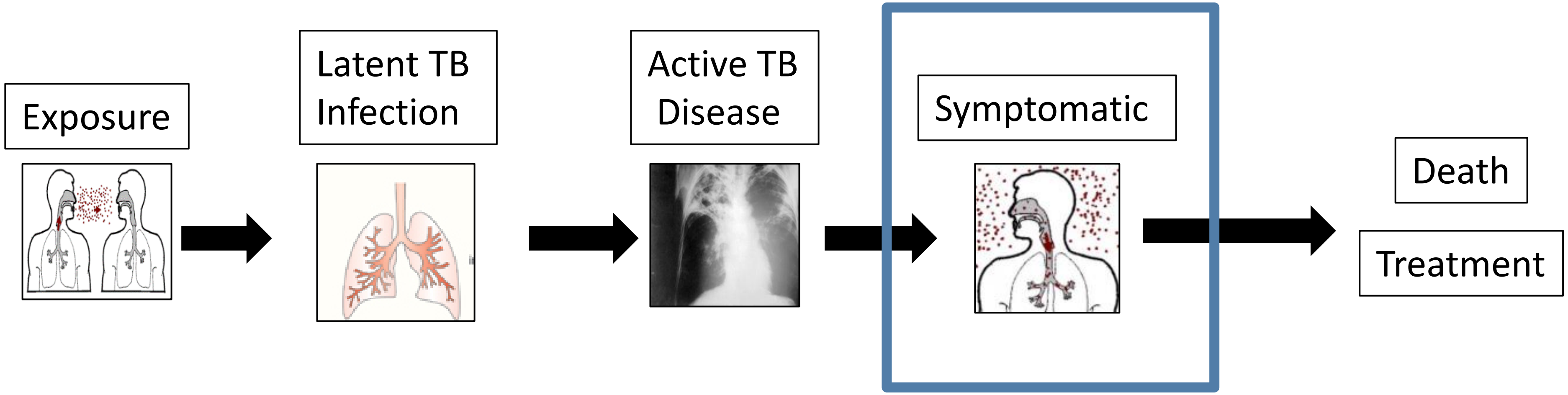
New TB Diagnostics: What will it take to end TB?

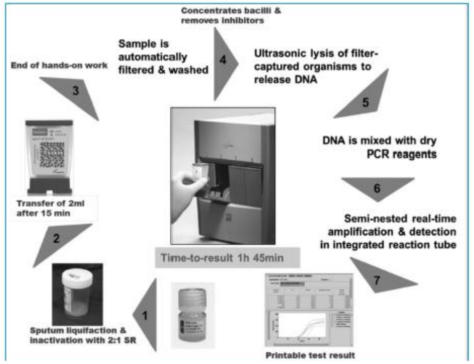
Yuka Manabe MD PhD
Infectious Disease
Department of Medicine
Johns Hopkins University

The Current TB Diagnostic Cascade



1. Present to care [after development of symptoms]
2. Identify site of potential disease
3. Collect specimens: **at site of disease**
4. Conduct Diagnostic Tests

Requires 10^4 organisms/ml

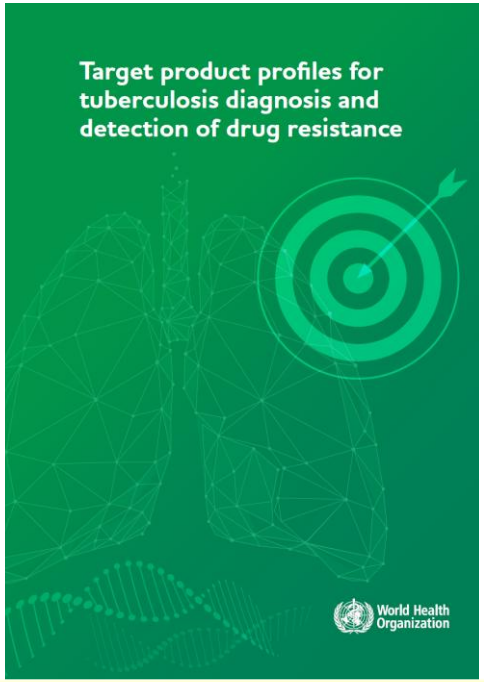


Not as sensitive as culture
Faster than culture

Growth: slow,
resource intensive

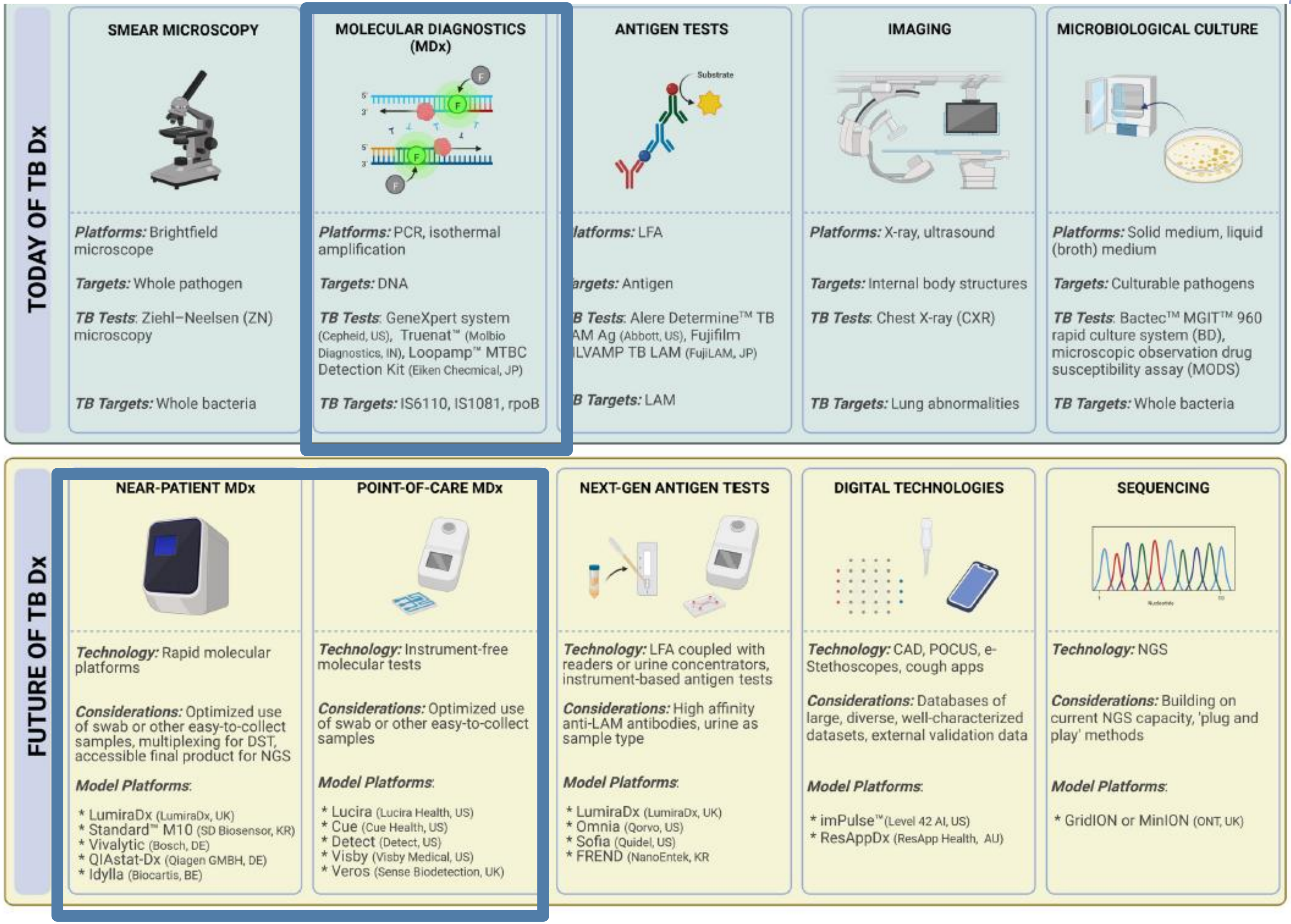
What do we need?

- Four ‘target product profiles’ (TPP) identified (slightly updated in 2024):
  1. Rapid sputum based tests for detecting TB at microscopy-level
     - Candidate: molecular detection
     - Process optimization: oral swabs
  2. Rapid biomarker based non sputum based test for detecting TB
     - Candidate: LAM
  3. A next generation drug susceptibility test to be implemented at the peripheral level of the health system
     - Candidate: NAATs, LPA
  4. Community based triage or referral test to identify people suspected of having TB



https://www.who.int/publications/i/item/9789240097698

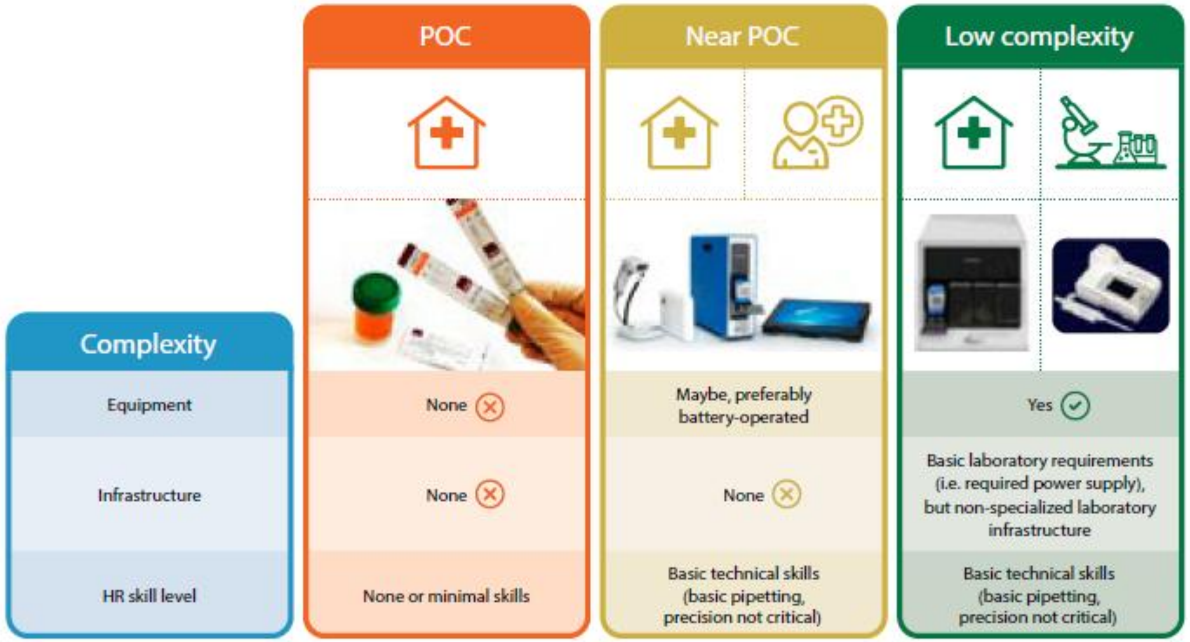
The Future of TB Diagnosis



Courtesy Adithya Cattamanchi

Considerations for rapid diagnostic (specimen/site-specific) tests

Fig. 1.1. TB diagnostic tests – proximity to health care and complexity



Performance		
Diagnostic sensitivity for TB detection		
Sputum, low-complexity assay	90%	≥95%
Sputum, near-POC	85%	
Sputum, POC	75%	
Non-sputum, low-complexity assay	80%	
Non-sputum, near-POC	75%	
Non-sputum, POC	65%	
Diagnostic specificity for TB detection	>98% for a single test when compared with liquid culture.	
Non-actionable (indeterminate + invalid) results	<5%	<3%

Characteristic	Minimal requirements	Optimal requirements
Pricing		
Price of individual tests (reagent costs only; at scale; ex-works)		
Low-complexity assay	≤US$ 8	≤US$ 5
Near-POC	≤US$ 6	≤US$ 4
POC	≤US$ 4	≤US$ 2

Characteristic	Minimal requirements
Capital cost for the instrument	<US$ 2000

Table 2.1. Modelled estimates of the minimum acceptable sensitivity values

Countries	POC		Near-POC		Low-complexity assays	
	Sputum-based	Non-sputum-based	Sputum-based	Non-sputum-based	Sputum-based	Non-sputum-based
India	74%	70%	77%	71%	82%	77%
South Africa	78%	65%	86%	70%	91%	75%
Kenya	71%	59%	79%	65%	80%	66%
Proposed minimum	78%	70%	86%	71%	91%	77%

POC: point of care.

Site specific tests: molecular detection of *M. tuberculosis* nucleic acid increase diagnostic yield over smear-microscopy

WHO 2021 Guidelines

- Rapid molecular test as first-line (varying recommendations)
  - Stratified by pulmonary and extrapulmonary TB (sputum, CSF, pleural, pericardial, synovial, LN tissue, urine, *blood*)
- Sputum, Gastric Aspirate, NP aspirate, Stool for children (with signs/symptoms of pulmonary TB)*

Test options

- Molecular tests
  - Xpert MTB/RIF and MTB/RIF Ultra
  - TB LAMP*
  - **Truenat MTB/MTB Plus and MTB-RIF***
  - **4 moderate complexity assays***

Challenges that need to be overcome:
M. tuberculosis nucleic acid may be sequestered to sites of disease (sampling)
Processing required to access nucleic acid (intracellular, mycolic acid cell wall)
Sensitivity not as good as mycobacterial culture

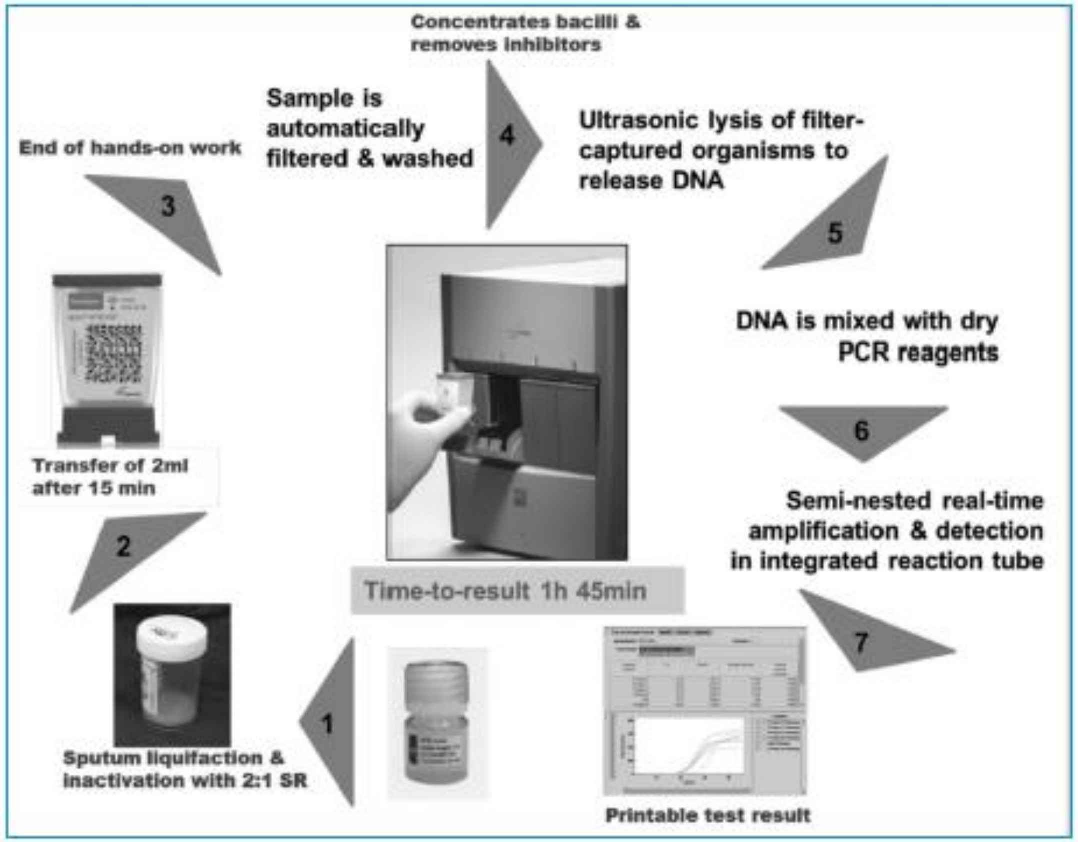
NAAT: (Cepheid) GeneXpert Xpert MTB/RIF and Ultra

- **Self-contained, closed, fully automated system with lower limit of detection than smear-microscopy**

- Detects *M.tb* and mutations conferring Rifampin resistance
- Use in lower levels of health system (peripheral labs)

- Sensitivity for Pulmonary TB
  – Smear-positive: 95–100%
  – Smear-negative: ~50-75%

- Specificity: ~98%



Can we do better?

Xpert MTB/RIF Ultra for detection of *Mycobacterium tuberculosis* and rifampicin resistance: a prospective multicentre diagnostic accuracy study

	Tuberculosis detection*				
	Sensitivity: all culture-positive (95% CI; n/N)	Sensitivity: smear-negative (95% CI; n/N)	Sensitivity: HIV-negative (95% CI; n/N)‡	Sensitivity: HIV-positive (95% CI; n/N)‡	Specificity (95% CI; n/N)
Xpert	83% (79 to 86; 383/462)	46% (37 to 55; 63/137)§	90% (84 to 94; 143/159)	77% (68 to 84; 88/155)	98% (97 to 99; 960/977)
Xpert Ultra	88% (85 to 91; 408/462)	63% (54 to 71; 86/137)§	91% (86 to 95; 145/159)	90% (83 to 95; 103/115)	96% (94 to 97; 934/977)
Difference (Xpert Ultra minus Xpert)	5·4% (3·3 to 8·0; 25/162)	17% (10 to 24; 23/137)	1·3% (–1·8 to 4·9; 2/159)	13% (6·4 to 21; 15/115)	–2·7% (–3·9 to –1·7; 36/977)
Non-inferiority margin	Not predefined	–7%	Not predefined	Not predefined	Not predefined

"The Ultra assay is non-inferior to the current Xpert® MTB/RIF assay for the diagnosis of MTB and the detection of rifampicin resistance and can be used as an alternative to the latter in all settings." -WHO 2017

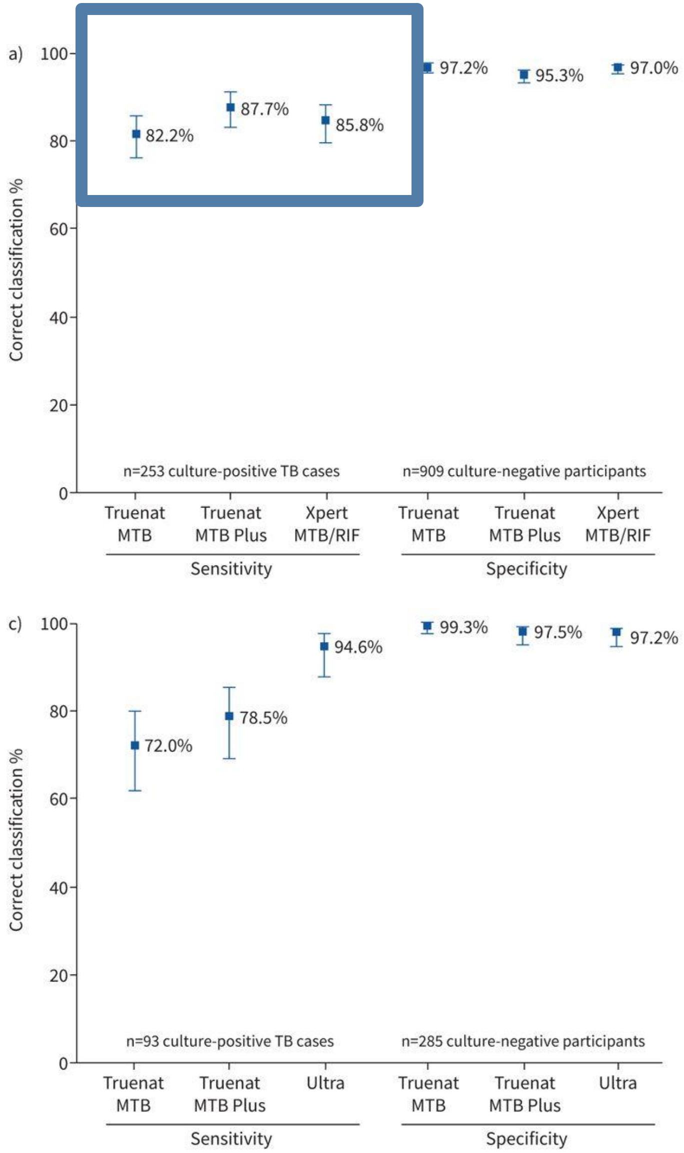
Dorman et al. Lancet ID 2018

WHO: Non-inferiority analysis of Xpert MTB/RIF Ultra compared to Xpert MTB/RIF 2017

Truenat (Molbio, India)

- Automated, battery-operated devices for DNA extraction and PCR
- Disposable PCR chip (MTB, MTB Plus, MTB RIF)
- Results in less than one hour
- Similar performance to Xpert in a trial including 1800 participants at 19 sites in 4 countries

First serious competitor to Xpert MTB/RIF



Penn-Nicholson A et al, ERJ 2021

The Future of TB Diagnosis

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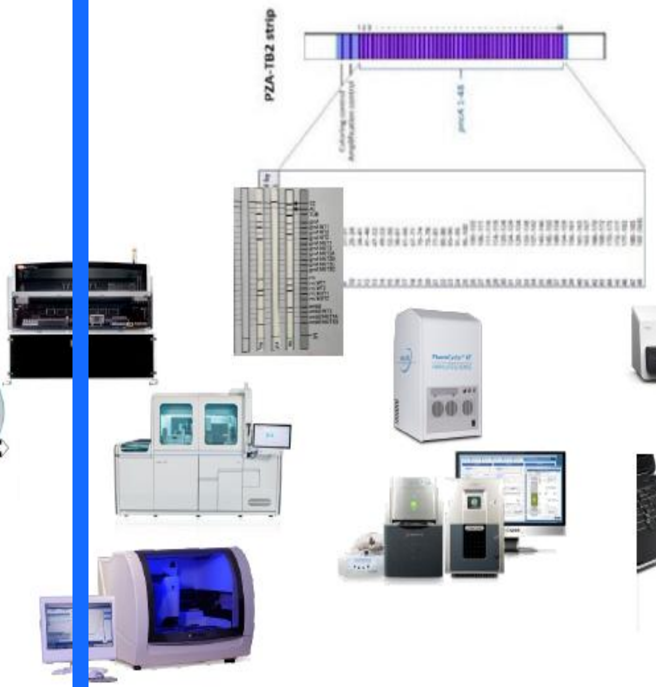
A BUSY PIPELINE OFFERING MANY NEW DIMENSIONS TO HOW TB COULD BE DIAGNOSED

POC MDx

non sputum
TB or no TB

Low complexity NAAT

Busy pipeline giving
cepheid a run for their
money



Moderate complexity NAAT

Rolled out in RSA

tNGS

WHO endorsed in 2023

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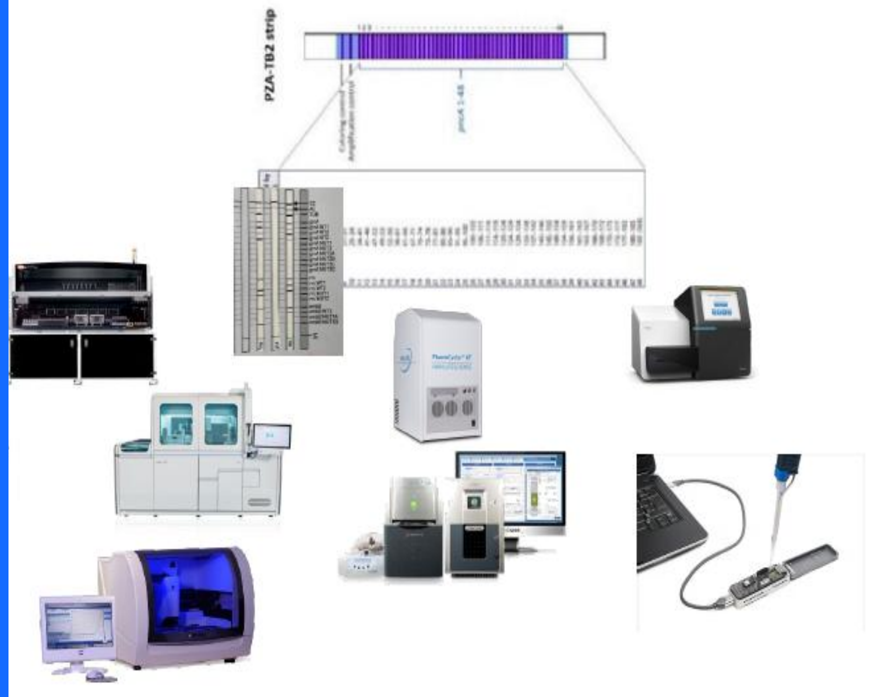

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Focus area: Addressing the 4.1 million detection gap

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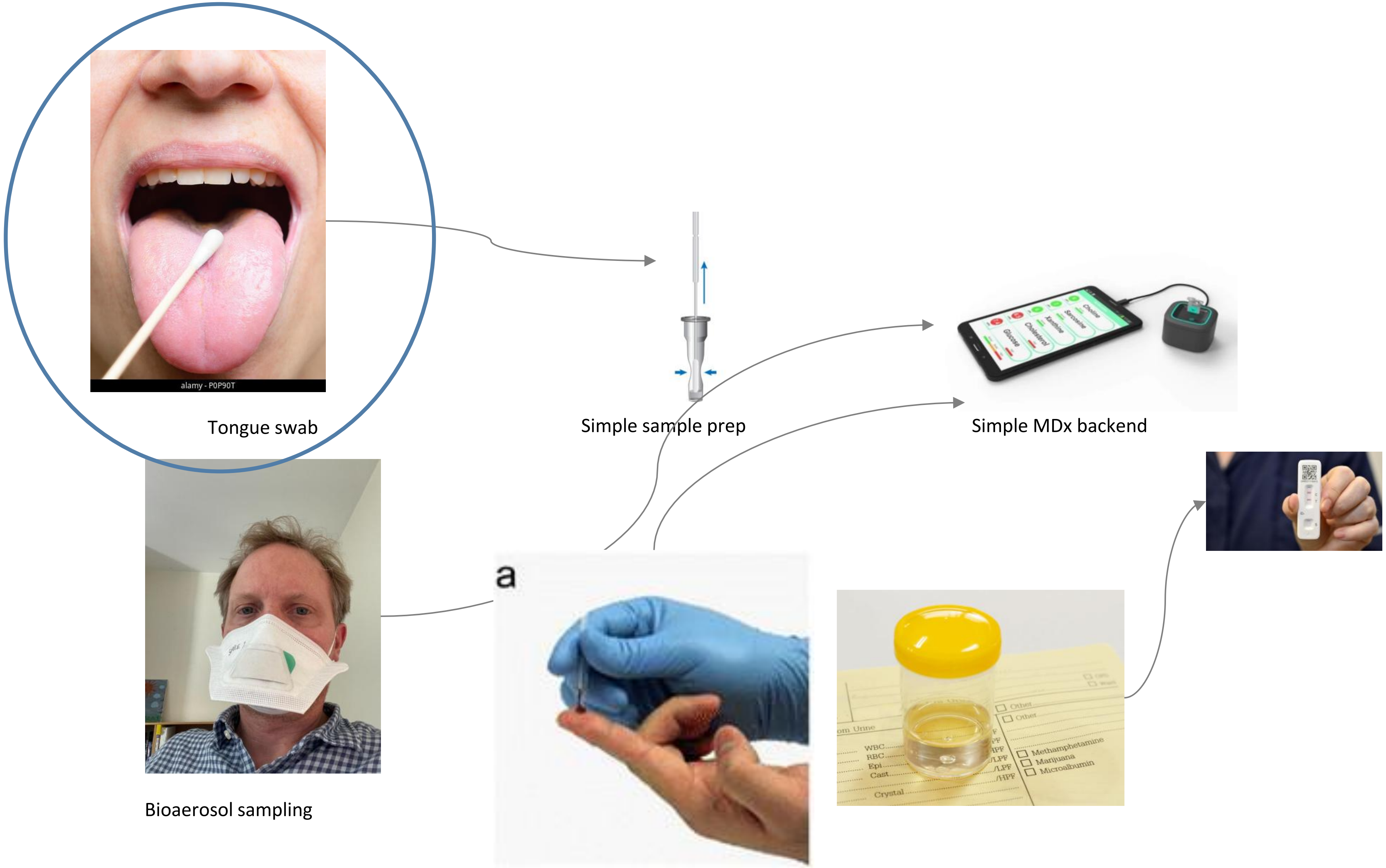
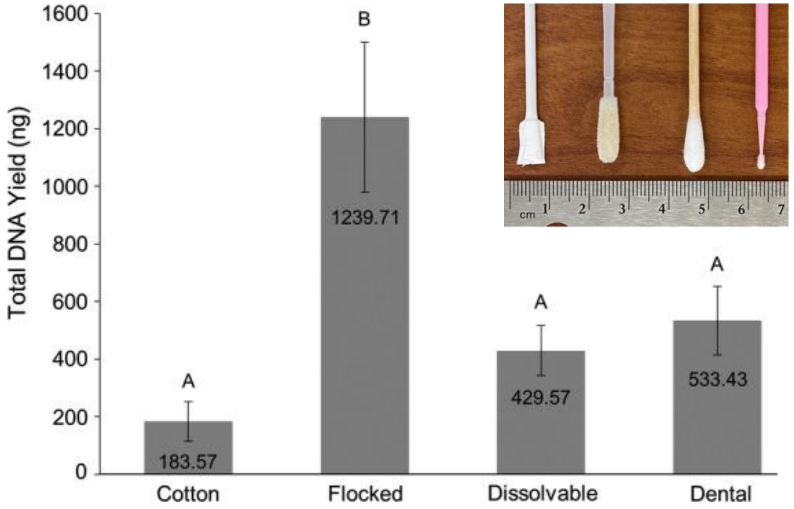


Slide adapted courtesy Morten Ruhwald, FIND

Tongue swabs – trade offs in sensitivity and yield

- Non-invasive, rapid sampling
- Simpler processing relative to sputum

Optimal swab type



Wise NM et al, MicrobiologyOpen 2021
Andama A et al, J Clin Micro 2022

Tongue swab collection and processing

Diagnostic accuracy (N=183 adults with presumed TB)

	Sputum Xpert Ultra reference standard	Microbiologic reference standard
Sensitivity	77.8 (64.4-88.0)	72.4 (59.1-83.3)
Specificity	100 (97.2-100)	100 (96.9-100)

Table 2: Comparison of semi-quantitative results

		Tongue swab Xpert Ultra (double swab SR method)					
		Negative	Trace	Very low	Low	Medium	**Total**
Sputum Xpert Ultra[a]	Negative	127	0	0	0	0	**127**
	Trace	2	0	0	0	0	**2**
	Very low	6	0	0	0	0	**6**
	Low	6	3	0	3	0	**12**
	Medium	0	3	5	7	0	**15**
	High	0	1	4	14	2	**21**
	Total	**141**	**7**	**9**	**24**	**2**	**183**

Slide courtesy of Adithya Cattamanchi

Tongue swab accuracy

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STATUS OF SWABS AS ALTERNATIVE SAMPLE TYPE ON EXISTING PLATFORMS

SUMMARY OF TONGUE SWAB STUDIES UNDER JSC AND SWAB CONSORTIUM

Study	Country	Index test	N (% HIV	Sensitivity % (95% CI)	Specificity % (95% CI)	Testing	Reference	Protocol
FEND-TB	Multiple	Xpert Ultra	595 (26%)	65.6 (57.0, 73.3)	100% (99.2, 100)	Fresh	Sputum Ultra	Draft Consensus
R2D2/ADAPT	Multiple	Xpert Ultra	1129	77.8 (71.5, 83.3)	97.6 (96.4, 98.5)	Fresh	Sputum Ultra	Draft Consensus
WITS Hillbrow*	South Africa	Xpert Ultra	323	78.8 (67.0–87.9)	100 (98.6–100)	Frozen	Sputum culture	Draft Consensus PBS, no heat, self collected
Wood RC et al, medRxiv 2023*	South Africa	Xpert Ultra	316 (33%)	75.4 (69.5, 80.7)	100 (95.0, 100)	Frozen	Sputum Ultra and culture	Draft Consensus Two heating and elution steps
GHLabs	Uganda	Molbio Ultima	237	98.5 (91.8, 99.9)	100 (97.8, 100)	Fresh	Sputum Ultra	Draft Consensus Bead beating lysis

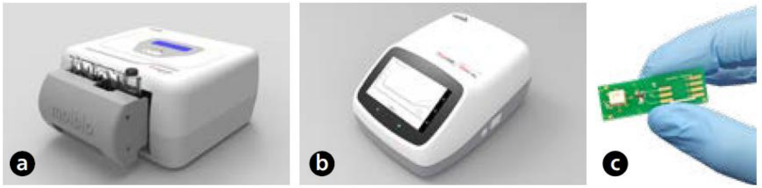
Tongue swab may not be perfect, but may allow increased testing

Swab-based TB assay on fully-integrated, POC molecular platform

Sherlock Biosciences, Veros

Boditech Med, IsoAmplar

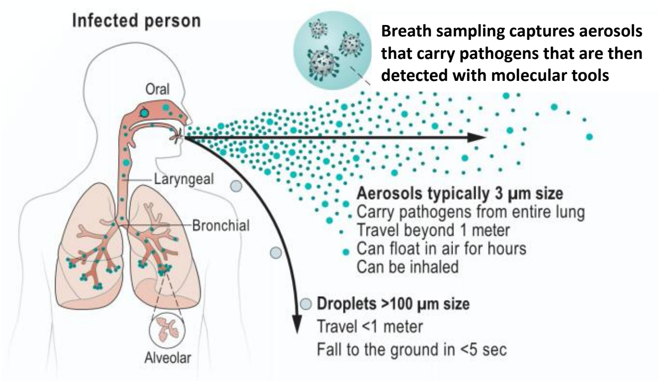
Co-Diagnostics, Co-Dx PCR Pro



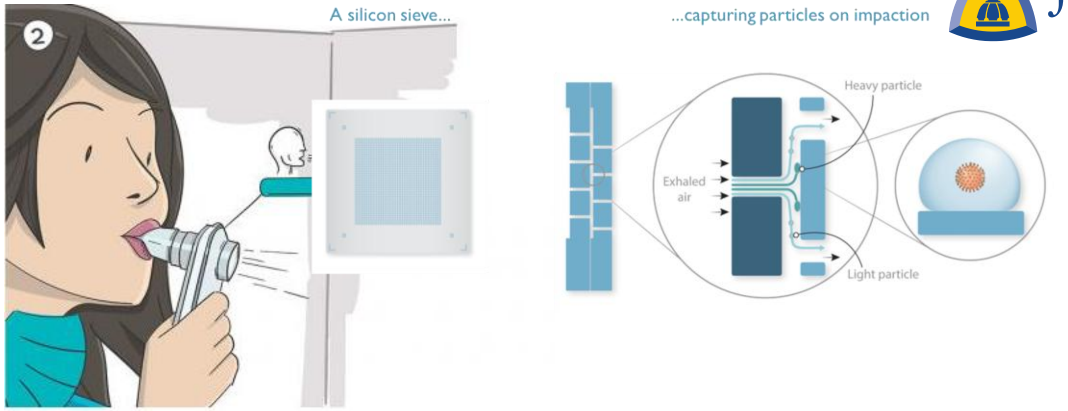
Molbio Diagnostics, Truenat

Minute Molecular Diagnostics, DASH

Breath aerosol sampling – promising early results



Breath sampling captures human aerosols that carry pathogens. After collection the pathogens' DNA or RNA is detected. (Adapted from Wang.Science.2021;373(6558):eabd9149)



- Ease of collection via non-invasive sampling methods (face mask)
- Link to infectiousness and transmission

Williams et al. Plos One 2020
Williams CM et al, Lancet ID 2020

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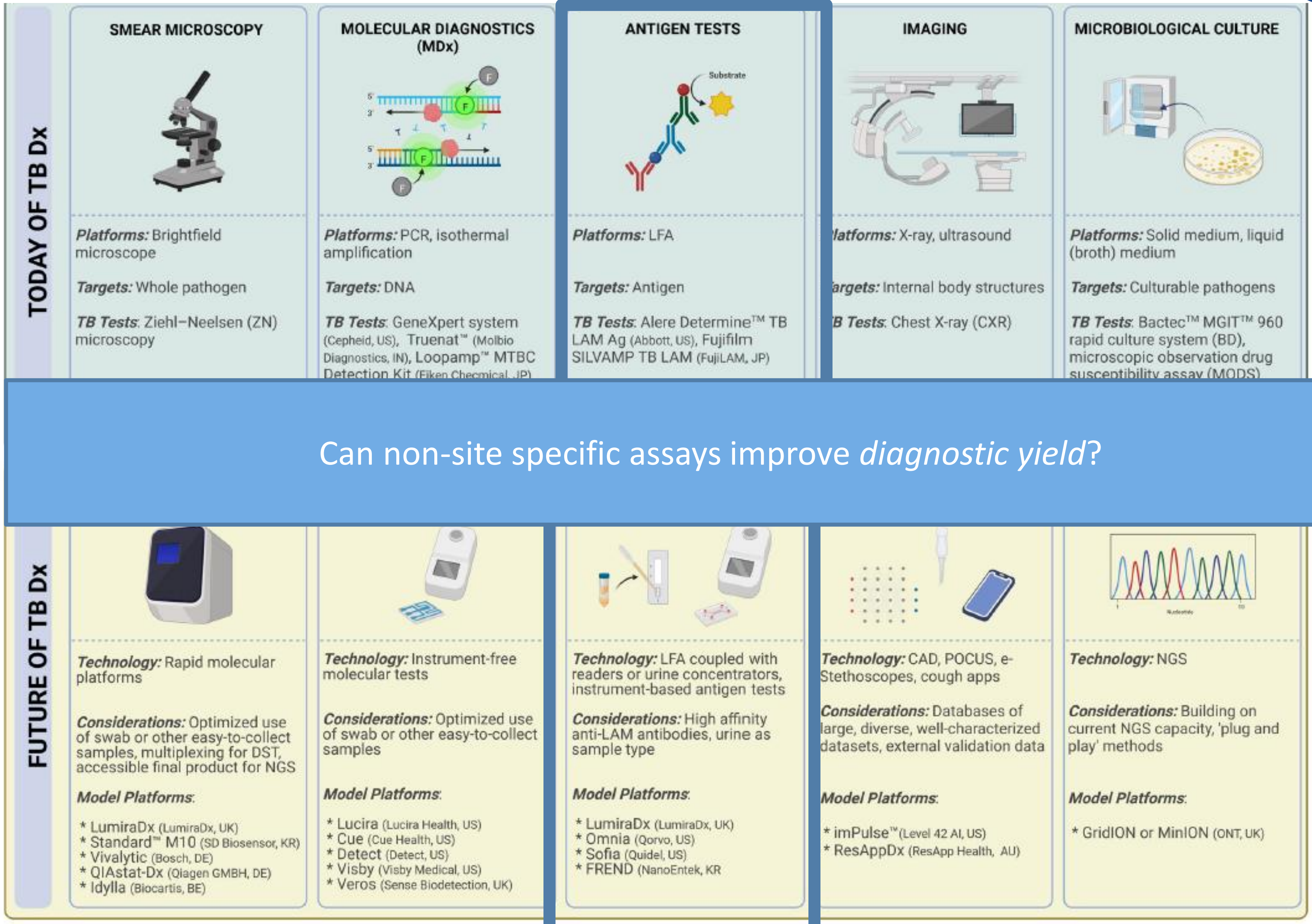


Can non-site specific assays improve *diagnostic yield*?

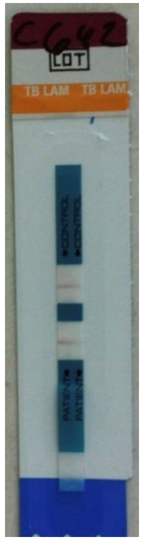
Lateral-Flow urine LAM (LF-LAM) for TB diagnosis

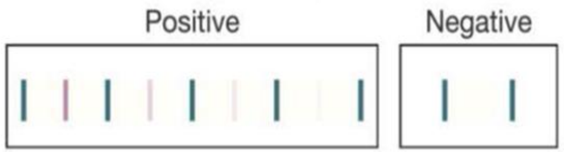
- LAM part of mycobacterial cell wall
- Point-of-care Strip test (urine)
- Equipment free
- Quick 25 min
- **Not site-specific diagnosis**

2019:

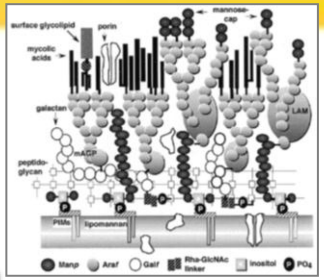
Sensitivity 42% (CrI 31 to 55)

Specificity 91% (CrI 85 to 95)





LAM antigenuria may vary by amount of TB disease



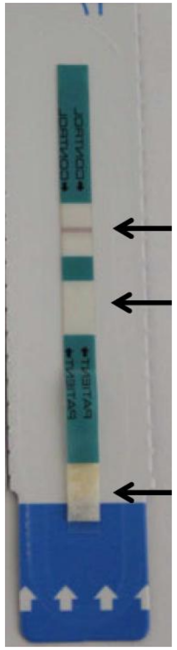
Site of Isolation (N)	Mean Optical Density (SD)	Median (IQR)	LAM Positive (Sensitivity, 95%CI)
Extrapulmonary alone(6)	.33(.6)	.03(.01-.38)	2 (33%, .04, .77)
Sputum only (139)	.63 (.99)	.12 (.0175-.70)	73 (53%, .44-.61)
Blood only (16)	1.08(1.05)	.86(.17-1.8)	13 (81%, .54-.96)
Sputum and Blood +/- other site(25)	1.6(1.12)	1.4(.43-2.8)	21 (84%, .64-.95)

Increasing antigen

Shah et al. JCM 2010; Shah et al. Cochrane 2016; Bjerrum et al Cochrane *2019*

Urine LAM testing performs best in sick individuals with a high bacterial burden

Type of analysis	Symptomatic participants			
	Studies (total participant)	Participants with TB (%)	Pooled sensitivity (95% CrI)	Pooled specificity (95% CrI)
Overall accuracy	8 studies (3449)	1277 (37%)	42% (31 to 55)	91% (85 to 95)
By setting				
Inpatient	6 studies (2253)	868 (39%)	52% (40 to 64)	87% (78 to 93)
Outpatient	4 studies (1196)	409 (34%)	29% (17 to 47)	96% (91 to 99)



Bjerrum et al. Cochrane 2019

Association of LF-LAM positivity and mortality

Setting	Studies	Population (all prospective cohorts except Bjerrum and Peter which were cross-sectional)*	Mortality in LAM positive vs LAM negative** (selected data shown)
Inpatients	LaCourse 2018 Lawn 2017 Manabe 2014 Gupta-Wright 2018***	HIV+ children (unselected) HIV+ adults (unselected) HIV+ adults (symptomatic) HIV+ adults (unselected)	134/100 person years vs 32/100 person years, aHR 4.61, P = 0.004 24.5%.vs 7.2%, aOR 4.2, 95% CI: 1.50-11.75 40% vs 28%, unadjusted HR for LAM positivity 1.67; P = 0.025 aOR 1.8, 95% CI 1.0–3.2, p = 0.04
Outpatients	Balcha 2014 Drain 2015 Drain 2017 Hanifa 2016 Lawn 2012 Peter 2015	HIV+ adults (symptomatic) HIV+ adults (symptomatic) HIV+ adults (unselected) HIV+ children (unselected) HIV+ adults (unselected) HIV+ adults (symptomatic)	20% vs 2.7% aHR 42.1 95% CI: 1.87-9.52, P = 0.02 31.2% vs 9.5% MHR 4.26 , 95% CI: 2.65-6.84 14% vs 5% HR 3.6 , 95% CI: 1.2-10.5, P = 0.04 21.7% vs 0% 25% vs 11%, ARR 14% P = 0.02
Both	Bjerrum 2015 Huerga 2017 Thit 2017	HIV+ inpatients (unselected) HIV+ inpatients (unselected) HIV+ inpatients (unselected)	49% vs 14% (p < 0.001) 22.8% vs 8.1, aOR 2.7, 95% CI: 1.5-4.9, P = 0.001 11.4% vs 10.5% (only study that showed no difference)

The Future of TB Diagnosis

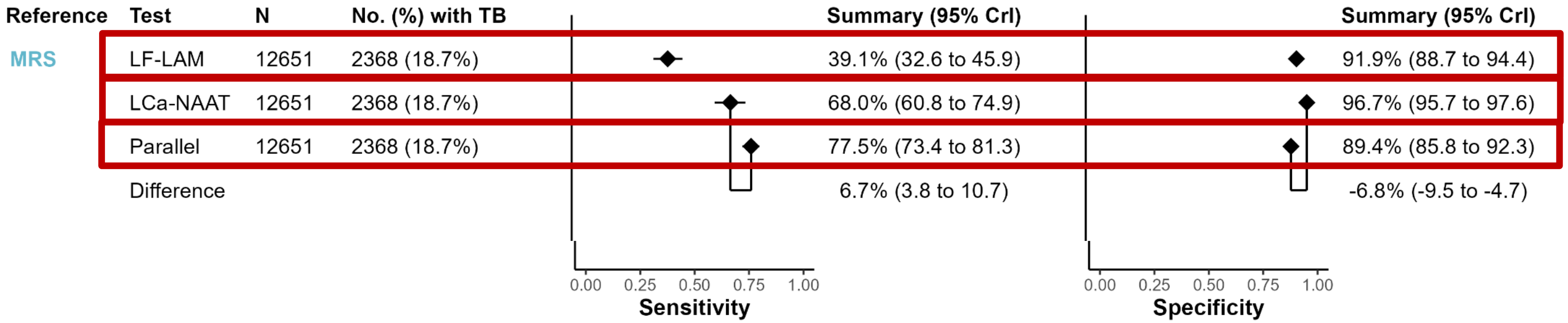
- WHO convened a new Guideline Development Group in 2024
- Evaluate ‘Low Complexity automated NAAT’ as a group rather than per test
- Evaluate Combinations of tests

Study-specific and summary difference in accuracy Parallel vs Respiratory LC-aNAAT, MRS

Study specific difference in sensitivity ranged from 0% to 38%
Study specific difference in specificity ranged from 0% to -34%

27 studies, involving 12,651 participants, 2,368 (18.7%) with tuberculosis
Reference standard: Liquid or solid culture on a any specimen or non-respiratory NAAT
Pooled difference in sensitivity: 6.7% (3.8 to 10.7)
Pooled difference in specificity: -6.8% (-9.5 to -4.7)

Should parallel LC-aNAATs on a respiratory sample and LF-LAM on urine vs. respiratory LC-aNAAT alone be used to diagnose TB in adults and adolescents with HIV and signs and symptoms or screened positive for TB, MRS?



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Diagnostic accuracy of parrallel testing strategies

Impact on time-to-diagnosis in adult inpatients with HIV.

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- Gupta-Wright 2018:
  - Shorter time to diagnosis
    - **median 0 days [IQR 0-1] versus 1 day [IQR 0-6]**
    - **aHR 1.55 (95% CI 1.29 - 1.87)**

- Åhsberg 2023:
  - shorter time-to-diagnosis
    - median**, 0 days** [IQR 0-2] **versus 2 days** [IQR 0-7];
    - P = 0.037

Gupta-Wright Lancet 2018
Åhsberg CID 2023

Proportion of diagnoses based on test

Gupta-Wright 2018:

- Distribution of positive tests:
  - TB LAM positive: 75% (158 /210)
  - Urine Xpert: 35% (74/210)
  - Sputum Xpert: 40% (85/210)

- Of those with a single positive test
  - Urine LAM (87, 41%)
  - Urine Xpert (13,6%)
  - Sputum Xpert (30, 14%)

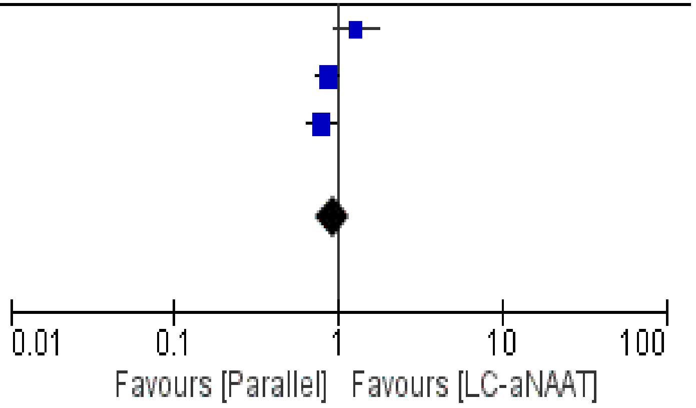
Gupta-Wright Lancet 2018

Impact on all cause mortality in adult inpatients with HIV

Study or Subgroup	Parallel Events	Parallel Total	LC-aNAAT Events	LC-aNAAT Total	Weight	Risk Ratio M-H, Random, 95% CI
Ahsberg 2023	56	173	62	246	25.9%	1.28 [0.95, 1.74]
Gupta-Wright 2018	235	1287	272	1287	39.0%	0.86 [0.74, 1.01]
Peter 2016	139	798	178	811	35.1%	0.79 [0.65, 0.97]
Total (95% CI)		**2258**		**2344**	**100.0%**	**0.93 [0.74, 1.17]**
Total events	430		512			

Heterogeneity: Tau² = 0.03; Chi² = 7.00, df = 2 (P = 0.03); I² = 71%
Test for overall effect: Z = 0.63 (P = 0.53)

Risk Ratio
M-H, Random, 95% CI



aRR 0.93 (0.74, 1.17)

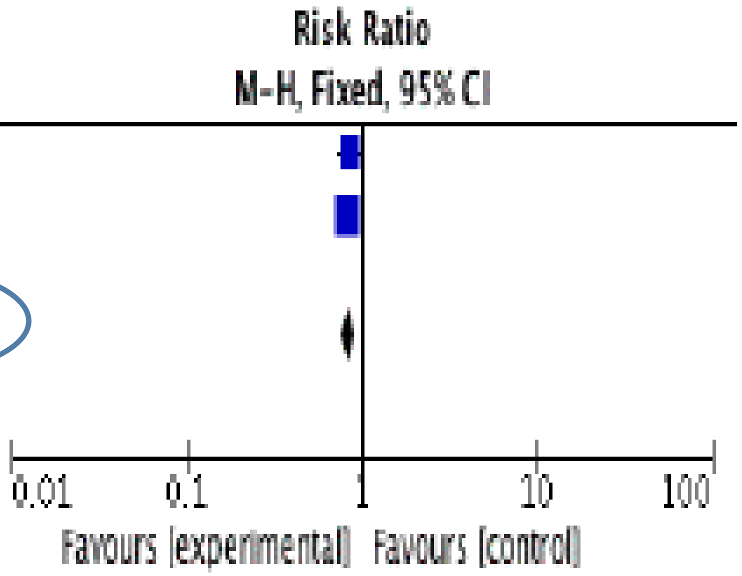
Peter Lancet 2016
Gupta-Wright Lancet 2018
Åhsberg CID 2023

Randomized trials show that LAM implementation among hospitalized HIV-infected individuals reduces mortality

Study or Subgroup	LAM Events	LAM Total	No LAM Events	No LAM Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gupta-Wright 2018	235	1287	272	1287	46.3%	0.86 [0.74, 1.01]
Peter 2016	261	1257	317	1271	53.7%	0.83 [0.72, 0.96]
Total (95% CI)		**2544**		**2558**	**100.0%**	**0.85 [0.76, 0.94]**
Total events	496		589			

Heterogeneity: $Chi^2 = 0.12$, df = 1 (P = 0.73); $I^2 = 0\%$

Test for overall effect: Z = 3.07 (P = 0.002)



Cochrane Reviews Bjerrum et al. 2019; WHO guidelines 2019

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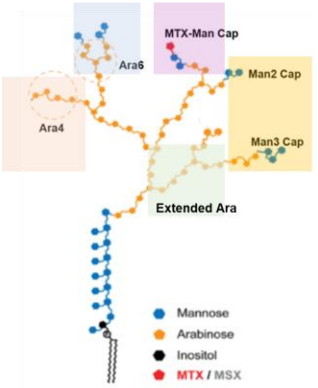
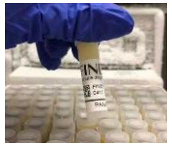
• 3RD GENERATION LAM TESTS

3rd Generation LAM assay
Ultra sensitive (<10 pg/mL) to detect LAM in all TB patients

Pre-analytical
Improved reagents



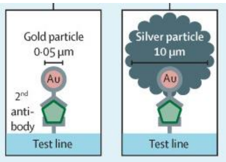


RUTGERS
MOLOGIC
PATH
FIND
Diagnosis for all

Pre-analytical
Sample Preparation

Abbott
SALUS

Innovative
Assay Design



SD BIOSENSOR
DCN Dx
MOLOGIC
GH+ Labs
LUMOS DIAGNOSTICS

Slide courtesy Morten Ruhwald

Newer LAM assays with improved sensitivity are coming in the future

Novel lipoarabinomannan point-of-care tuberculosis test for people with HIV: a diagnostic accuracy study

Tobias Broger, Bianca Sossen*, Elloise du Toit, Andrew D Kerkhoff, Charlotte Schutz, Elena Ivanova Reipold, Amy Ward, David A Barr, Aurélien Macé, Andre Trollip, Rosie Burton, Stefano Ongarello, Abraham Pinter, Todd L Lowary, Catharina Boehme, Mark P Nicol, Graeme Meintjes†, Claudia M Denkinger†*

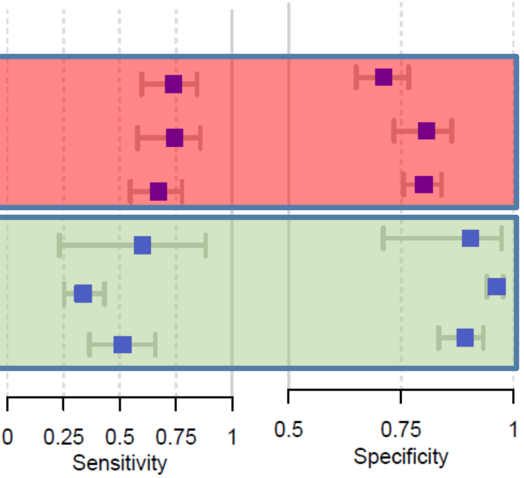
A

	Test	n	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
MRS	FujiLAM	968	455	33	145	335	70·4% (53·0 to 83·1)	90·8% (86·0 to 94·4)
	AlereLAM	968	268	18	332	350	42·3% (31·7 to 51·8)	95·0% (87·7 to 98·8)
	Difference						28·1%	-4·2%

Broger et al. Lancet 2019

LOT-TO-LOT VARIABILITY: BACK TO THE DRAWING BOARD

Lot Number	N	Sensitivity [95%CI]	Specificity [95%CI]
19001	275	73.9 [59.7–84.4]	71.2 [65.0–76.7]
19002	180	74.3 [57.9–85.8]	80.7 [73.5–86.3]
19003	408	67.2 [54.7–77.7]	80.1 [75.6–84.0]
20002	26	60.0 [23.1–88.2]	90.5 [71.1–97.4]
20003	535	33.7 [25.3–43.2]	96.3 [94.1–97.7]
20004	191	51.2 [36.5–65.8]	89.3 [83.4–93.3]



MEDECINS SANS FRONTIERES

n =1575 all PLHIV, 4 countries, outpatient sympt, asymptomatic with advanced HIV

	Sensitivity % (95% CI)	Specificity % (95% CI)
Lot 19003	76 (57-89)	77 (72-81)
Lot 20002	75 (41-93)	91 (81-96)
Lot 20003	59 (36-79)	98 (93-99)
Lot 20004	48 (34-62)	97 (94-99)

Huerga et al preprint, http://dx.doi.org/10.2139/ssrn.4175222

KNCV TUBERCULOSISFOUNDATION

ASTIIE study, n =600 all PLHIV, 2 countries.

	Sensitivity	Specificity
Lot 19002/3	56.3% (29.9 - 80.2)	86.4% (80.3 - 91.2)
Lot 20003	35.0% (15.4 - 59.2)	97.4% (95.3 - 98.8)

Tiemersma E et al in preparation

Slide courtesy Morten Ruhwald

What about Drug Resistance?

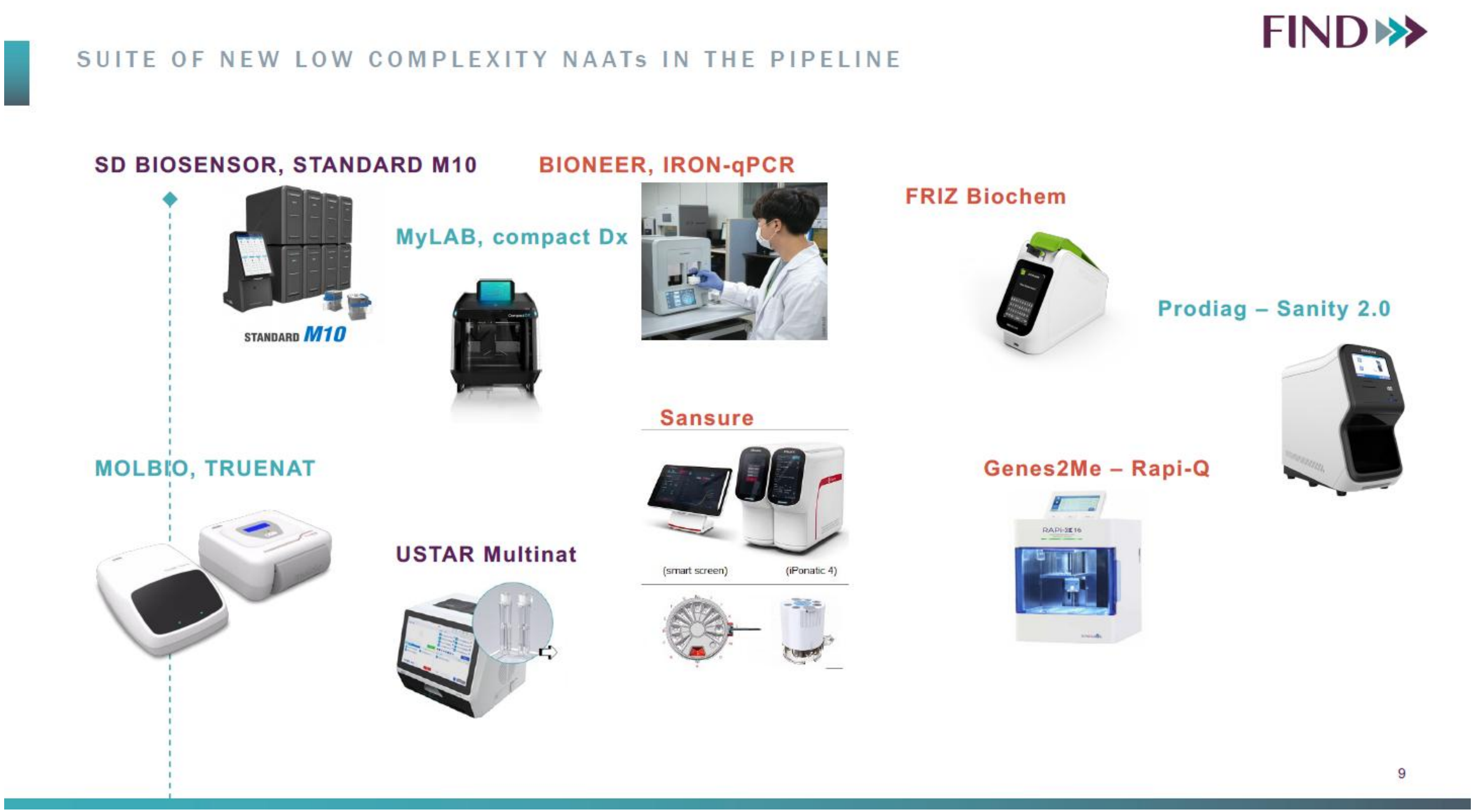
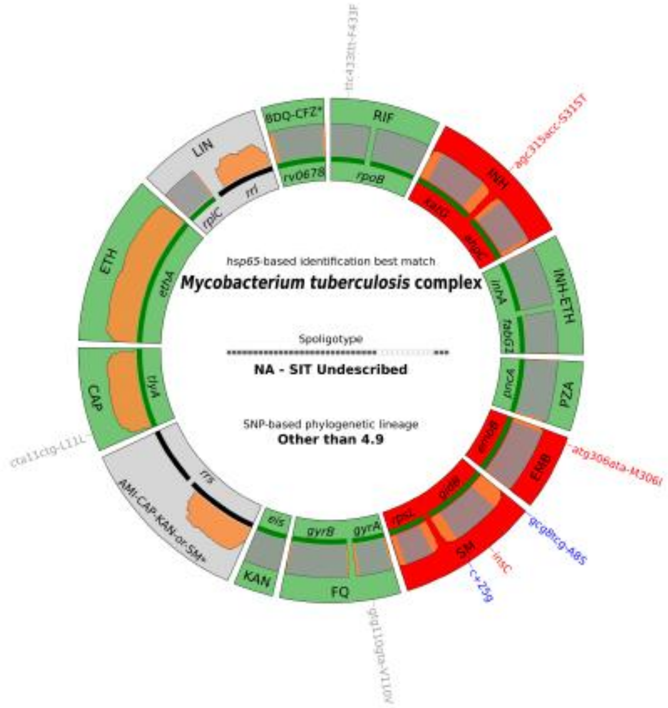


Table 3. Sensitivity and Specificity of the Investigational Assay, with DNA Sequencing as the Reference Standard, in the Main Analysis Population for Drug-Susceptibility Testing.*

Drug	Investigational-Assay Result + DNA Sequencing Result†				Sensitivity		Specificity	
	M+M	M+NM	NM+M	NM+NM				
	no. of specimens				*no./total no.*	*% (95% CI)*	*no./total no.*	*% (95% CI)*
Isoniazid‡	151	0	3	149	151/154	98.1 (94.4–99.6)	149/149	100.0 (97.6–100.0)
Fluoroquinolones§	91	0	4	208	91/95	95.8 (89.6–98.8)	208/208	100.0 (98.2–100.0)
Kanamycin¶	38	1	3	256	38/41	92.7 (80.1–98.5)	256/257	99.6 (97.9–100.0)
Amikacin¶	30	0	1	267	30/31	96.8 (83.3–99.9)	267/267	100.0 (98.6–100.0)

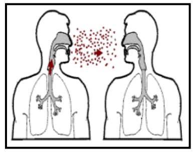
Date of submission	**Jul, 20 2022 13:21:41**
Analysis mode	**Deeplex Myc-TB V3.0 - Extended catalogue**
Quality	⛔
Experiment set	**Mol Run**



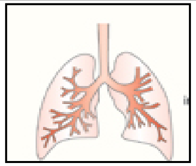
Xie et al. NEJM 2017

Diagnosis of Latent TB

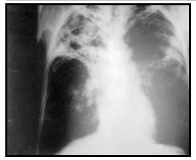
Exposure



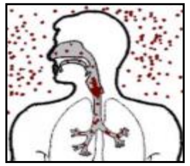
Latent TB Infection



Active TB



Symptomatic



Death

Treatment

- Tuberculin Skin Tests (TST, PPD)
- Interferon Gamma Release Assays (IGRA)

- Indirectly assess TB infection
- Assess immunologic reaction to mycobacterial antigens

NO REFERENCE STANDARD:
The Truth is Unknown

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Home / News / WHO announces updates on new TB antigen-based skin tests for the diagnosis of TB infection

WHO announces updates on new TB antigen-based skin tests for the diagnosis of TB infection

4 April 2022 | Departmental news |Reading time: Less than a minute (254 words)

https://www.who.int/news/item/04-04-2022-who-announces-updates-on-new-tb-antigen-based-skin-tests-for-the-diagnosis-of-tb-infection

TB-antigen skin tests (TBST) compared to TST (tuberculin skin test)

- Three tests available:
  - C-TB (India), C-TST (China), Diaskintest (Russia)

Recommendations

- *Mycobacterium tuberculosis* antigen-based skin tests (TBSTs) may be used to test for TB infection.
  Conditional recommendation for the intervention, very low certainty of the evidence

- Overall, pooled sensitivity and specificity for TB infection detection were:
  - Sensitivity: 76.0% (95% confidence interval [CI]: 70.0 to 81.0)
  - Specificity: 98.0% (95% CI: 94.0 to 99.0)

- Difference in specificity between TBST and TST among those who were BCG vaccinated and was higher for TBST.

Rapid communication: TB antigen-based skin tests for the diagnosis of TB infection. Geneva: World Health Organization; 2022 (WHO/UCN/TB/2022.1)

Conclusions: the future is promising (if access and cost issues can be addressed)

- Active TB:
  - Yield versus sensitivity
  - Easier specimen collection may allow identification of a greater number of individuals
  - POC technologies are emerging (molecular and antigen)
  - Combination testing with multiple platforms
  - *Computer assisted diagnosis of CXR*
  - *Host response*

- Latent TB infection: mostly focused on IGRAs and TB antigen skin tests