Lateral Flow Device Tests for Diagnosis of Invasive Aspergillosis: What is their role in 2022?

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- Thermo Fisher Scientific
- MRM Health
- TECOmedical

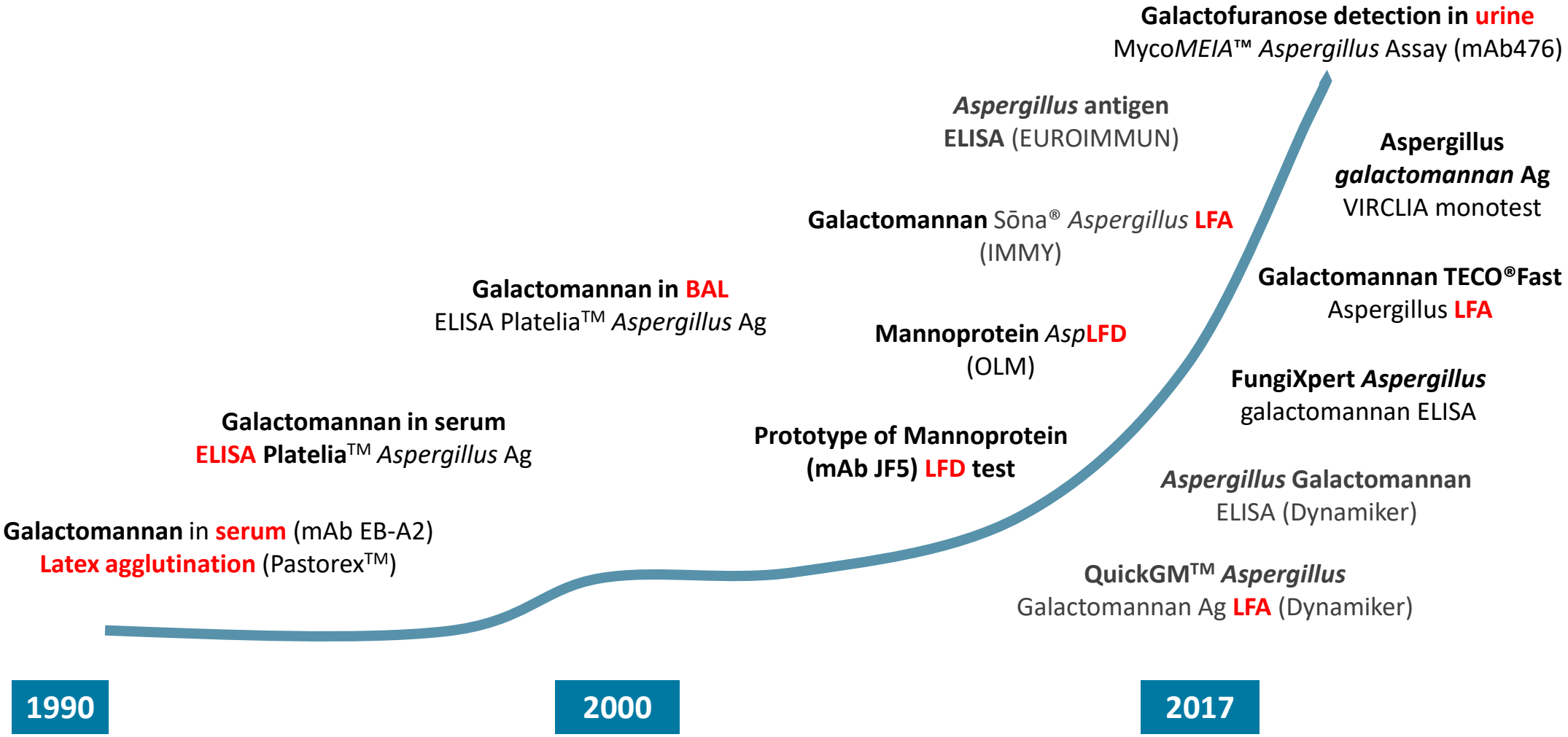
Emerging risk factors

New antifungal drugs

New diagnostic tests

CHALLENGING CONTEXT

Expansion of antigen detection assays for invasive aspergillosis

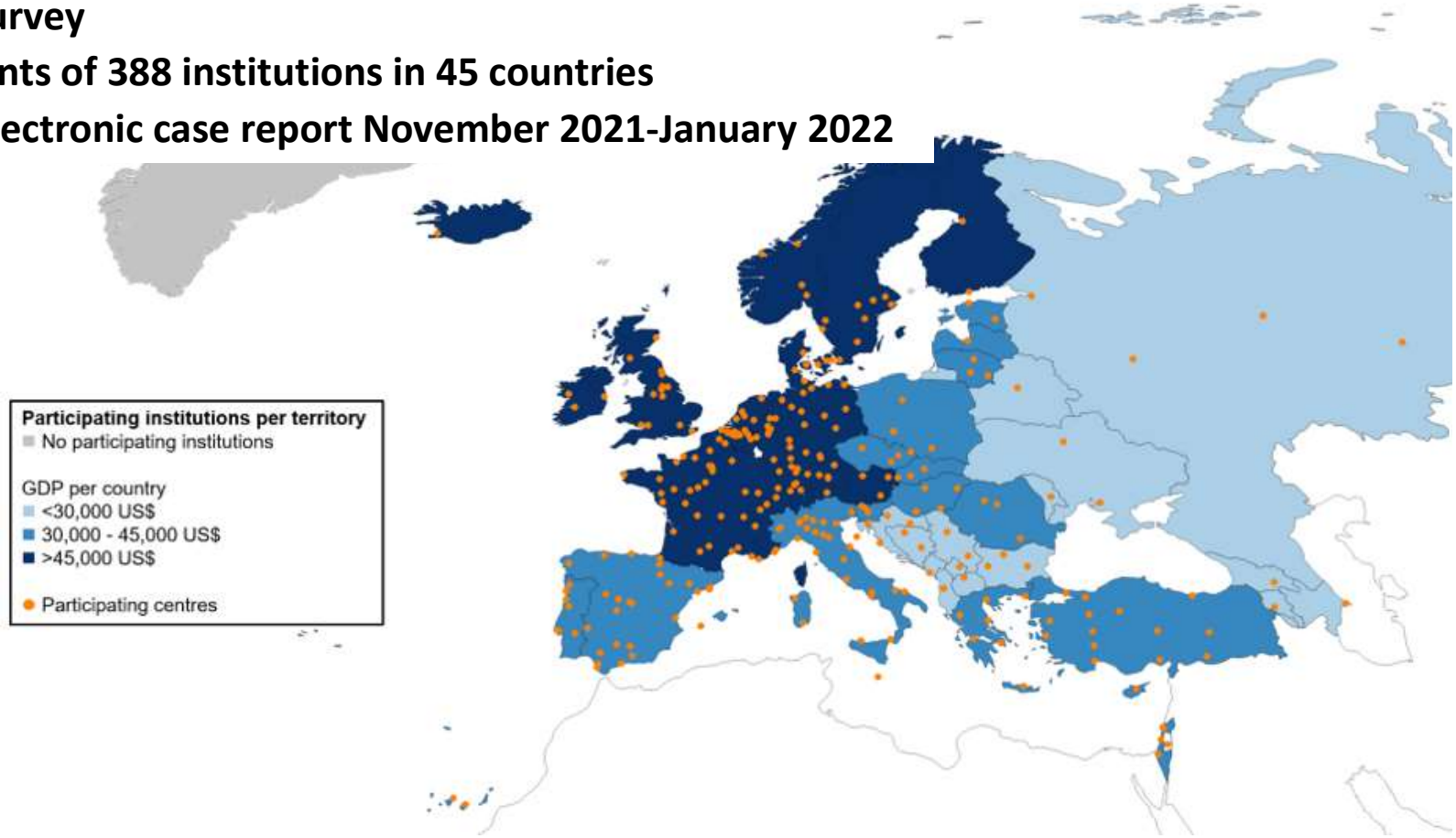


Current state of laboratory mycology in Europe

ECMM survey

Participants of 388 institutions in 45 countries

Online electronic case report November 2021-January 2022



Jon Salmanton-Garcia et al. The Lancet Microbe 2022

Current state of laboratory mycology in Europe

Type of institution	n	%
Public hospital	140	36.1%
University hospital	247	67.7%
Aspergillus antigen detection		
Aspergillus LF (mannoprotein)		
Onsite	53	13.7
Outsourced	41	10.6
Aspergillus LF (galactomannan)		
Onsite	80	20.6
Outsourced	49	12.6
Galactomannan ELISA		
Onsite	258	66.5
Outsourced	82	21.1

Jon Salmanton-Garcia et al. The Lancet Microbe 2022

olm

AspLFD

Aspergillus Lateral-Flow Device

For the rapid detection of Invasive Pulmonary Aspergillosis

Detects extracellular mannoproteins which bind to the JF5 MAb

CE IVD

IMMY

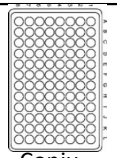
Aspergillus GM LFA

Detects galactomannan by 2 MAbs:

- ME-A5, likely binds to a similar GM epitope as EB-A2
- Undisclosed MAb

CE | Serum & BAL

Procedure of LF assays (OLM/IMMY) compared to Platelia ELISA

GM	Sample	Buffer			Conju-gate	Super-natans	Incubate	Wash 5x	Chromo-gen	Incubate	Stopping solution	Readout
												

Courtesy Toine Mercier

Galactomannan ODI values of different assays/sample types may not be the same

TECO®*Fast* Aspergillus IVD CE

Galactomannan Ag Lateral Flow Assay

- Same assay as Dynamiker QuickGM™ Lateral Flow Assay
- Different standard curve for serum and BAL samples with the aim to use 1 threshold (but different thresholds in definitions)
- P412 on Friday by R. Aerts et al. but procedure has been adapted recently (extra centrifugation step)

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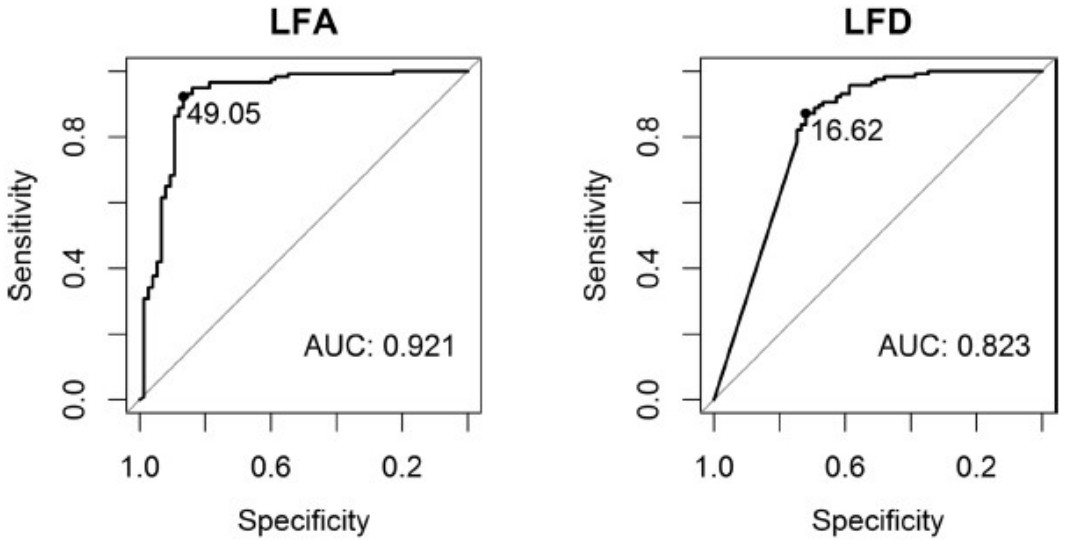
Evaluation of lateral flow device tests

Haematology/cancer patients

Comparison Sōna® *Aspergillus* Galactomannan LFA (IMMY) and AspLFD (OLM) on BAL

- Retrospective
- Multicentre (n=4)
- Case/control
- 235 patients/235 **BAL**
- 2008 EORTC/MSG definitions
- 11 proven/64 probable IA



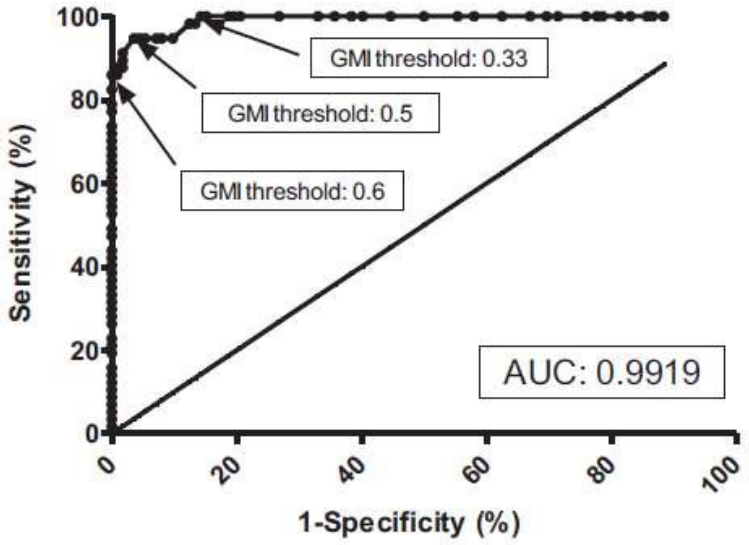
Identical specificity but higher sensitivity and better NPV for the LFA

T. Mercier et al. Med Mycology 2020, 58: 444-452

Evaluation Sōna® *Aspergillus* galactomannan LFA in patients at risk for IFD

- Retrospective
- Single centre
- Case/control

- 134 patients/179 **serum**
- 82% patients with haematological malignancy
- 27 proven/probable IA
- 2020 EORTC/MSGERC criteria



Performance parameters	Galactomannan index positivity threshold: 0.33	0.5	0.61
Sensitivity (95% CI)	100% (89.3–100)	96.9% (94.3–99.5)	90.6% (75.8–96.8)
Specificity (95% CI)	87.0% (79.0–92.2)	98.0% (93.0–99.5)	100% (96.3–100)
PPV (95% CI)	71.1% (56.6–82.3)	93.9% (80.4–98.3)	100% (88.3–100)
NPV (95% CI)	100% (95.8–100)	99.0% (94.5–99.8)	97.1% (91.8–99.0)
LR +tive	7.69	48.44	>906*
LR –tive	<0.0001*	0.03	0.09
DOR	>76,900*	1,519	>10,067*
Youden's statistic	0.87	0.95	0.91

- The LFA outperformed the GM-EIA
- Median GMI was significantly greater with LFA compared to GM-EIA
- The LFA is a rapid alternative to the well-established GM-EIA when used with a cube reader

PL White et al. 2020, 58

Comparison Sōna® *Aspergillus* Galactomannan LFA (IMMY) and AspLFD (OLM) on serum

- Prospective
- Single centre
- 229 patients/229 **serum**
- 5 proven/36 probable IA
- 2020 EORTC/MSGERC criteria

	SENS (%)	SPEC (%)	NPV (%)	PPV (%)
GM ELISA	44	99	89	93
LFA (IMMY)	49	95	90	69
LFD (OLM)	24	89	84	33
LFA **OR** BDG (Wako) ≥2.359	63	86	92	50
LFD OR BDG (Wako) ≥2.359	56	83	90	42
GM ELISA (Platelia) **OR** BDG ≥2.359	60	88	91	53

- Optimal combination: BDG + GM ELISA or LFA
- LFA (IMMY) can replace GM ELISA
- Performance LFD suboptimal, lowest diagnostic performance of all assays evaluated

Mercier T, et al. Clin Infect Dis. 2021:1577–84.

Comparison Sōna® *Aspergillus* Galactomannan LFA (IMMY) and AspLFD (OLM) on serum

Performance in subgroup after exclusion of galactomannan as a the mycological criterion

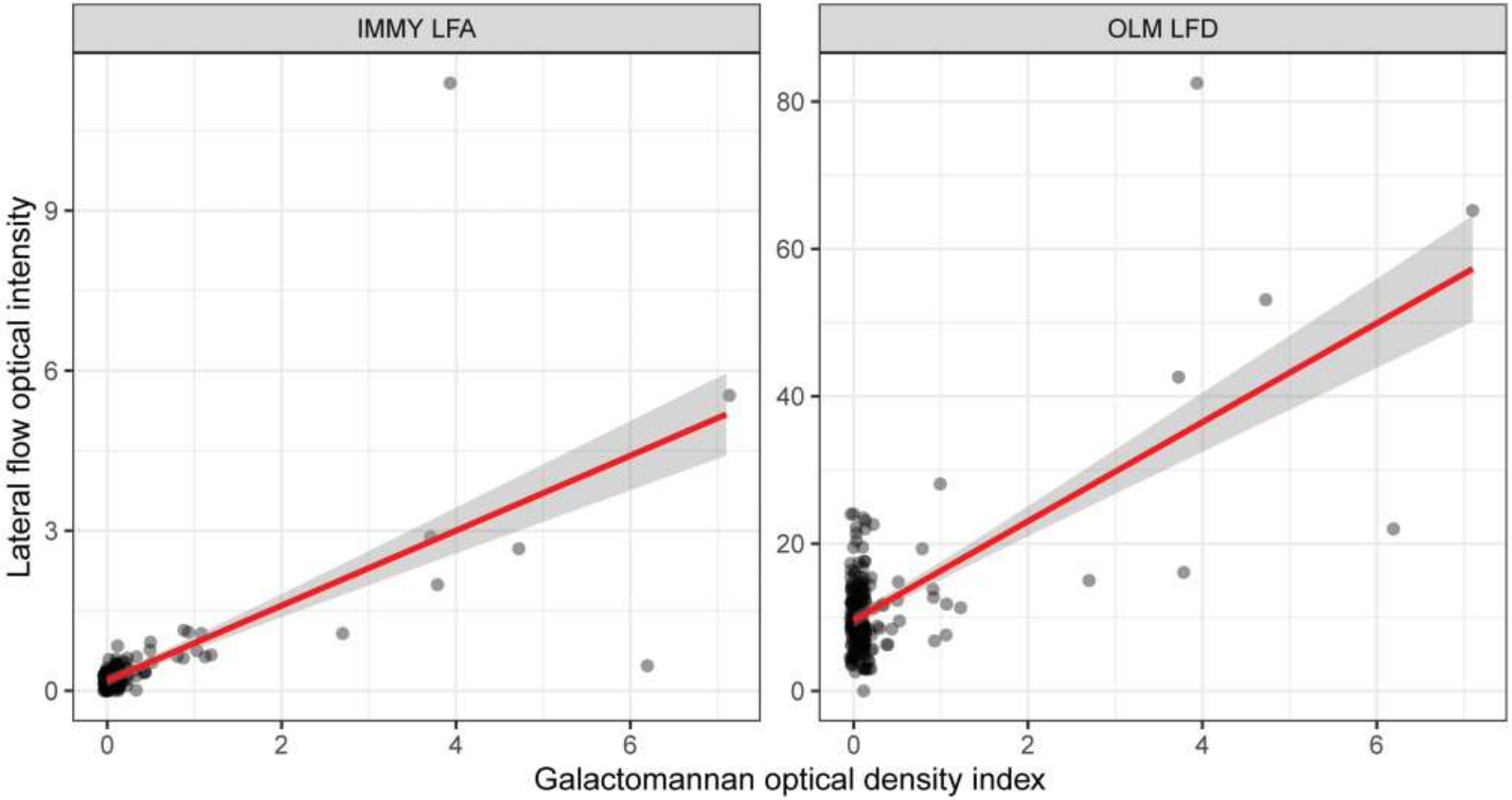
	SENS (%)	SPEC (%)	NPV (%)	PPV (%)
GM ELISA	31	99	89	89
LFA (IMMY)	41	95	90	61
LFD (OLM)	18	89	86	23

LFA outperforms LFD

Mercier T, et al. Clin Infect Dis. 2021:1577–84.

Comparison Sōna® *Aspergillus* Galactomannan LFA (IMMY) and AspLFD (OLM) on serum

Larger variability



Mercier T, et al. Clin Infect Dis. 2021:1577–84.

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Evaluation of lateral flow device tests

COVID-19 associated pulmonary aspergillosis (CAPA)

Evaluation of Sōna® *Aspergillus* Galactomannan LFA for diagnosis of CAPA

- Retrospective
- Multicentre
- Case/control
- ECMM/ISHAM criteria (exclusion Aspergillus LFA)
- 196 respiratory samples/148 serum

	0.5 ODI cutoff		1.0 ODI cutoff	
	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Respiratory samples				
Tracheal aspirate (TA) (N_{CAPA}=16; $N_{ØCAPA}$=18)	100% (79–100)	44% (22–69)	81% (54–96)	67% (41–87)
Nondirected bronchial lavage (NBL) (N_{CAPA}=20; $N_{ØCAPA}$=52)	90% (68–99)	83% (70–92)	80% (56–94)	88% (77–96)
Bronchoalveolar lavage fluid (BALF) (N_{CAPA}=29; $N_{ØCAPA}$=61)	72% (53–87)	79% (66–88)	52% (33–71)	98% (91–100)
BALF and NBL combined[b] (N_{CAPA}=49; $N_{ØCAPA}$=113)	80% (66–90)	81% (72–87)	63% (48–77)	94% (88–97)
All combined[b] (N_{CAPA}=58; $N_{ØCAPA}$=127)	83% (71–91)	76% (67–83)	66% (52–78)	90% (83–94)
Serum samples (N_{CAPA}=46; $N_{ØCAPA}$=102)	20% (9–34)	93% (86–97)	9% (2–21)	99% (95–100)

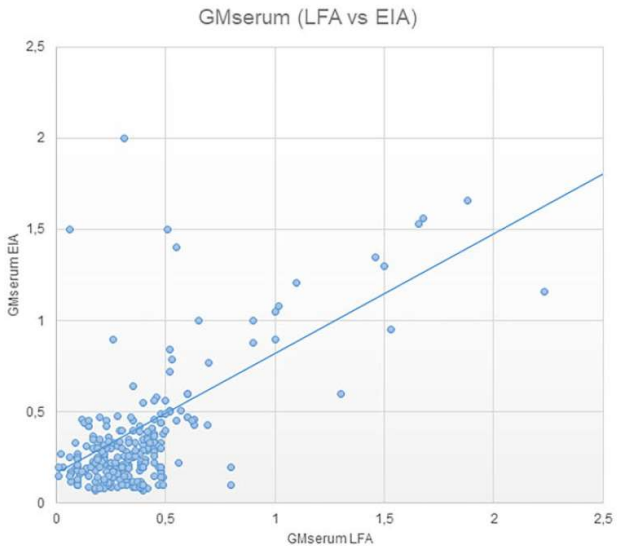
- Aspergillus GM LFA shows good performance especially on respiratory samples with the 1.0 ODI cutoff
- Can be implemented as screening test on tracheal aspirates, triggering BAL analysis if positive
- Isolated ODI slightly above the 0.5 ODI should lead to further mycological investigations

B. Autier et al. JCM 2022

Evaluation of Sōna® *Aspergillus* Galactomannan LFA for screening for CAPA

- Prospective
- Multicentre (Argentina)
- 2020 ECMM/ISHAM criteria (exclusion *Aspergillus* LFA)
- 185 critically ill COVID patients/578 serum/35 BAL
- Weekly screening:
  - first two weeks: 1 sample/week, following weeks: 2 samples/week

Probably CAPA incidence 10.3% with LFA and 9% with EIA

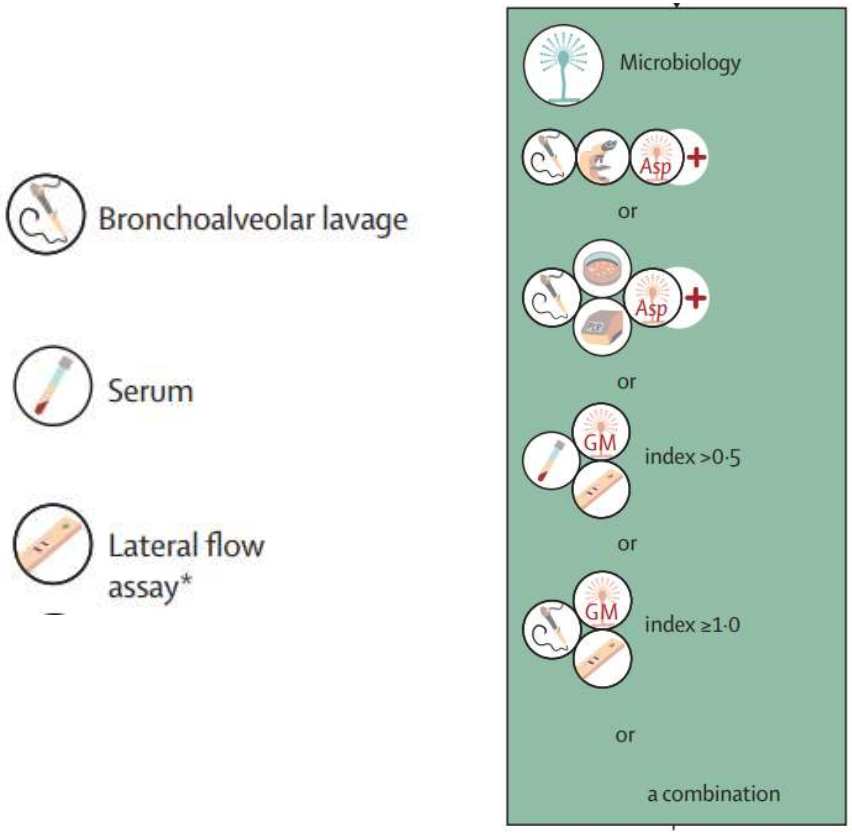


Results differ from European cohorts

- 18/19 patients with probable CAPA due to positive LFA had a positive serum test
- CAPA diagnosis during first week of ICU stay in 95% of CAPA patients
- Mortality CAPA versus non CAPA: 42% versus 33% (NS)

G. Giusiano et al. Med Mycology 2022

Defining and managing COVID-19-associated pulmonary aspergillosis: the 2020 ECMM/ISHAM consensus criteria for research and clinical guidance



Although the lateral flow testing of bronchoalveolar lavage for IPA appears to be reliable, specific data for the diagnosis of CAPA are scarce.

Visual reader must be used for a primary result and confirmatory galactomannan testing should be sought

P. Koehler et al. Lancet Infect Dis 2021

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Diagnosis of IFI's in LMIC

Importance of POCT

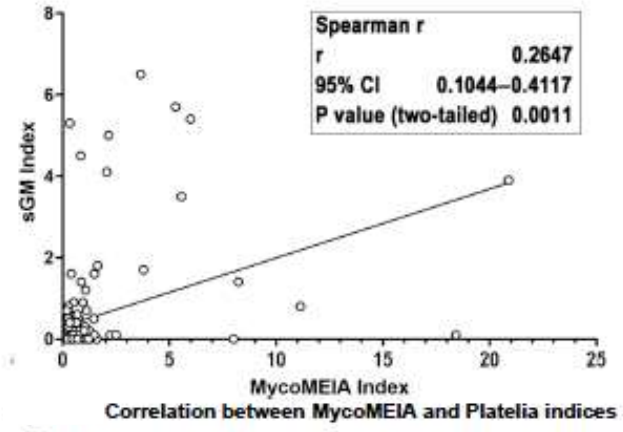
Diagnosis of IFI in LMICs

- Characteristics of a **suitable test for LMICs** (ASSURED criteria of WHO):
  - Affordable
  - Sensitive and specific
  - User-friendly
  - Rapid and robust
  - Equipment-free
  - Delivered to those who need it
- **POCT** requires rigorous evaluation in LMIC setting. POCT has the potential to revolutionise the management of IFIs in LMICs
- *Aspergillus* antigen is on WHO essential diagnostic list
- Urine is an interesting sample type for POCT especially in LMIC setting

Osaigbovo I and Bongomin F. Ther Adv Infect Dis. 2021
WHO. Technical Report Series. The selection and use of essential in vitro diagnostics. https://www.who.int/publications/i/item/9789240019102

MycoMEIA *Aspergillus* Assay for urine testing

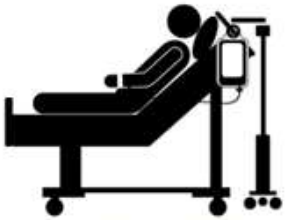
- Platelia assay is insensitive to detect galactomannan in human urine samples
- MycoMEIA assay is optimized to detected specific β-galactofuranose in urine
- Antigen detected by mAb476 is abundantly present in urine on fungus-derived extracellular vesicles and also as a free glycan
- ELISA kit CE marked 4/2022; 510k planned 4Q2022
- Dipstick test is being developed and validated
- Promising results from small cohorts, significant but low correlation with Platelia galactomannan assay



Correlation between MycoMEIA and Platelia indices

Pearl DIAGNOSTICS

Aerts et al., TIMM 2021



POINT OF CARE TESTING

- No sample transportation
- Short turn around time
- No additional result reporting step

- No/minimal sample pretreatment possible
- Training of personnel
- Quality control

RAPID TESTING IN MICROBIOLOGY/ MYCOLOGY LAB

- Sample pretreatment possible
- Experienced personnel
- Result in LIS

- Sample transportation needed
- Longer turn around time

Conclusions

- Several lateral flow device tests for the diagnosis of invasive aspergillosis are currently available
- Check validation data for the specific test you consider implementing both for serum/BAL and different patient populations
- Validation data are still limited
- Most data available for IMMY galactomannan lateral flow assay which reveal that the performance of the IMMY test is at least as good as the Platelia galactomannan test and thus may replace this test
- Performance evaluation for diagnosis of CAPA is difficult due to incorporation bias (presence of the evaluated laboratory test in the reference mycological criteria) which may lead to an overestimation of the diagnostic accuracy
- Lateral flow device tests are most useful when a rapid response is important and the number of samples is low