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Supplementary appendix 3

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Gupta-Wright A, Ha H, Abdulgadar S, et al. Evaluation of the Xpert MTB Host Response assay for the triage of patients with presumed pulmonary tuberculosis: a prospective diagnostic accuracy study in Viet Nam, India, the Philippines, Uganda, and South Africa. *Lancet Glob Health* 2024; **12:** e226–34.

Appendix

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Supplementary methods

Table S1. R2D2 TB Network study enrolment sites and ethics committees

City, Country	Enrollment sites	Ethics Committee*
Vellore, India	CMC Pulmonary Outpatient Department, Primary care clinics in Vellore (Shalom/LCC, Chittor, CHAD) and Chitoor (CMC satellite campus)	Christian Medical College Institutional Review Board (13256)
Hanoi, Vietnam	Outpatient departments, Hanoi Lung Hospital	Ministry of Health Ethical Committee for National Biological Medical Research (94/CN-HĐĐĐ); National Lung Hospital Ethical Committee for Biological Medical Research (566/2020/NCKH); Hanoi Lung Hospital Science and Technology Initiative Committee (22/BVPHN)
Dasmariñas City, Philippines	Community-based screening in Dasmariñas City and nearby municipalities, outpatient clinics in Dasmariñas City	De La Salle Health Sciences Institute Independent Ethics Committee (2020-33-02-A)
Cape Town, South Africa	Scottsdene and Wallacedene primary care clinics; Brooklyn Chest Hospital; Khayelitsha District Health Center; Kraaifontein Community Health Clinic	Stellenbosch University Health Research Ethics Committee (M20/07/020)
Kampala, Uganda	Mulago Outpatient Department, Kisenyi Health Center,	Makerere University, College of Health Sciences, School of Medicine, Research Ethics Committee (2020-182)

* The study was additionally approved by the University of California San Francisco Institutional Review Board (20-32670), and the University of Heidelberg Ethics Committee of the Medical Faculty (S-539/2020).

Table S2. Procedure summary during participant enrolment and follow up

LEGEND. X: applies to all participants; Y: applies to people without a known TB diagnosis

Procedure	Enrolment		Follow- up Visit 1[1]	Notes
	Day 1	Day 2		
Demographic/Clinical questionnaire	X		Y	
TB symptom assessment	X		Y	
Chest X-ray	Y		Y	• All CXRs undergo digitization
Finger prick blood collection	X			• All participants: HIV, Hemoglobin A1c (in some sites this is done using blood collected from venipuncture in a central lab) • novel blood tests
Venipuncture[4]	Y			• HbA1c if done in a central lab • CD4 cell count (if HIV-positive) • novel blood tests

Spot sputum[4] collection	X		Y	• Participants without known TB diagnosis: Xpert Ultra x 1, Smear microscopy and MGIT culture x 2, storage. Sputum collection will be repeated on Day 2 if initial Xpert Ultra results are indeterminate or trace-positive. • Participants with RIF-resistance by Xpert: MGIT culture, DNA extraction, novel rDST assays, storage • Sputum induced if participants are unable to expectorate
Urine collection[4]	Y			• Urine Xpert Ultra conducted on HIV-positive participants only then discontinued part-way through the study due to low yield.
Other TB testing per clinician discretion	X	X	X	• Results of any additional mycobacterial culture or Xpert testing from other samples (e.g. pleural fluid, tissue biopsy, etc.) requested by clinicians recorded

[1] Follow-up visit 1 conducted at 3-months if the participant has a negative/indeterminate sputum Xpert Ultra result at baseline AND no positive culture

[2]For all participants without confirmed TB but a positive novel TB triage or diagnostic test result, trained study staff collect 1 follow-up spot sputum specimen for Xpert Ultra (x1) and mycobacterial culture (1 liquid, 1 solid) and perform a CXR.

[3]All left-over samples stored.

Reasons for South Africa using capillary blood

Cepheid instructs that blood may be collected for Xpert TB Host Response using either capillary sampling or venipuncture (phlebotomy) sampling. If capillary sampling is used, blood must not be held in the minivette for more than 15 minutes due to risk of clogging. If using venipuncture, an EDTA blood collection tube can be stored at 2-8 °C up to 24 h before testing. Due to onsite logistical constraints, South Africa was the only site able to conduct the test immediately following blood collection, allowing for capillary sampling.

Details of reference standards

Primary: Microbiologic reference standard (MRS)
The primary reference standard for all novel tests will be a microbiologic reference standard defined by Xpert Ultra for sputum, Xpert Ultra for urine, and sputum MGIT culture. The MRS is based only on baseline test results and does not incorporate any results from follow-up visits.

- TB positive will include participants with:
  - A positive result on sputum Xpert Ultra (grade very low, low, medium, high) **OR**
  - A positive culture in MGIT **OR**
  - A positive culture in solid culture media (e.g. 7H10 or LJ agar*) **OR**
  - Two trace Xpert Ultra results on sputum
- TB negative will include participants with:
  - No positive result (sputum Xpert Ultra, culture) **AND EITHER**
    - 2 negative cultures in MGIT **OR**
    - 2 negative cultures in solid media (e.g. 7H10 or LJ agar*) **OR**
    - 1 negative culture in MGIT and 1 negative in solid media (e.g. 7H10 or LJ agar*)†
- Indeterminate will include participants with:
  - No positive result (sputum Xpert Ultra, urine Xpert Ultra, culture), **AND**
  - <2 trace Ultra results on sputum and/or urine **AND**
  - <2 negative cultures due to contamination or pending results.

* Cultures on solid media will not routinely be done but may be done when MGIT is not available.

† The initial protocol in India included only one sputum culture from August 16 to November 18 2021. Therefore, participants enrolled in India during this period are considered to be TB negative by MRS if they do not have a positive sputum Xpert result AND their single sputum culture result is negative.

Secondary: Sputum Xpert Ultra Reference Standard (SXRS)
Additionally, we will consider a simplified reference standard using the same definitions as the MRS but using sputum Xpert Ultra results only to classify participants as TB positive or Not TB positive.

The objective of inclusion of this reference standard is to assess sensitivity of a novel triage test in the context of a programmatic setting where only sputum Xpert Ultra is available as a confirmatory diagnostic test (*i.e.,* culture is not done as part of routine care). Sensitivity is therefore the focus of this reference standard, nevertheless specificity will be calculated for secondary analyses.

- TB positive will include participants with:
  - A positive baseline sputum Xpert Ultra result (grade very low, low, medium, high), **OR**

    - Two trace baseline sputum Xpert Ultra results
- TB negative will include participants with:
    - A negative baseline sputum Xpert Ultra result, **WITHOUT** any trace or positive baseline sputum Xpert Ultra results.
- TB indeterminate will include participants where neither criteria for TB positive nor TB negative are met.

Supplementary results

Indeterminate reference standard results

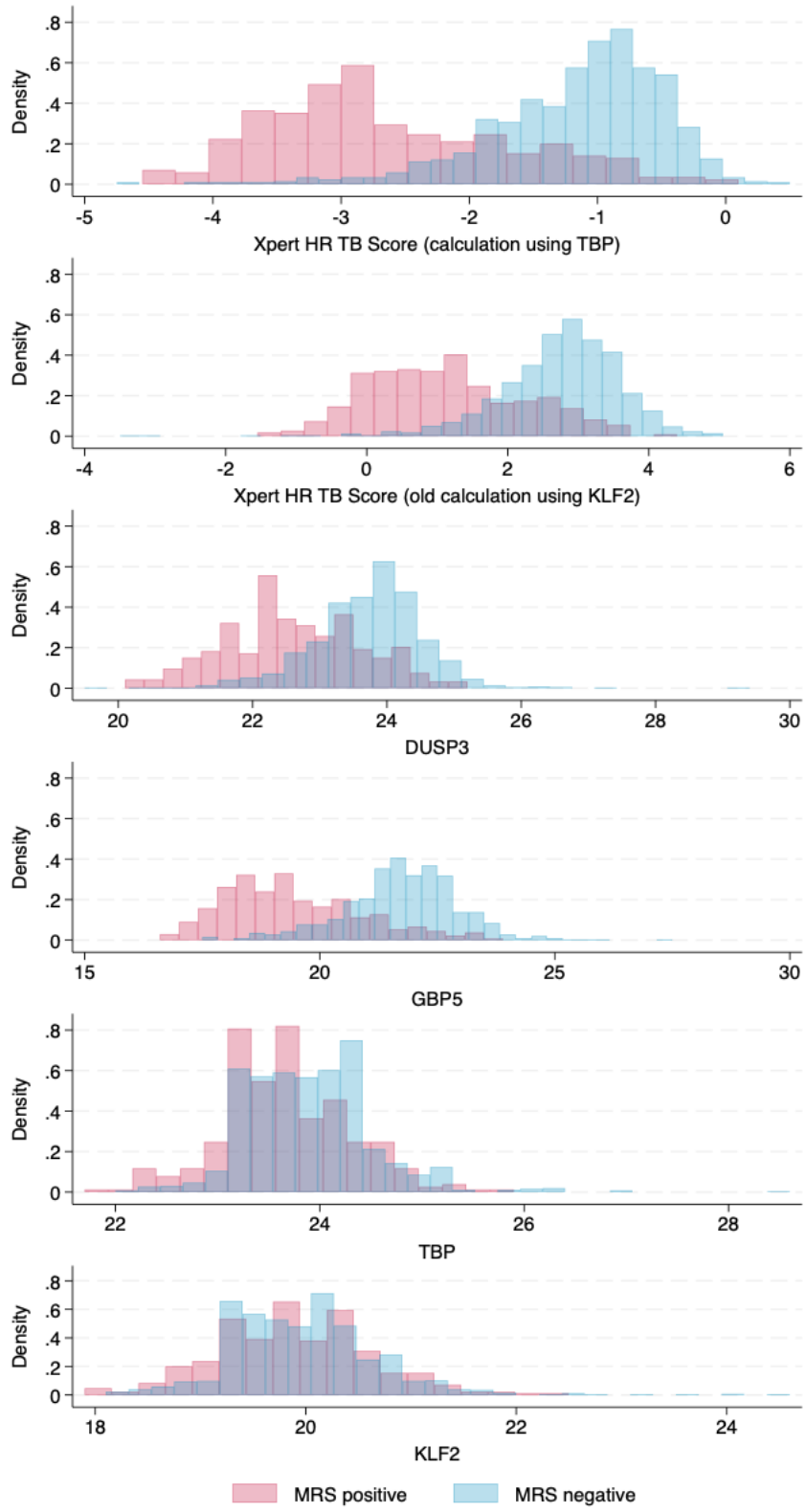
Of the 115 indeterminate reference standard results: 15 had two contaminated cultures; 87 had one contaminated culture and one negative culture result; 2 had one contaminated culture and one culture positive for non-tuberculous mycobacteria; 8 had one negative and one missing culture result. Of these 115, 68 had follow-up sputum culture results of which none were positive for TB.

Table S3: Demographical and clinical characteristics overall and by Microbiological Reference Standard (MRS) result

		Overall	MRS TB Negative	MRS TB Positive	p-value
N		1499	1170	329	
Country	**Philippines**	325 (21.7%)	296 (25.3%)	29 (8.8%)	<0.001
	Vietnam	284 (18.9%)	176 (15.0%)	108 (32.8%)	
	South Africa	300 (20.0%)	243 (20.8%)	57 (17.3%)	
	Uganda	314 (20.9%)	205 (17.5%)	109 (33.1%)	
	India	276 (18.4%)	250 (21.4%)	26 (7.9%)	
Sex	**Male**	813 (54.2%)	590 (50.4%)	223 (67.8%)	<0.001
	Female	686 (45.8%)	580 (49.6%)	106 (32.2%)	
Age, mean (SD), years		42.3 (15.5)	43.2 (15.4)	39.1 (15.5)	<0.001
BMI, median (IQR)		21.4 (19.1, 25.2)	22.5 (19.8, 26.4)	19.4 (17.8, 21.0)	<0.001
Cough for 2 weeks		1499 (100.0%)	1170 (100.0%)	329 (100.0%)	
Fever		533 (35.6%)	344 (29.4%)	189 (57.4%)	<0.001
Weight loss		702 (46.8%)	475 (40.6%)	227 (69.0%)	<0.001
Night Sweats		528 (35.2%)	358 (30.6%)	170 (51.7%)	<0.001
Prior TB diagnosis[a]	**Yes**	290 (19.3%)	231 (19.7%)	59 (17.9%)	0.46
Person living with HIV[b]	**Yes**	229 (15.3%)	184 (15.8%)	45 (13.7%)	0.37
	Median CD4, cells/µL (IQR)	399 (206, 667)	445.5 (240.0, 675.5)	258.5 (115.0, 529.0)	<0.001
Diabetes	**Yes**	202 (13.5%)	142 (12.1%)	60 (18.2%)	0.004
Sputum Xpert status[c]	**Negative**	1201 (80.1%)	1169 (99.9%)	32 (9.7%)	<0.001
	Positive	297 (19.8%)	0 (0.0%)	297 (90.3%)	
Venous or capillary blood collection	**Capillary**	1170 (78.1%)	231 (19.7%)	55 (16.7%)	0.22
	Venous	329 (21.9%)	939 (80.3%)	274 (83.3%)	

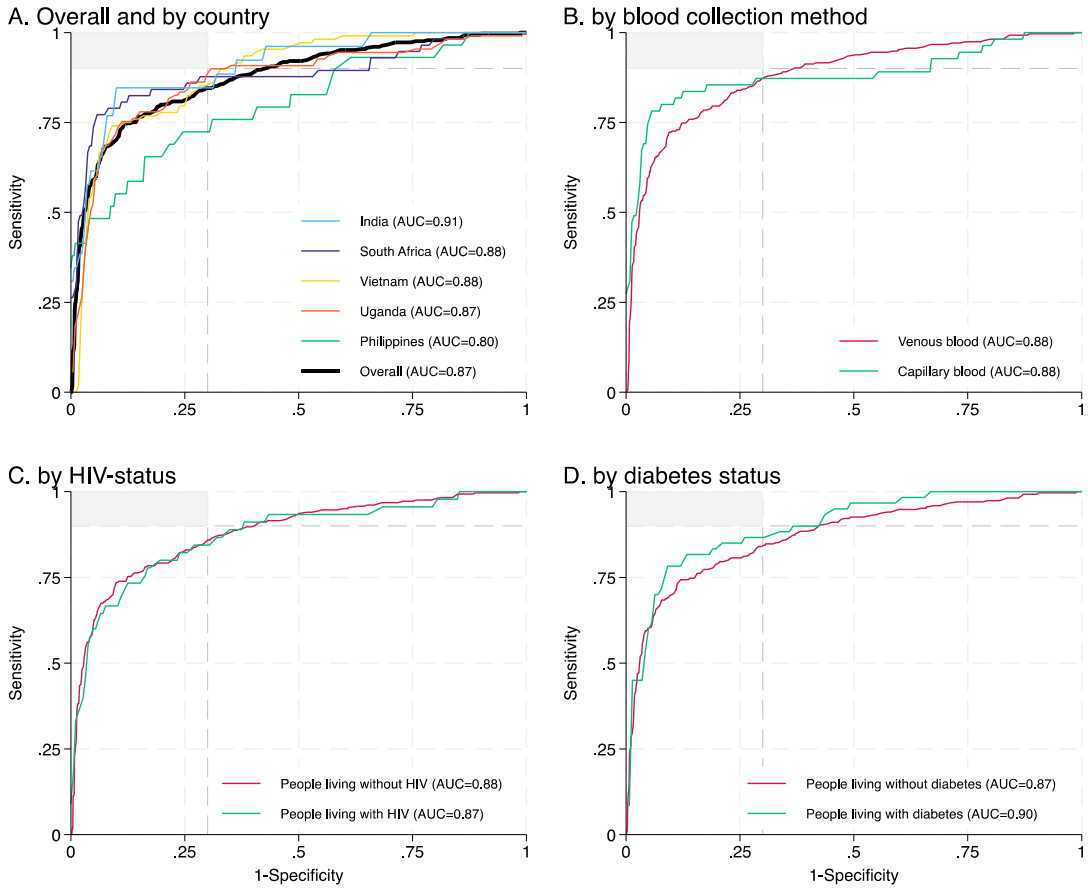
[a]3 participants were unsure about prior TB diagnoses. [b]3 participants had an unknown HIV status. [c]1 participant was missing a sputum Xpert result.
MRS microbiological reference standard. SD Standard Deviation; IQR Interquartile Range

Figure S1. Histogram of Xpert HR TB Score and its components



Xpert HR TB Score (panel 1) is calculated as (Ct *GBP5* + Ct *DUSP3*)/2 − Ct *TBP. A previous version of the assay used an alternate caluation using KLF2 in place of TBP (panel 2). Ct* Cycle threshold; *GBP5 guanylate binding protein 5; DUSP3 dual specificity phosphatase 3; KLF2 Krüppel-like factor 2; TBP TATA-binding protein; MRS microbiological reference standard. Median TB Score was -2.85 (IQR -3.28 to -2.18) for participants positive by MRS, and -1 (IQR -1.5 to -0.7) for participants negative by MRS.*

Figure S2. Xpert TB HR Receiver Operating Characteristic (ROC) curve using previous calculation against microbiologic reference standard.



Previous studies calculated the TB score using KLF2 instead of TBP. Here we present the ROC curves using this calculation: Ct GBP5 + Ct DUSP3)/2 − Ct KLF2. The median TB Score calculated in this manner was 1.00 (IQR 0.30 to 1.9) for participants positive by MRS, and 2.85 (IQR 2.30 to -3.30) for participants negative by MRS. Using this calculation, the optimal cut-point defining a positive test in this population would be ≤2.7. Using this cut-point, sensitivity against the MRS is 90.3% (297/329, 95%CI 86.5-93.3), and specificity against the MRS is 56.8% (664/1170, 95% CI 53.9-59.6).

Table S4: Univariable regression between TB Score and other variables

		Coefficient	95% CI	R^2	p-value
Country	**Philippines**	0.71	0.56 - 0.86		
	Vietnam	0.48	0.33 -0 .63		
	South Africa	0.63	0.48 - 0.77	0.072	<0.001
	Uganda	0.63	0.48 - 0.77		
	India	0.25	0.10 - 0.40		
Sex	**Male**	0.13	0.03 - 0 .23	0.005	0.009
Age, years		-0.16	-0.31- 0.28	0.026	0.839
BMI		-0.05	-0.06 - -0.04	0.077	<0.001
Person living with HIV[a]	**Yes**	0.30	0.16 – 0.43	0.012	<0.001
Diabetes	**Yes**	0.13	-0.11 – 0.28	0.002	0.07
Sputum Xpert semi-quantitative grade[b]	**Trace**	-0.12	-0.73 – 0.49		
	Low	0.41	0.11 – 0.72	0.097	<0.001
	Medium	0.78	0.47 – 1.10		
	High	0.66	0.34 – 0.97		
C-reactive protein		0.01	0.01 – 0.01	0.24	<0.001

Linear regression to assess associations with TB Score, transformed to a positive value. N=1,499. Continuous variables assumed to be linear and based on a one unit increase. Categorical variables fitted as factors. [a]3 participants missing their HIV status. [b]303 participants with positive Xpert results included in this analysis

Table S5: Area Under the Receiver Operating Characteristic (ROC) curve, overall and by subgroups

		Number of observations	Area under the ROC curve	(95%CI)	χ^2 test p-value
Overall		1499	0.89	(0.86-0.91)	
Country	Philippines	325	0.83	(0.75-0.91)	0.244*
	Vietnam	284	0.88	(0.84-0.92)	0.938*
	South Africa	300	0.90	(0.84-0.95)	0.694*
	Uganda	314	0.87	(0.82-0.92)	0.463*
	India	276	0.91	(0.85-0.97)	0.448*
Sex	Male	813	0.87	(0.83-0.91)	0.375
	Female	686	0.89	(0.87-0.92)	
Person living with HIV	No	1267	0.88	(0.81-0.94)	0.774
	Yes	229	0.89	(0.87-0.91)	
Diabetes	No	1297	0.89	(0.84-0.95)	0.790
	Yes	202	0.88	(0.86-0.91)	

*Area under the ROC (AUROC) were compared using DeLong's test. *For country, the p-value is comparing the ROC for that country to the AUROC for the other countries.*

Table S6: Diagnostic accuracy of Xpert-HR by blood sampling method, stratified by HIV-status

	Living with HIV			Not living with HIV		
Blood sampling method for Xpert-HR	***N (row %)***	***Sensitivity (95% CI)***	***Specificity (95% CI)***	***N (row %)***	***Sensitivity (95% CI)***	***Specificity (95% CI)***
Venous	114 (9.4%)	95.8% (78.9 - 99.9%)	45.6% (35.0-56.4%)	1,099 (90.6%)	89.6% (85.1-93.1%)	66.1% (62.8-69.3%)
Capillary	115 (40.6)	95.2% (76.2 - 99.9%)	44.7% (34.4-55.3%)	168 (59.4%)	87.9% (71.8 - 96.6%)	64.4% (55.8-72.5%)

Capillary blood sampling occurred at only at the South Africa site. Using Chi-squared tests, the p-values for specificity comparing venous and capillary sampling is 0.891 for people living with HIV and 0.665 for people not living with HIV

Table S7: Cross tabulation of TB culture results and highest Xpert Ultra semi-quantitative grade for participants positive by the microbiological reference standard

	TB culture not done	**TB culture positive**	**TB culture negative**
Trace	3*	2	0
Very low	44	0	0
Low	95	0	0
Medium	76	0	0
High	79	0	0
Xpert negative	0	30	1,170

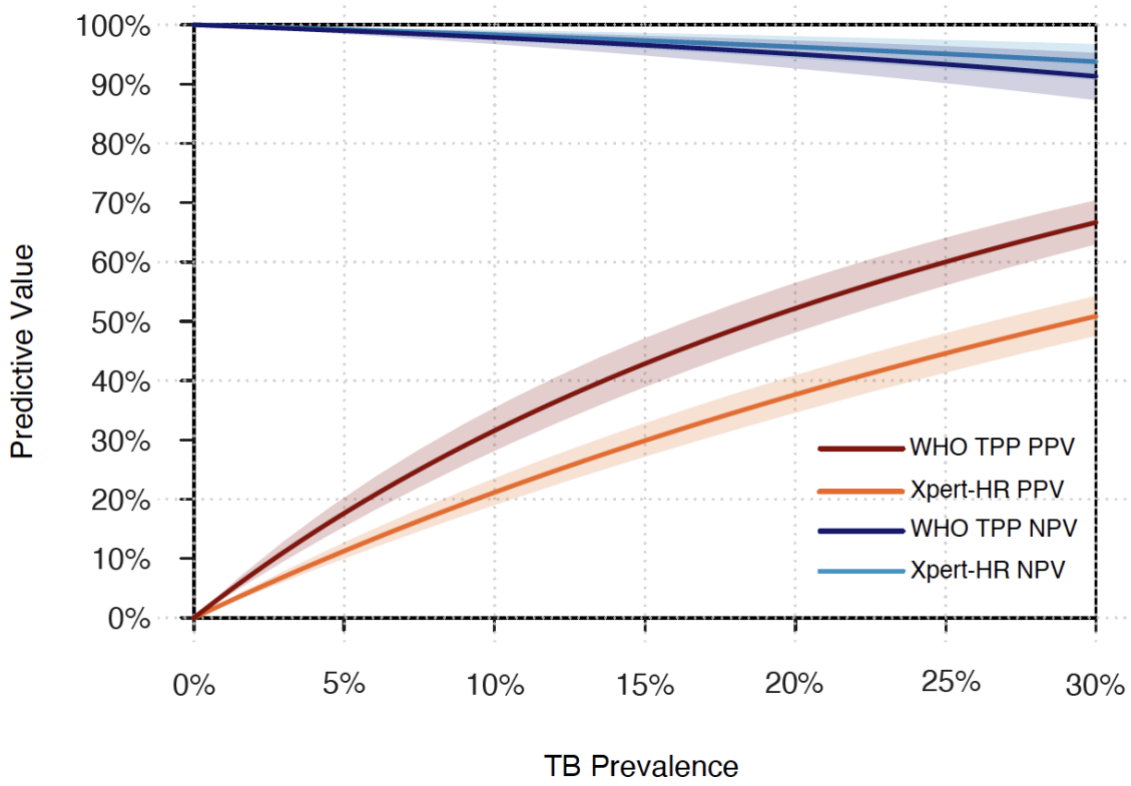
**3 patients had 2 Xpert Ultra trace results*

Table S8: Cross tabulation of TB culture results and highest Xpert Ultra semi-quantitative grade for participants positive by the microbiological reference standard

	TB culture not done	**TB culture positive**
Trace	3*	2
Very low	44	0
Low	95	0
Medium	76	0
High	79	0
Xpert negative	0	30

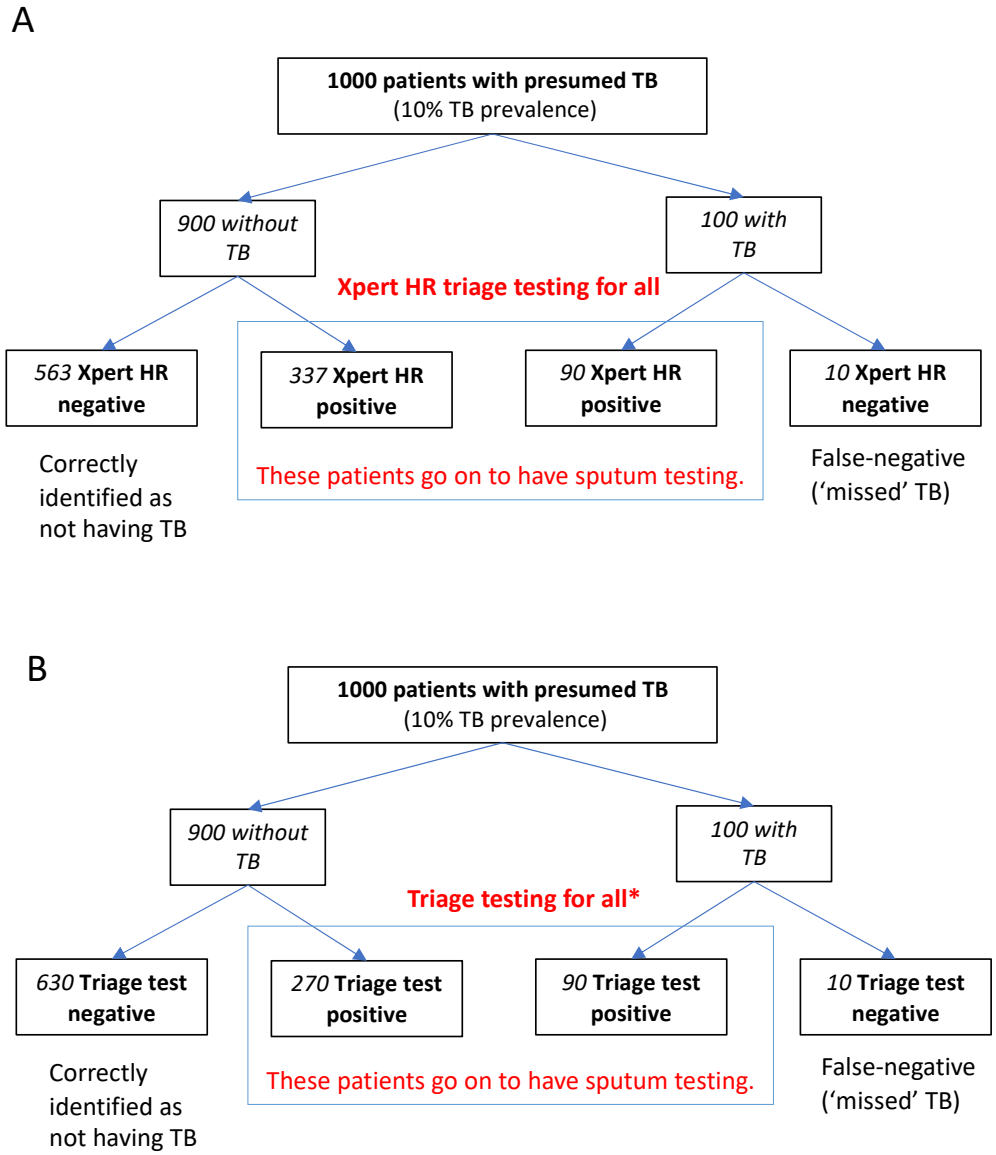
**3 patients had 2 Xpert Ultra trace results*

Figure S3: Positive and negative predictive values for the Xpert-HR and WHO minimum Target Product Profile accuracy for a range of TB prevalence



Positive and negative predictive values plotted for different TB prevalence, based on a cut-point of ≤-1.25 (i.e. sensitivity of 90.3% and specificity of 62.6%). The WHO TPP lines are based on a hypothetical triage test minimum criteria (sensitivity of 90% and specificity of 70%). Shaded areas represent 95% confidence intervals. Analysis done using 'plot-curve' in R. Xpert HR PPVs are 11.3%, 21.2%, 29.9% and 37.6%, and NPVs 99.2%, 98.3%, 97.3% and 96.3% for TB prevalence of 5%, 10%, 15% and 20% respectively. PPV positive predictive value; NPV negative predictive value; WHO World Health Organization; TPP Target Prodict Profile.

Figure S4: Numbers needing sputum testing based on a hypothetical cohort of 1000 patients with presumed TB and 10% TB prevalence



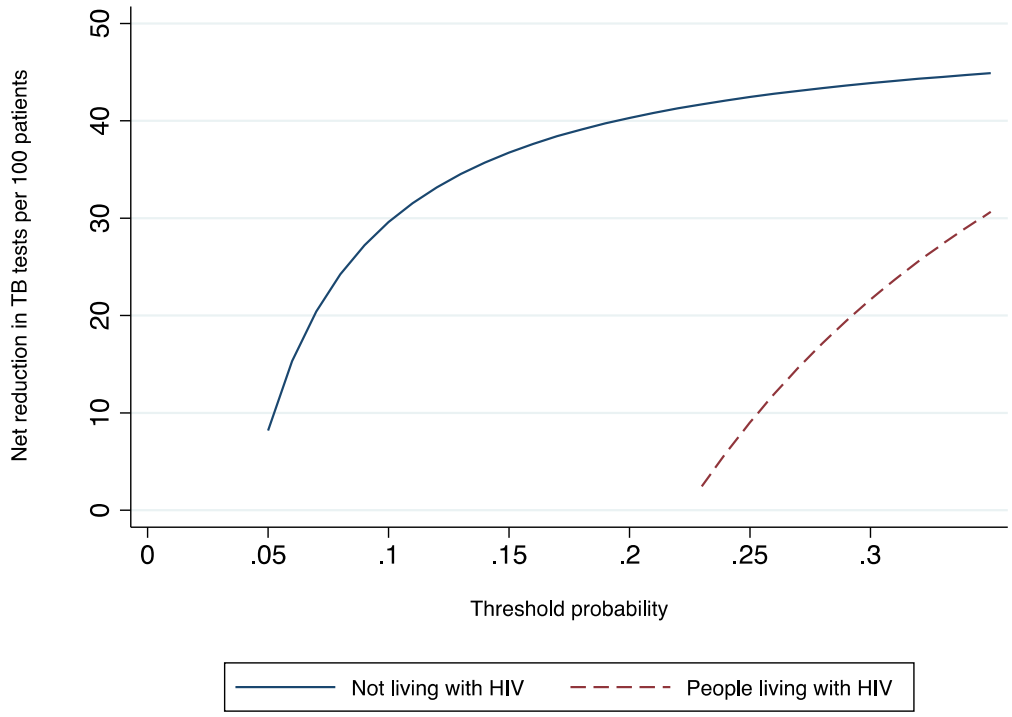
Panel A presents a hypothetical cohort tested with the Xpert-HR triage test. Panel B is based on a hypothetical triage test that meets WHO minimum TPP targets. Assumes all patients have valid test results.

Table S9: Diagnostic Accuracy for the Xpert-HR based on Microbiological Reference Standard overall and by subgroup

Category		TP	FP	FN	TN	TB prevalence (%)	Sensitivity (%)	(95%CI)	Specificity (%)	(95%CI)	PPV (%)	(95%CI)	NPV (%)	(95%CI)
Overall (cut-point ≤-1.25)		297	438	32	732	21.9	90.3	(86.5-93.3)	62.6	(59.7-65.3)	40.4	(36.8-44.1)	95.8	(94.1-97.1)
Country														
	Philippines	22	78	7	218	8.9	75.9	(56.5-89.7)	73.6	(68.2-78.6)	22.0	(14.3-31.4)	96.9	(93.6-98.7)
	Vietnam	102	82	6	94	38.0	94.4	(88.3-97.9)	53.4	(45.8-60.9)	55.4	(47.9-62.7)	94.0	(87.4-97.8)
	South Africa	52	105	5	138	19.0	91.2	(80.7-97.1)	56.8	(50.3-63.1)	33.1	(25.8-41.1)	96.5	(91.7-98.8)
	Uganda	97	75	12	130	34.7	89.0	(81.6-94.2)	63.4	(56.4-70.0)	56.4	(48.6-63.9)	91.5	(84.2-94.8)
	India	24	98	2	152	9.4	92.3	(74.9-99.1)	60.8	(54.4-66.9)	19.7	(13.0-27.8)	98.7	(95.2-99.8)
Sex														
	Female	203	210	20	380	15.5	88.7	(81.1-94.0)	60.7	(56.6-64.7)	29.2	(24.3-34.5)	96.7	(93.8-98.0)
	Male	94	228	12	352	27.4	91.0	(86.5-94.4)	64.4	(60.4-68.3)	49.2	(44.2-54.1)	95.0	(92.2-96.8)
HIV status														
	HIV +ve	43	101	2	83	19.7	95.6	(84.9-99.5)	45.1	(37.8-52.6)	29.9	(22.5-38.0)	97.6	(91.4-99.7)
	HIV -ve	253	336	30	648	22.3	89.4	(85.2-92.7)	65.9	(62.8-68.8)	43.0	(38.9-47.1)	95.6	(93.4-96.8)
Diabetes														
	Yes	53	44	7	98	29.7	88.3	(77.4-95.2)	69.0	(60.7-76.5)	54.6	(44.2-64.8)	93.3	(86.4-97.2)
	No	244	394	25	634	20.7	90.7	(86.6-93.9)	61.7	(58.6-64.7)	38.2	(34.5-42.1)	96.2	(94.1-97.3)
Collection method														
	capillary	50	101	5	130	19.2	90.9	(80.0-97.0)	56.3	(49.6-62.8)	33.1	(25.7-41.2)	96.3	(91.3-98.7)
	venous	247	337	27	602	22.6	90.1	(86.0-93.4)	64.1	(60.9-67.2)	42.3	(38.2-46.4)	95.7	(93.5-96.9)

TP True positive, FP False positive, FN False Negative, TN true negative, PPV positive predictive value, NPV negative predictive value

Figure S5: Decision Curve Analysis stratified by HIV status



Decision curve analysis, shown as net reduction in (sputum-based) TB tests per 100 patients tested with Xpert-HR weighted by a range of threshold probabilities from 5 to 30%, stratified by HIV status. The threshold probability describes how clinicians and patients value different outcomes, and can be defined as the minimum probability of TB disease at which further testing would be warranted. A low threshold probability could reflect a clinician and/or patient who are very concerned about missing TB disease and therefore likely to do further TB testing. For example, a 5% threshold probability (equivalent to a risk:benefit odds of 1:19) where missing TB disease is 19 times worse than unnecessary testing, would lead to a net reduction of approximately 9 TB tests per 100 patients in people not living with HIV, but no net benefit in PLHIV. In contrast, clinicians and/or patients may be less worried about TB and not want to do further sputum-based testing, leading to a higher threshold probability. For example a 25% threshold probability, (equivalent to a risk:benefit odds of 1:3) the risk of missing TB is 3 times worse than unnecessary investigations for TB, and would lead to a net reduction in approximately 42 TB tests per 100 patients in people not living with HIV, but only 10 TB tests per 100 patients in PLHIV.

Table S8: Demographical and clinical characteristics overall and by country for secondary analysis using Sputum Xpert Reference Standard

		Overall	Philippines	Vietnam	South Africa	Uganda	India
N		1606	352	303	340	328	283
Sex	**Male**	874 (54.4%)	156 (44.3%)	187 (61.7%)	173 (50.9%)	189 (57.6%)	169 (59.7%)
	Female	732 (45.6%)	196 (55.7%)	116 (38.3%)	167 (49.1%)	139 (42.4%)	114 (40.3%)
Age, mean (SD), years		42.5 (15.5)	40.1 (15.4)	51.6 (15.9)	40.0 (12.2)	34.9 (12.7)	47.5 (15.5)
BMI, median (IQR)		21.5 (19.1, 25.2)	23.6 (20.2, 27.5)	20.2 (18.7, 21.9)	22.3 (19.4, 28.3)	20.8 (19.0, 24.0)	22.4 (19.0, 26.0)
Cough for 2 weeks		1606 (100.0%)	352 (100.0%)	303 (100.0%)	340 (100.0%)	328 (100.0%)	283 (100.0%)
Fever		568 (35.4%)	51 (14.5%)	106 (35.0%)	123 (36.2%)	222 (67.7%)	66 (23.3%)
Weight loss		754 (46.9%)	99 (28.1%)	88 (29.0%)	218 (64.1%)	226 (68.9%)	123 (43.5%)
Night Sweats		566 (35.2%)	57 (16.2%)	94 (31.0%)	188 (55.3%)	201 (61.3%)	26 (9.2%)
Prior TB diagnosis[b]	**Yes**	316 (19.7%)	46 (13.1%)	63 (20.8%)	127 (37.4%)	41 (12.5%)	39 (13.8%)
Person living with HIV[a]	**Yes**	254 (15.8%)	3 (0.9%)	2 (0.7%)	138 (40.8%)	101 (30.8%)	10 (3.5%)
	Median CD4, cells/μL (IQR)	396.0 (204.0, 654.0)	527.0 (184.0, 812.0)	547.0 (497.0, 597.0)	402.5 (205.0, 667.0)	355.0 (200.0, 613.0)	587.0 (220.0, 692.0)
Diabetes	**Yes**	213 (13.3%)	46 (13.1%)	71 (23.4%)	19 (5.6%)	26 (7.9%)	51 (18.0%)
Sputum Xpert status[c]	**Negative**	1309 (81.5%)	330 (93.8%)	207 (68.3%)	291 (85.6%)	222 (67.7%)	259 (91.5%)
	Positive	297 (18.5%)	22 (6.2%)	96 (31.7%)	49 (14.4%)	106 (32.3%)	24 (8.5%)
TB Microbiologic reference standard	**TB Negative**	1165 (72.8%)	296 (84.1%)	176 (58.1%)	241 (70.9%)	203 (61.9%)	249 (89.6%)
	TB Positive	327 (20.4%)	29 (8.2%)	108 (35.6%)	56 (16.5%)	109 (33.2%)	25 (9.0%)
	Indeterminate	109 (6.8%)	27 (7.7%)	19 (6.3%)	43 (12.6%)	16 (4.9%)	4 (1.4%)
Venous or capillary blood collection	**Capillary**	325 (20.2%)	0 (0.0%)	0 (0.0%)	325 (95.6%)	0 (0.0%)	0 (0.0%)
	Venous	1281 (79.8%)	352 (100.0%)	303 (100.0%)	15 (4.4%)	328 (100.0%)	283 (100.0%)

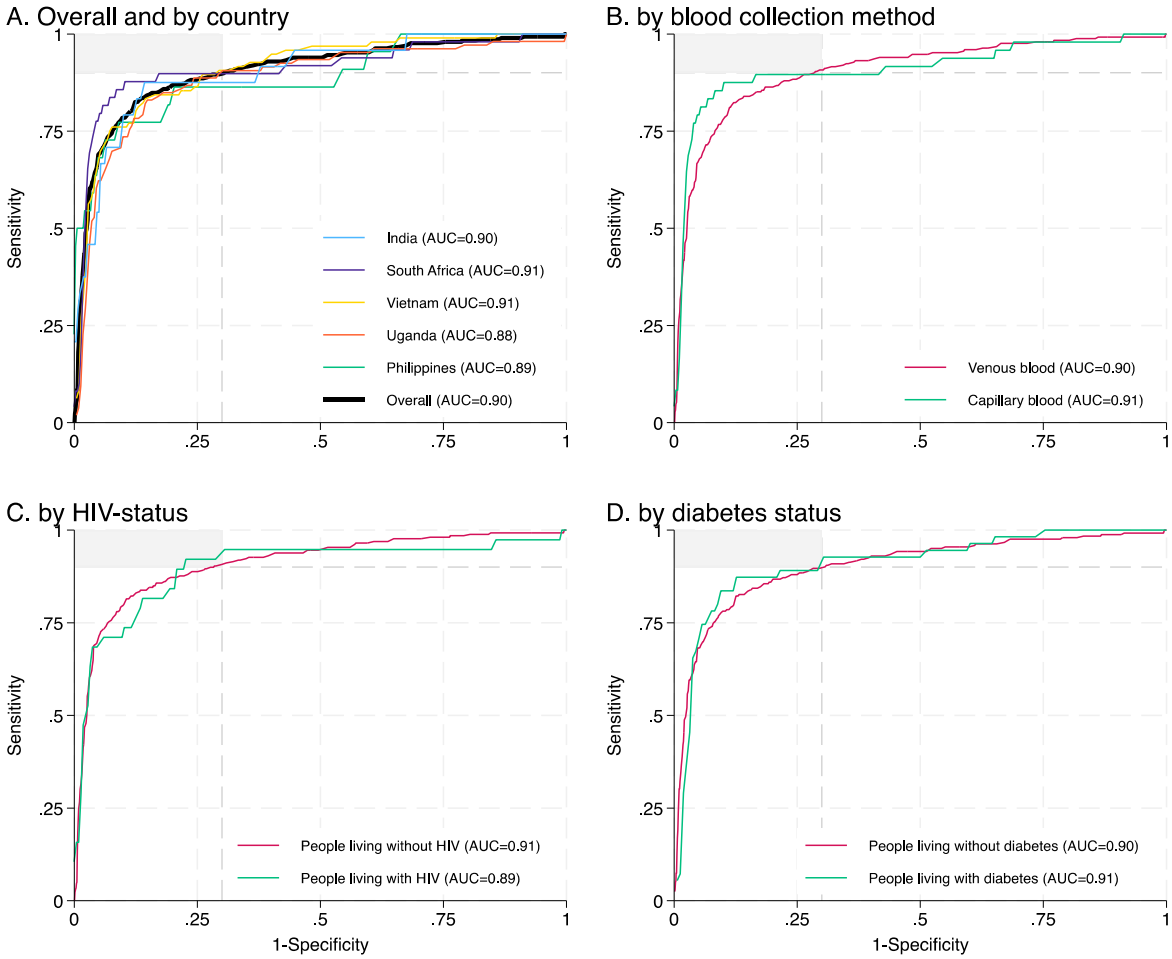
[a]3 participants were unsure about prior TB diagnoses. [b]3 participants had an unknown HIV status. [c]1 participant was missing a sputum Xpert result.

Table S9: Diagnostic Accuracy for the Xpert-HR based on Sputum Xpert Reference Standard overall and by subgroup

Category		TP	FP	FN	TN	TB prevalence (%)	Sensitivity (%)	(95%CI)	Specificity (%)	(95%CI)	PPV (%)	(95%CI)	NPV (%)	(95%CI)
Overall (cut-point <-1.45)		908	29	401	268	18.5	90.2	(86.3-93.4)	69.4	(66.8-71.9)	40.1	(36.3-43.9)	96.9	(95.6-97.9)
Country														
	Philippines	267	4	63	18	6.2	81.8	(59.7-94.8)	80.9	(76.2-85.0)	22.2	(13.7-32.8)	98.5	(96.3-99.6)
	Vietnam	132	7	75	89	31.7	92.7	(85.6-97.0)	63.8	(56.8-70.3)	54.3	(46.3-62.1)	95.0	(89.9-98.0)
	South Africa	180	5	111	44	14.4	89.8	(77.8-96.6)	61.9	(56.0-67.5)	28.4	(21.4-36.2)	97.3	(93.8-99.1)
	Uganda	152	10	70	96	32.3	90.6	(83.3-95.4)	68.5	(61.9-74.5)	57.8	(49.9-65.4)	93.8	(88.9-97.0)
	India	177	3	82	21	8.5	87.5	(67.6-97.3)	68.3	(62.3-74.0)	20.4	(13.1-29.5)	98.3	(95.2-99.7)
Sex														
	Female	473	21	197	183	12.7	91.4	(83.8-96.2)	68.1	(64.3-71.7)	29.4	(24.2-35.0)	98.2	(96.5-99.2)
	Male	435	8	204	85	23.3	89.7	(84.7-93.5)	70.6	(67.0-74.0)	48.2	(43.0-53.3)	95.7	(93.6-97.3)
HIV status														
	HIV +ve	801	27	290	232	15.0	94.7	(82.3-99.4)	49.1	(42.2-55.9)	24.7	(17.9-32.5)	98.1	(93.5-99.8)
	HIV -ve	106	2	110	36	19.2	89.6	(85.2-93.0)	73.4	(70.7-76.0)	44.4	(40.1-48.8)	96.7	(95.3-97.8)
Diabetes														
	Yes	795	23	356	219	25.8	89.1	(77.8-95.9)	71.5	(63.8-78.4)	52.1	(41.6-62.5)	95.0	(89.3-98.1)
	No	113	6	45	49	17.4	90.5	(86.1-93.9)	69.1	(66.3-71.7)	38.1	(34.1-42.2)	97.2	(95.8-98.2)
Collection method														
	capillary	172	5	105	43	14.8	89.6	(77.3-96.5)	62.1	(56.1-67.8)	29.1	(21.9-37.1)	97.2	(93.5-99.1)
	venous	172	5	105	43	19.4	90.4	(86.0-93.7)	71.3	(68.5-74.1)	43.2	(38.9-47.6)	96.8	(95.3-98.0)

TP True positive, FP False positive, FN False Negative, TN true negative, PPV positive predictive value, NPV negative predictive value, CI confidence interval

Figure S5. Xpert TB HR Receiver Operating Characteristic (ROC) curve analysis against sputum Xpert reference standard.



N=1606 participants with valid sputum Xpert Ultra results. Median TB Score was -2.90 (IQR -3.35 to -2.20) for participants positive by SXRS, and -1.05 (IQR -1.55 to -0.70) for participants negative by SXRS.

STARD checklist

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT	**1**	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	1&2
ABSTRACT	**2**	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	3
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	5
	4	Study objectives and hypotheses	5
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	6
Participants	**6**	Eligibility criteria	6
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	6
	8	Where and when potentially eligible participants were identified (setting, location and dates)	6
	9	Whether participants formed a consecutive, random or convenience series	6
Test methods	**10a**	Index test, in sufficient detail to allow replication	6
	10b	Reference standard, in sufficient detail to allow replication	6-7
	11	Rationale for choosing the reference standard (if alternatives exist)	NA
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	7
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	7
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	7

	13b	Whether clinical information and index test results were available to the assessors of the reference standard	7
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	7
	15	How indeterminate index test or reference standard results were handled	7
	16	How missing data on the index test and reference standard were handled	7
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	7
	18	Intended sample size and how it was determined	7
RESULTS			
Participants	**19**	Flow of participants, using a diagram	8, Figure 1
	20	Baseline demographic and clinical characteristics of participants	9
	21a	Distribution of severity of disease in those with the target condition	9/Appendix
	21b	Distribution of alternative diagnoses in those without the target condition	NA
	22	Time interval and any clinical interventions between index test and reference standard	12
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	Appendix, table S7
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	10/ Figure 3/ Appendix table S9
	25	Any adverse events from performing the index test or the reference standard	NA
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	16-17
	27	Implications for practice, including the intended use and clinical role of the index test	16-17
OTHER INFORMATION			
	28	Registration number and name of registry	ClinicalTrials.gov Identifier: NCT04923958
	29	Where the full study protocol can be accessed	On request from authors
	30	Sources of funding and other support; role of funders	8, 18