

Innovations in non-sputum TB diagnostics for adults and children

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27th Annual Union-North America Region Conference

Access to TB diagnostics

Fig. 3.2.2 Percentage of people newly diagnosed with pulmonary TB who were **bacteriologically confirmed** at country level, 2021

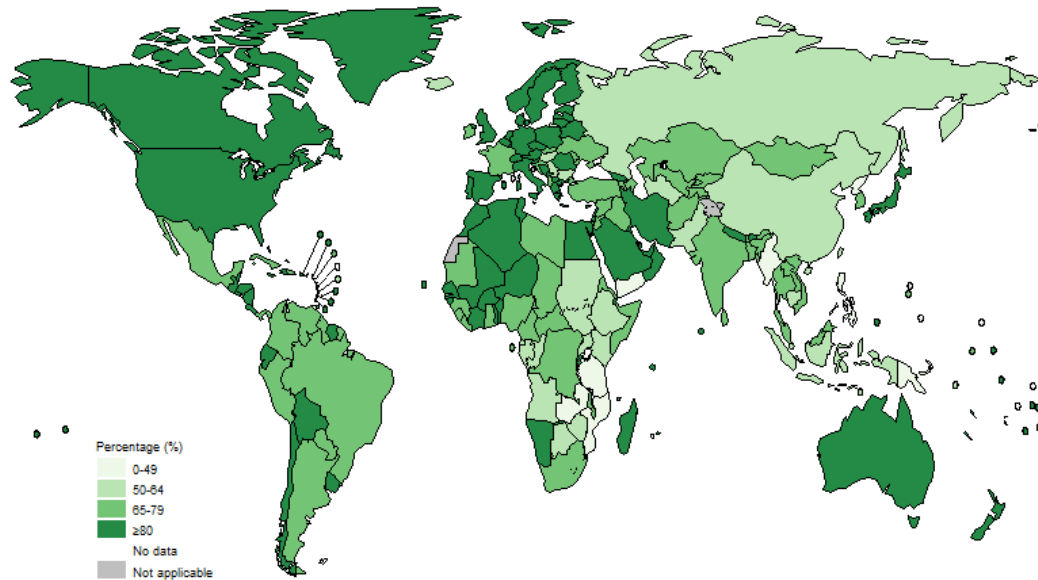
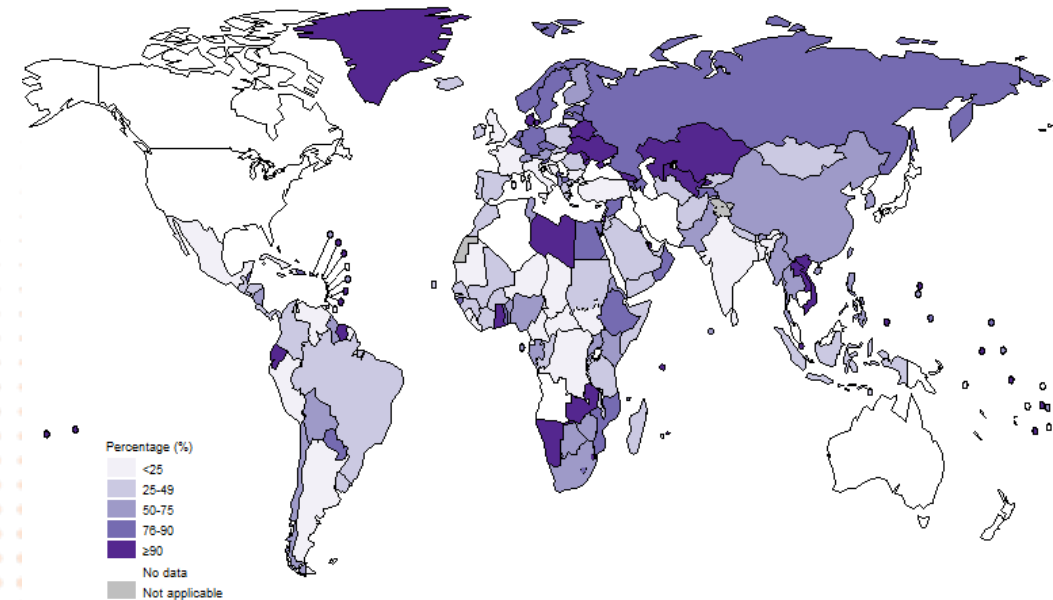


Fig. 3.2.5 Percentage of people newly diagnosed with TB who were **initially tested with a WHO-recommended rapid test** at country level, 2021



Detecting *M. tuberculosis*
(microbiological tests as molecular tests, culture tests)

Detecting incipient TB
(prognostic tests as evaluation of RNA transcripts)

Detecting Mtb infection
(persistent infection tests as IGRA, TST, new IGRA or IP-10 ELISA)



Uninfected



TB infection



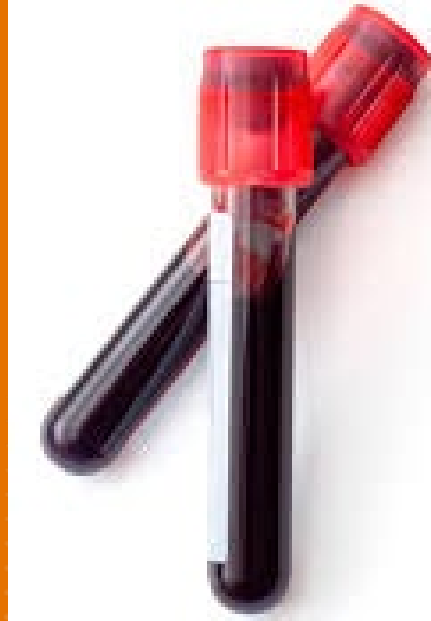
Incipient TB



Sub clinical TB

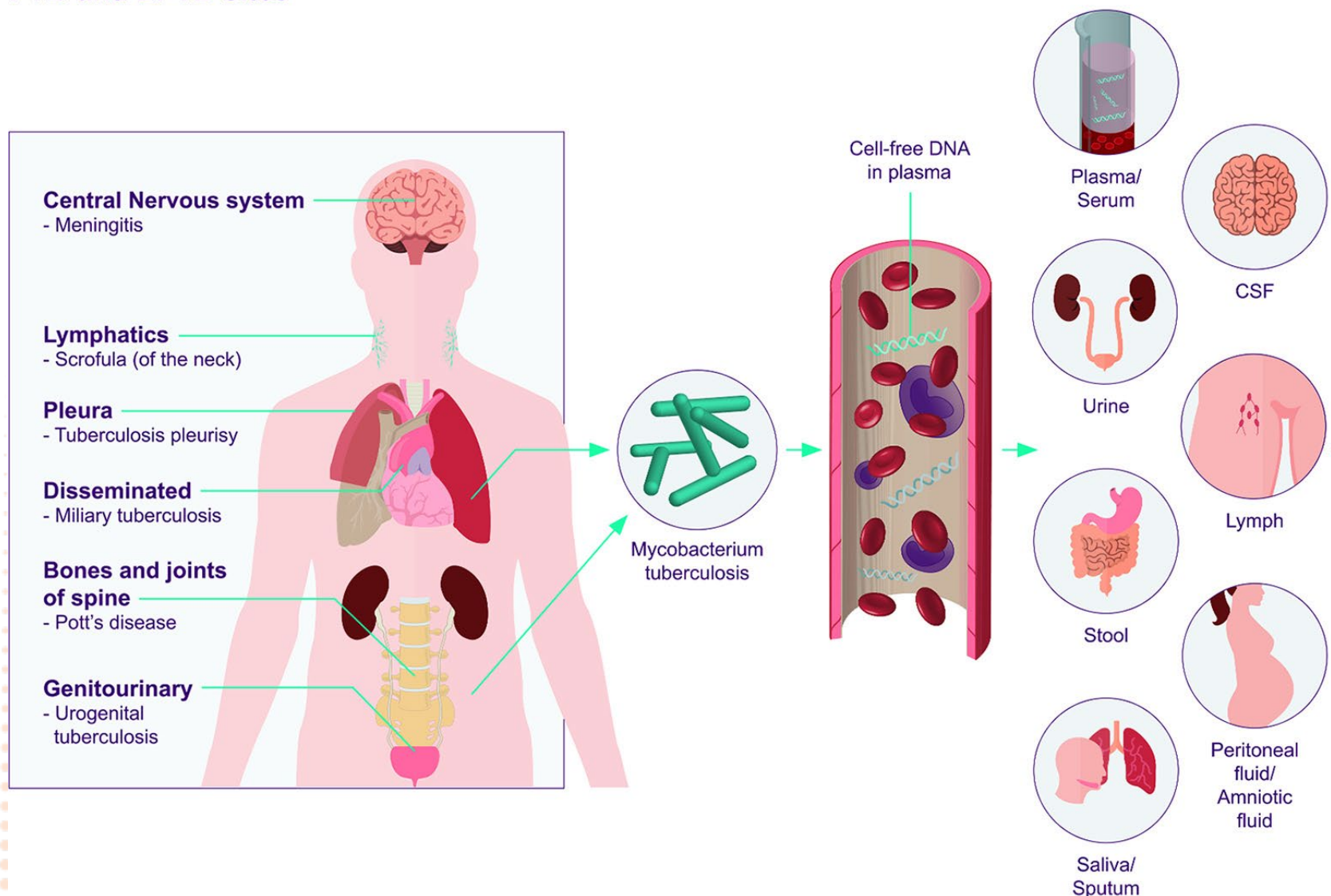


TB disease



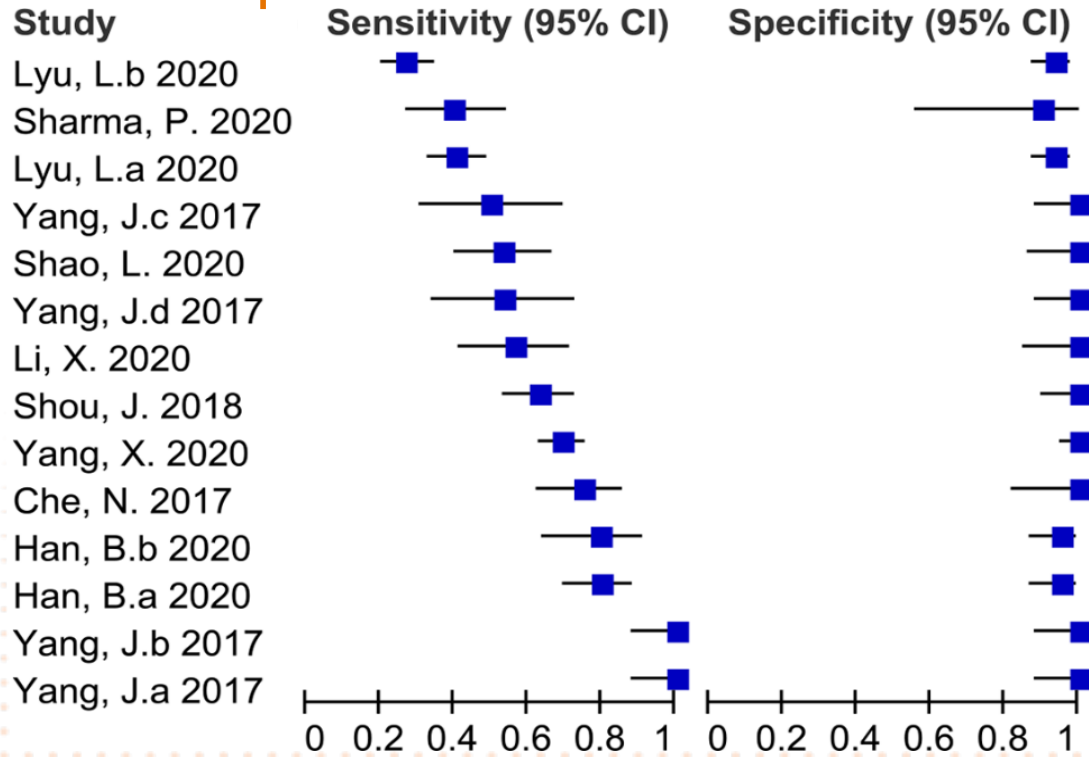
Cell-free *M. tuberculosis* DNA

PTB and EPTB sites



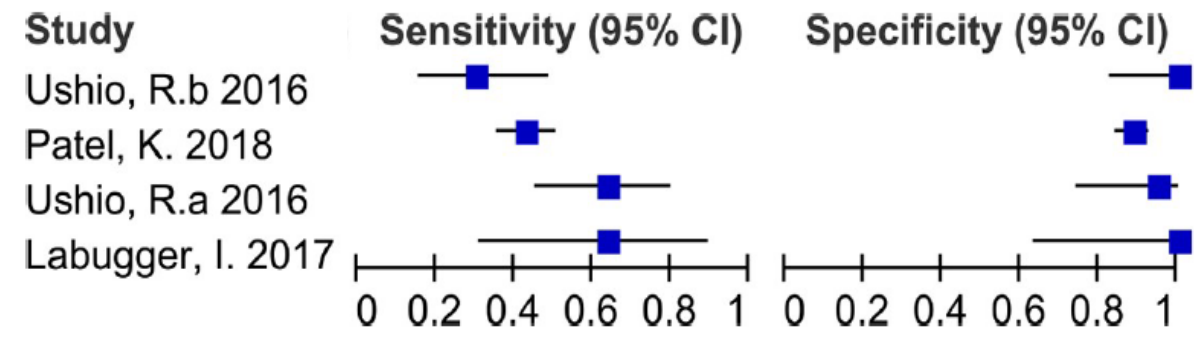
Cell-free *M. tuberculosis* DNA

Composite reference standard



Pooled sensitivity: 68%; Specificity: 98%

Microbiologic reference standard



Pooled sensitivity: 48%; Specificity: 91%

PTB > EPTB
 Plasma > other bodily fluids
 Digital PCR > rt-PCR
 IS6110 > other target genes



Karius test

Age group	TB status	Cell-free DNA detected by commercial-reporting threshold <i>n/N</i> (%) (95% CI)	Cell-free DNA detected by RUO-reporting threshold <i>n/N</i> (%) (95% CI)
Children			
	Sm ⁺ /Cx ⁺ (<i>n</i> = 4)	2/4 (50) (7–93)	3/4 (75) (19–99)
	Sm ⁻ /Cx ⁺ (<i>n</i> = 6)	0/6 (0) (0–46)	1/6 (17) (0–64)
	Clinically diagnosed (Sm ⁻ /Cx ⁻) (<i>n</i> = 10)	0/10 (0) (0–31)	0/10 (0) (0–31)
	TB ruled out (Sm ⁻ /Cx ⁻) (<i>n</i> = 10)	0/10 (0) (0–31)	0/10 (0) (0–31)
Adults			
	Sm ⁺ /Cx ⁺ (<i>n</i> = 5)	3/5 (60) (15–95)	5/5 (100) (48–100)
	Sm ⁻ /Cx ⁺ (<i>n</i> = 5)	0/5 (0) (0–52)	0/5 (0) (0–52)

CI = confidence interval; RUO = research use only; Sm = smear; + = positive; Cx = culture; - = negative.



<https://kariusdx.com/resources/video-library/clinical-overview>

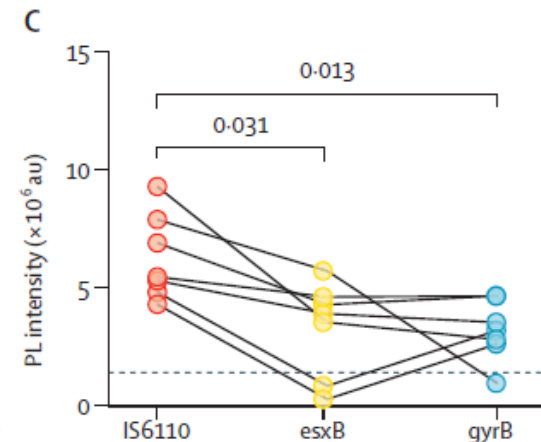
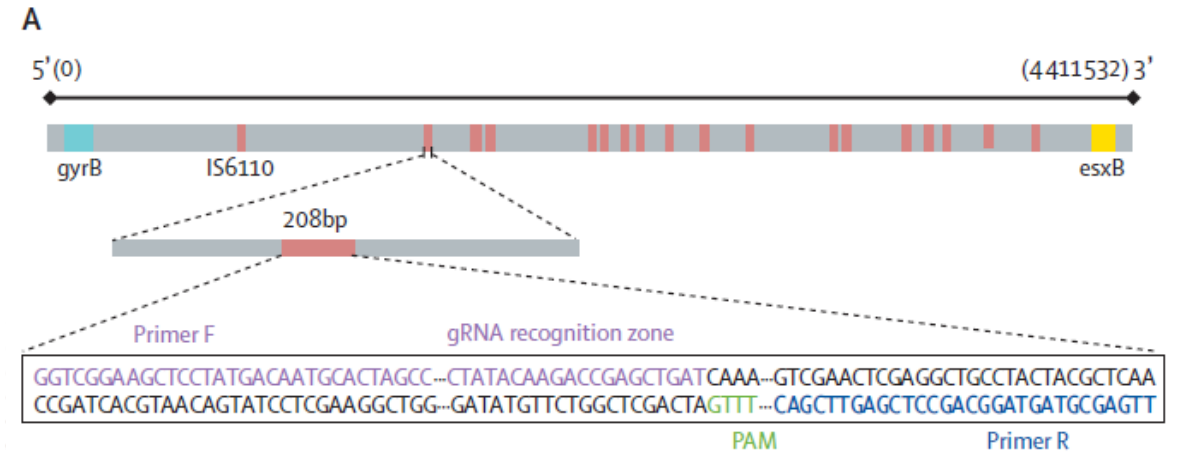
Pollack et al, IJTLD, Jun 2021; 25(5)

CRISPR detection of circulating cell-free *Mycobacterium tuberculosis* DNA in adults and children, including children with HIV: a molecular diagnostics study

Zhen Huang, Sylvia M LaCourse, Alexander W Kay, Joshua Stern, Jaclyn N Escudero, Brady M Youngquist, Wenshu Zheng, Debrah Vambe, Muyalo Dlamini, Godwin Mtetwa, Lisa M Cranmer, Irene Njuguna, Dalton C Wamalwa, Elizabeth Maleche-Obimbo, Donald G Catanzaro, Christopher J Lyon, Grace John-Stewart, Andrew DiNardo, Anna M Mandalakas, Bo Ning, Tony Y Hu

CRISPR-TB:

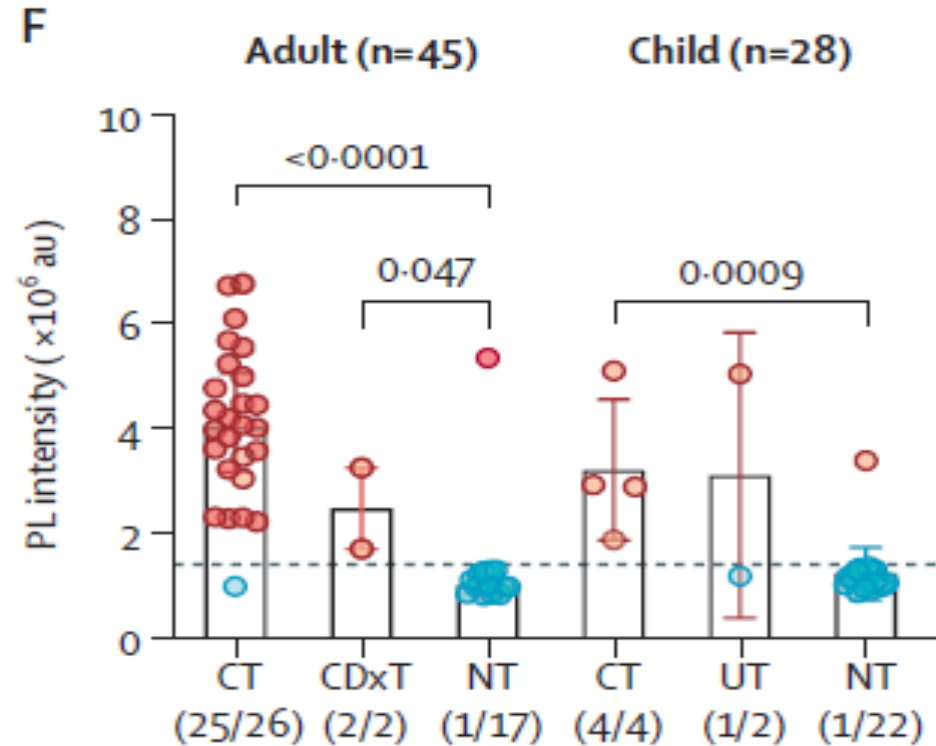
- CRISPR-Cas12a fluorescence assay
- detects cell free *Mtb*-DNA in serum
- measured in adults, children +/- HIV and asymptomatic household contacts.



↑ LOD of 0.06 copy/uL

CRISPR detection of circulating cell-free *Mycobacterium tuberculosis* DNA in adults and children, including children with HIV: a molecular diagnostics study

73 TB and non-TB participants from Eswatini



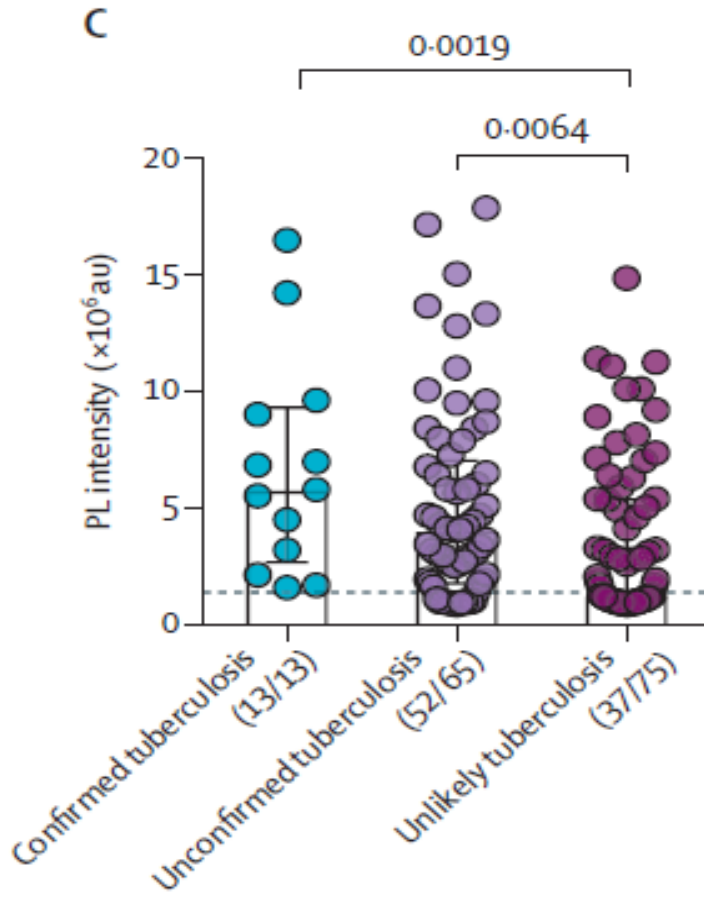
Sensitivity: 96%
Specificity: 94%

Sensitivity: 83%
Specificity: 95%



CRISPR detection of circulating cell-free *Mycobacterium tuberculosis* DNA in adults and children, including children with HIV: a molecular diagnostics study

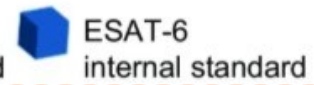
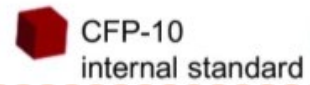
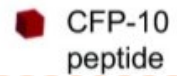
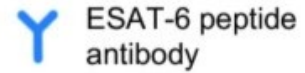
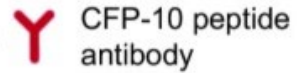
153 CLHIV at risk for TB from Kenya



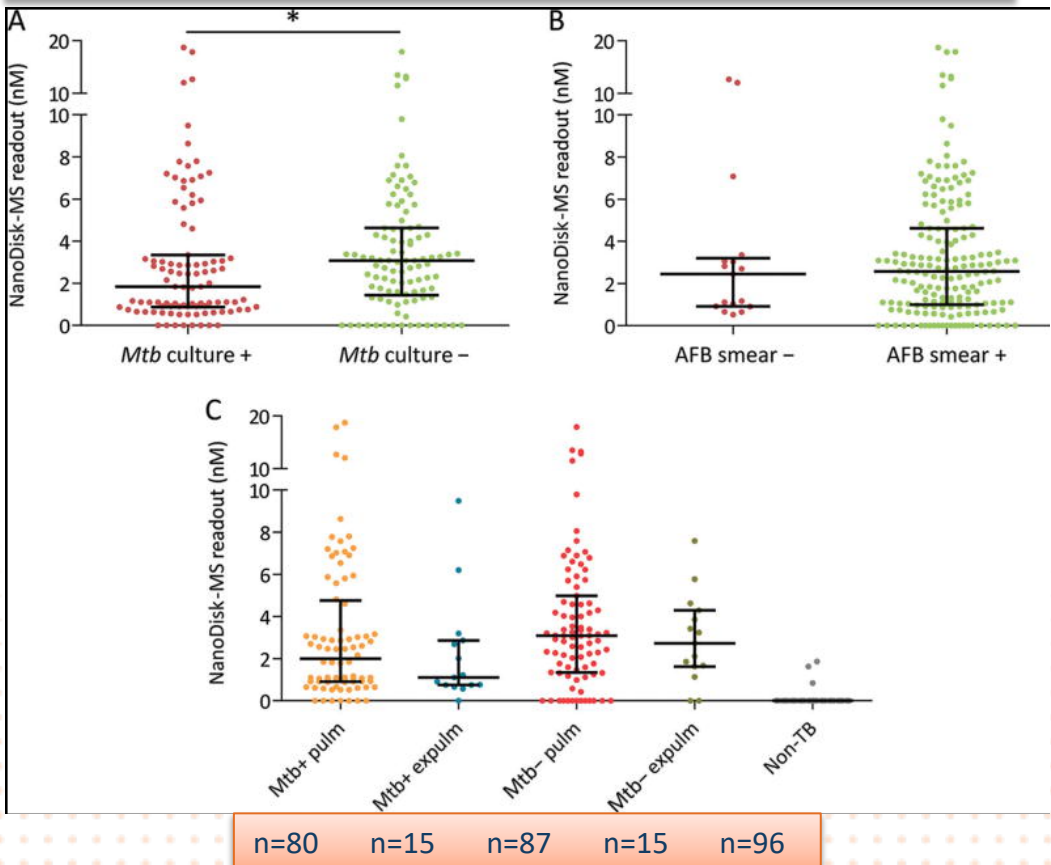
- Detected 100% of children with confirmed TB
- Detected 80% of children with unconfirmed TB
 - Early detection in 10/12
- Unlikely TB:
 - 0 NIH criteria: 79% had negative CRISPR-TB
 - 1 NIH criterion: 44% had negative CRISPR-TB

A

Circulating antigens



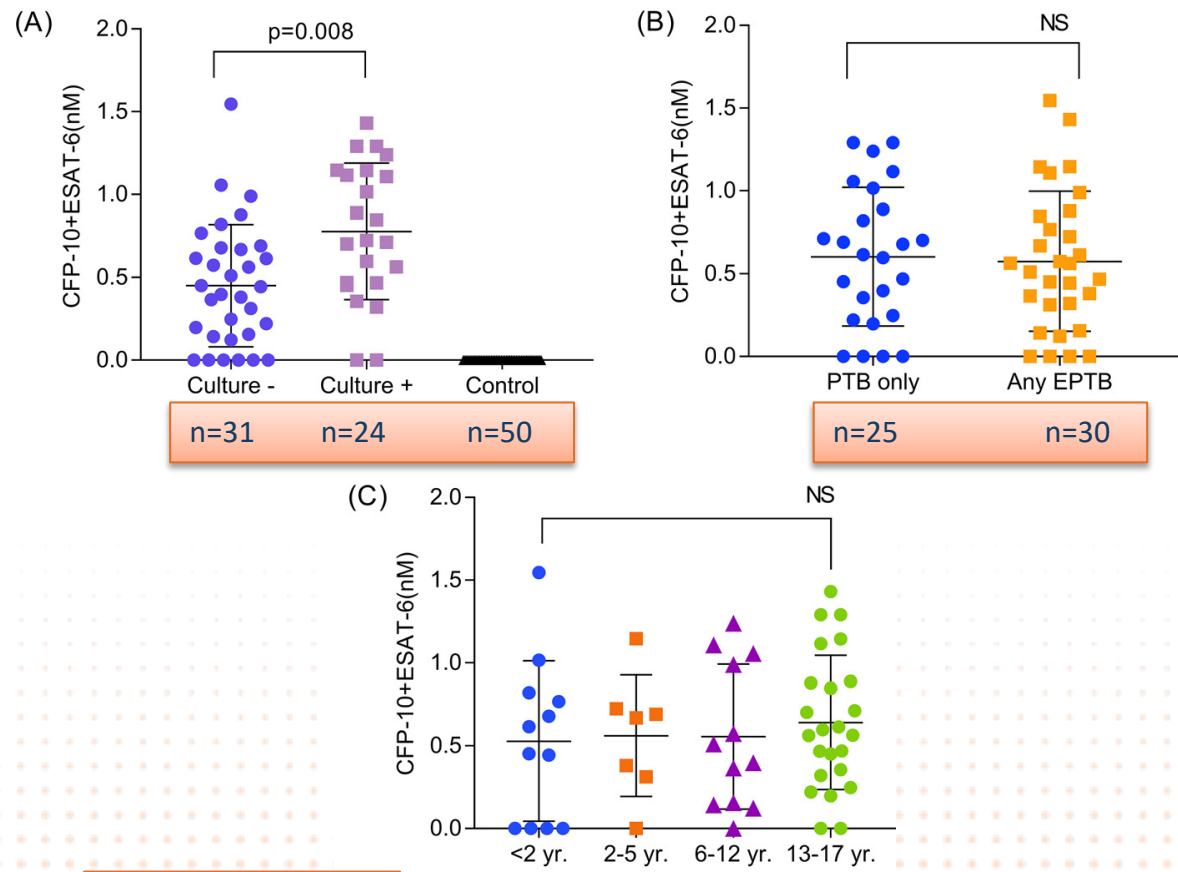
N=376 adults without HIV, undergoing evaluation for TB



n=80 n=15 n=87 n=15 n=96

Sensitivity: 88%
 Cx+PTB: 91%
 Cx+EPTB: 93%
 Cx-PTB: 85%
 Cx-EPTB: 87%
Specificity: 96%

N=105 children <18y enrolled in TB surveillance study



n=31 n=24 n=50

n=25 n=30

Sensitivity: 86%
 Cx+TB: 88%
 Cx-TB: 84%
 Cx-PTB: 78%
 Cx-EPTB: 86%
Specificity: 96%





FujiFILM SILVAMP

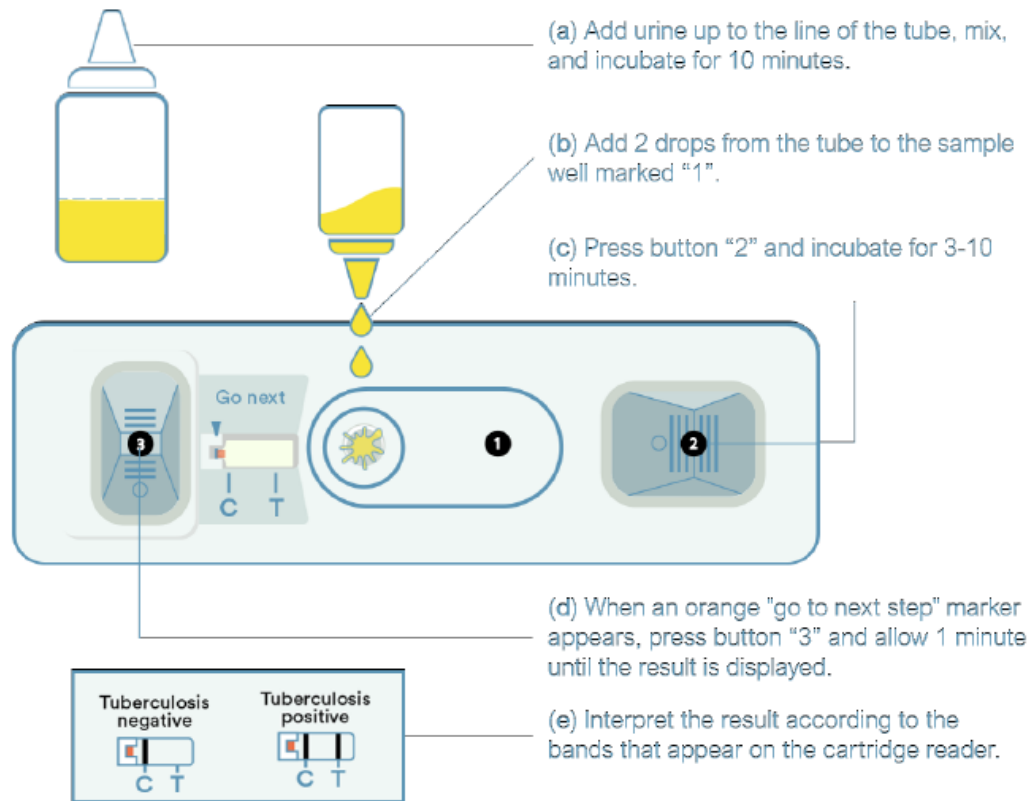
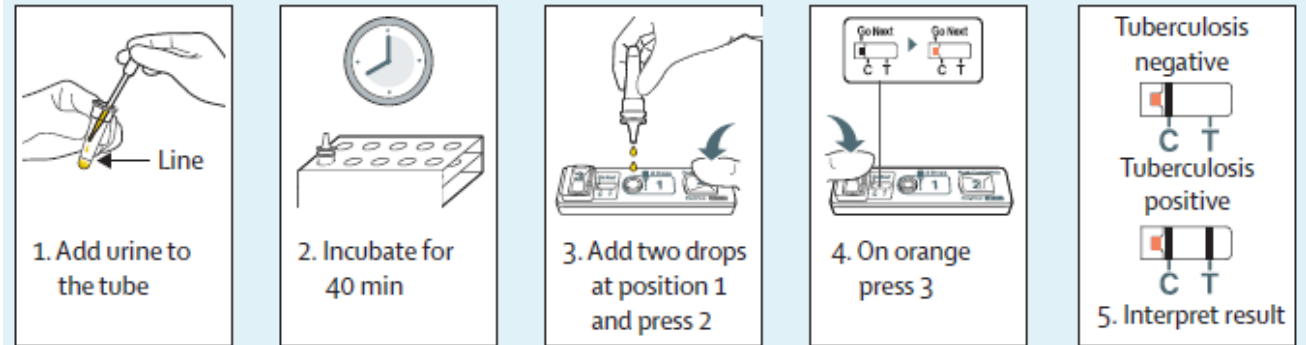


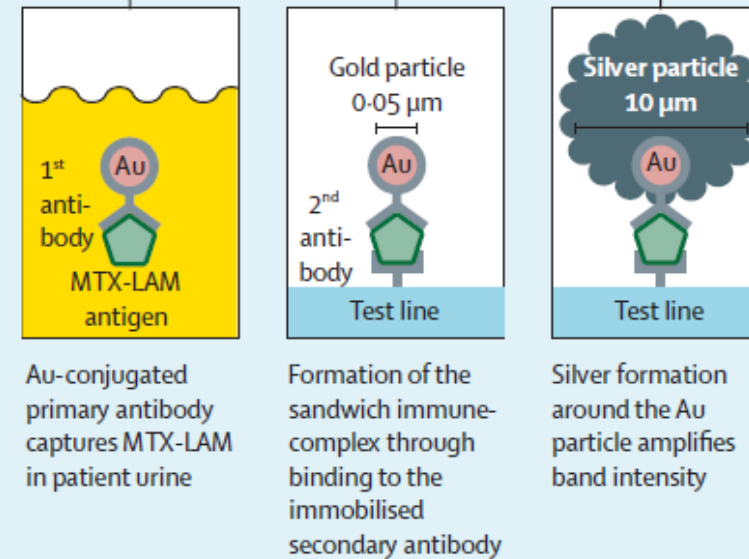
Figure 1. Outline of the procedures to perform the Fujifilm SILVAMP TB-LAM assay.

Tuberculosis test procedure

60 min from sample collection to result



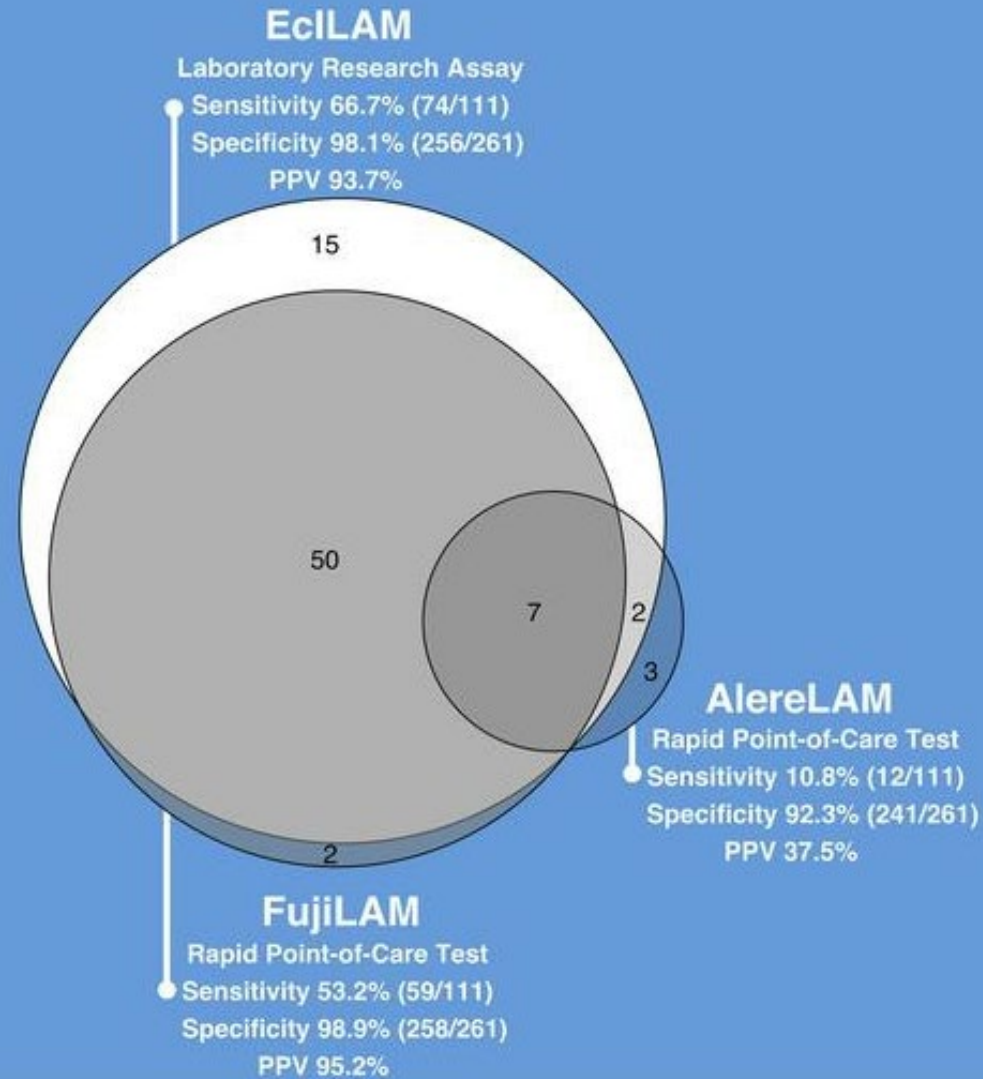
Tuberculosis test principle



SILVAMP performance among adults with HIV

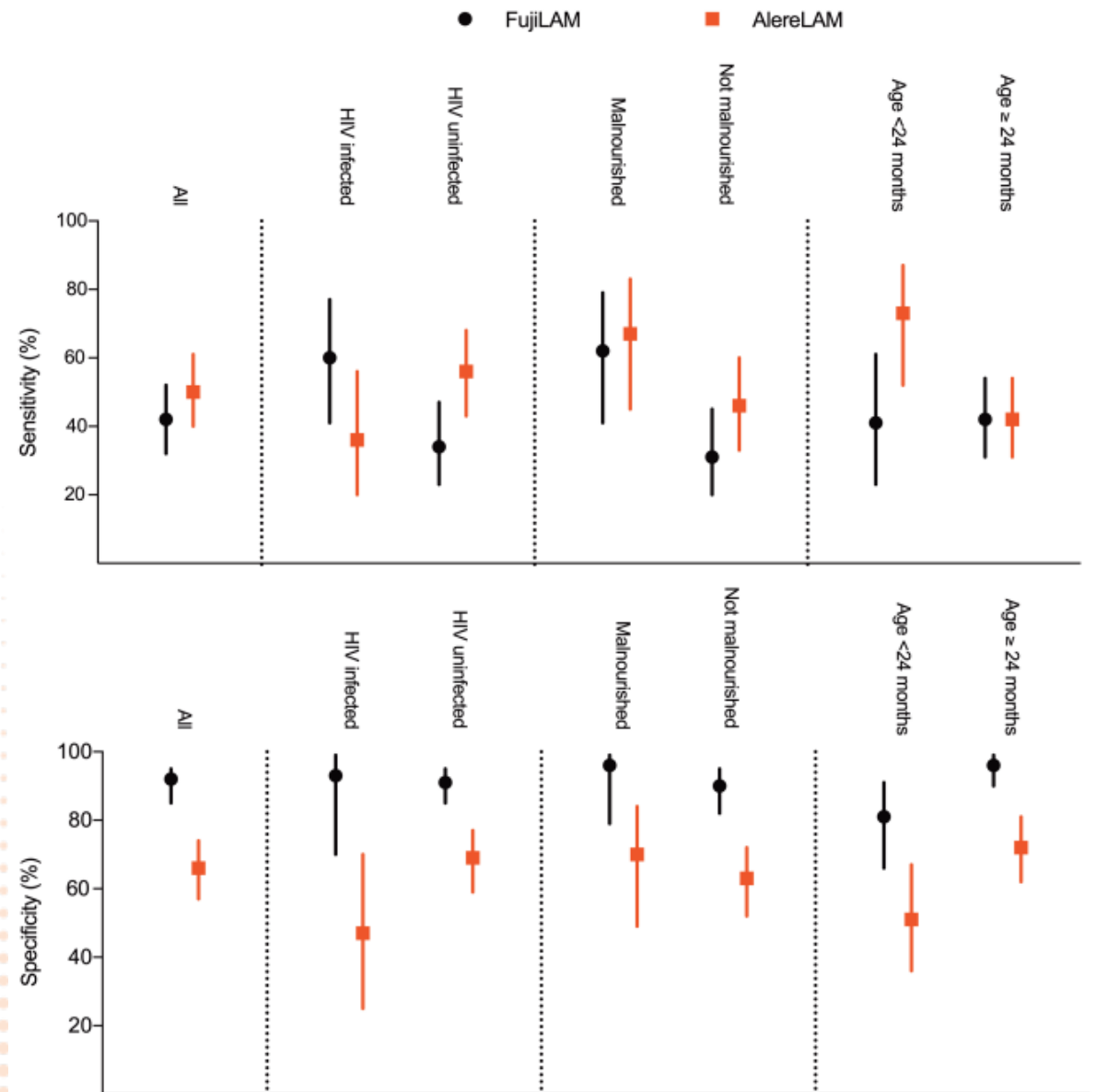
- ~20-30% more sensitive than Alere LF-LAM
 - Overall sensitivity 71% compared to microbiologic reference standard
 - Sensitivity of 66% compared to composite reference standard
- Specificity is high, >91%
- Performs better among those with CD4<200,
- No significant differences among inpatients or outpatients.
- Prospective analysis: symptomatic and asymptomatic adults
 - SILVAMP sensitivity 60% compared to MRS
 - Similar results among symptomatic and asymptomatic people
 - Better performance among those with CD4<200
- **Lot to lot variability**

Diagnostic accuracy of three urine lipoarabinomannan (LAM) tuberculosis assays in HIV-negative outpatients

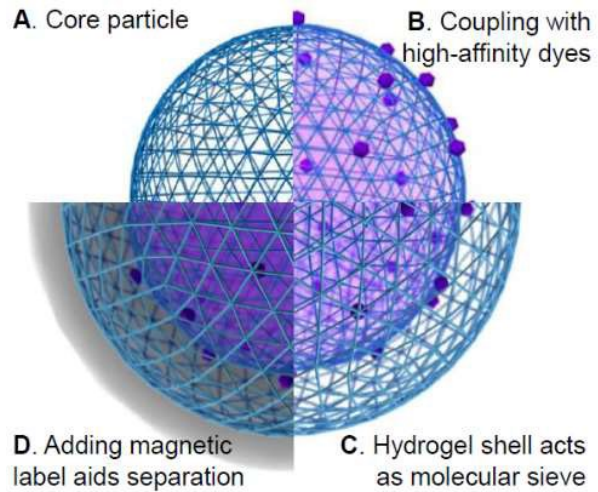


SILVAMP among children

- Modest sensitivity ~51-65%
- Lower in children without HIV
- Improved with:
 - Advanced stage of disease
 - Underweight/stunted
- Specificity ~83-95%
- **Need more data**



Ceres Nanotrap



3rd generation LAM tests

Pre-analytic steps:

Liberation of LAM

Concentration of LAM

Pre-analytic steps:

Liberation of LAM
Concentration of LAM

**Capture & detection
of LAM:**

**Integrated testing
platform**

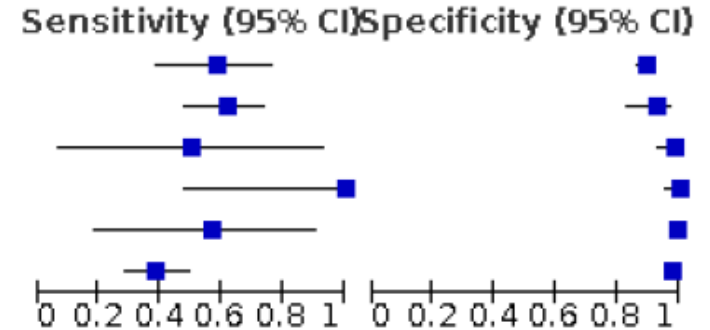
**3rd generation
LAM tests**



Xpert MTB/RIF Ultra on stool in children

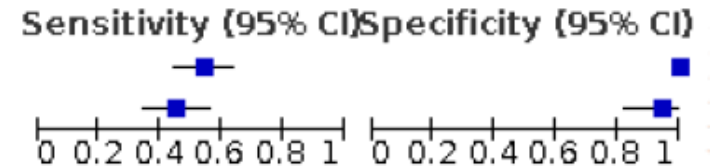
Xpert Ultra, stool, all ages, culture

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Kabir 2020	17	43	12	374	0.59 [0.39, 0.76]	0.90 [0.86, 0.92]
Liu 2021	37	5	23	61	0.62 [0.48, 0.74]	0.92 [0.83, 0.97]
NCT04121026	2	1	2	77	0.50 [0.07, 0.93]	0.99 [0.93, 1.00]
NCT04203628	5	0	0	77	1.00 [0.48, 1.00]	1.00 [0.95, 1.00]
NCT04240990	4	1	3	226	0.57 [0.18, 0.90]	1.00 [0.98, 1.00]
NCT04899076	37	8	58	359	0.39 [0.29, 0.49]	0.98 [0.96, 0.99]



Xpert Ultra, stool, all ages, composite reference standard

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Kabir 2020	60	0	51	335	0.54 [0.44, 0.64]	1.00 [0.99, 1.00]
Liu 2021	40	2	48	36	0.45 [0.35, 0.56]	0.95 [0.82, 0.99]



- Pooled sensitivity 56% compared to culture
- Pooled specificity 98% compared to culture
- (similar performance compared to composite reference standard)

Xpert MTB/RIF Ultra on stool

- WHO endorsed
- Modest performance
 - specimen might be more feasible to collect?
- Mostly reflective of pulmonary TB



TB-SPEED STOOL PROCESSING
Evaluation of Four Stool Processing Methods Combined With Xpert MTB/RIF Ultra for Diagnosis of Intrathoracic Paediatric Tuberculosis

Conclusion

- Progress has been made, but more work to do
- Numerous tests have only modest performance
- Multiple testing options are needed to meet the needs across populations