LFA and *Aspergillus terreus* growth in BALF culture) but initially did not fulfil Blot criteria due to lack of symptoms, although they did 14 days later when symptoms began. In addition, 80% of cases who fulfilled Blot entry criteria, but not criteria of putative IPA, did not have predefined “typical” signs and symptoms according to Blot, while fulfilling all other criteria and also having very frequently positive test results with the LFA and/or LFD.

Overall performance of the LFD and LFA showed sensitivities ranging between 58% and 69%, with specificities between 68% and 75%. In particular, the LFD test correlated well with BALF GM levels. This performance may be deemed acceptable given the imperfect definitions of IPA in non-neutropenic patients. In contrast, a recent smaller study reported markedly higher sensitivities (78%-89%) and specificities (88%-100%) for both the LFD and the LFA in patients with haematological malignancies,<sup>28</sup> where better definitions of IPA exist. Overall sensitivity and specificity observed in this study were below those published for the LFD prototype test in comparable patient collectives,<sup>3,11</sup> which was surprising, given that the newly formatted LFD was previously shown to be equally sensitive but more specific than the prototype.<sup>25</sup> Importantly, when the LFA and LFD were combined, sensitivity increased to

81% while specificity remained just above 60%, making this a reasonable approach in patients with high clinical suspicion of IPA. Importantly, this study could not evaluate performance of conventional GM EIA and culture as they were both used as mycological standard for defining probable and putative IPA. In patients with probable and/or putative IPA and *Aspergillus* spp. growth in culture, positivity rates for the LFD and LFA were comparable to those of BALF GM. Only one patient in this study had histologically proven IPA and had negative BALF GM, negative *Aspergillus* LFA, but positive *Aspergillus* LFD.

Our study has several limitations, including its single-centre design, which meant that the numbers of putative/probable and proven cases of IPA were low. While larger cohorts of proven IPA cases may overcome some of the limitations of the current IPA classification and may allow for evaluation of BALF GM against the new point-of-care assays, proven IPA mostly represents advanced disease stages so the diagnostic performances of biomarkers and tests in proven IPA may not translate to similar performance in earlier stages of disease.

In conclusion, our study indicates that both the LFA and the LFD tests may be useful for point-of-care diagnosis of IPA in BALF in non-neutropenic patients when IPA is clinically suspected. Due to imperfect specificities, these point-of-care tests may be more useful for targeted testing in those patients in whom there is clinical suspicion of IPA, rather than for general screening of all patients with BALF. Our study also outlines the need for updated and more broadly applicable consensus definitions for classification of IPA in non-neutropenic patients. Work on these new definitions is currently in progress.<sup>30</sup>

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*Aspergillus*-specific LFDs were provided by OLM Diagnostics, Newcastle upon Tyne, UK, while *Aspergillus* galactomannan LFAs were provided by IMMY, Norman, Oklahoma, USA. Neither company had a role in study design, data collection, analysis, interpretation, decision to publish, in the writing of the manuscript or in the decision to submit the manuscript for publication. The work was also partially supported by grants from the National Institutes of Health: MH113477 and P30MH062512. The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

## AUTHOR CONTRIBUTION

MH and JJ designed the study, performed the tests and drafted the manuscript. Data were analysed by MH, JJ, SM, SR, RT and SA. Samples were collected by SR, MH and SM. The manuscript was critically revised and important intellectual content provided by SM, SR, RT and SA. The final version for publication was approved by all authors. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## CONFLICT OF INTEREST

M. Hoenigl received research grants from Gilead. R. Taplitz served as a consultant for Merck. All other authors no conflict.

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