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Evaluation of LyoDx TB-SIX as a Non-Sputum TB Screening Test in a High-Burden Setting

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Background

- Blood-based host transcriptomic signatures, including the 6-gene RISK6 panel, have shown accuracy suitable for TB-screening
- The TB-SIX assay (LyoDx, UK) operationalises RISK6 as a multiplexed, semi-automated RT-qPCR test.

The LyoDx TB-SIX Assay



RISK6 signature genes

↑ Upregulated in TB	↓ Downregulated in TB
GBP2	TUBGCP6
FCGR1B	TRMT2A
SERPING1	SDR39U1

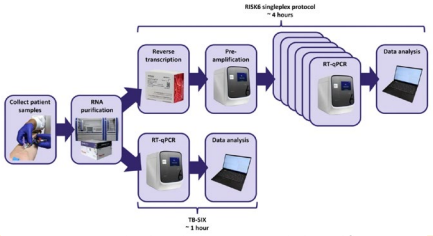
Study objectives

1. Evaluate the diagnostic accuracy of TB-SIX among outpatients with presumed TB and compare with WHO targets for a high sensitivity TB screening test (90% sensitivity; 60% specificity).
2. Assess concordance between TB-SIX and research-grade RISK6.

Methods

Prospective diagnostic accuracy study at two outpatient clinics in Kampala, Uganda (Apr–Jun 2025).

1. **Population:** consecutive people ≥12 y with presumed TB
2. **Procedures:** whole blood collected into PAXgene RNA tubes
3. **Index tests:** TB-SIX & RISK6, blinded operators
4. **Microbiological reference standard (MRS):** MGIT culture



TB-SIX single-tube multiplex vs RISK6 singleplex workflow

TB-SIX score: 6 transcript Ct values → TB-SIX Score Calculator → TB-SIX Score
(mean of 9 up/downregulated transcript-pair ratio scores)

Analysis:
- ROC analysis against MRS and Xpert Ultra
- Sensitivity and specificity at 1) cut-point maximizing overall accuracy and 2) achieving sensitivity ≥90%
- Pearson and Spearman correlation (TB-SIX vs. RISK6)

Results

Participants (N = 101)

36.5 y Mean age range 12–74	**51.5%** Female n = 52	**26.7%** Living with HIV n = 27
18.8% Diabetes n = 19	**29.7%** Culture-pos. TB n = 30	**82.2%** Valid MRS n = 83

Diagnostic accuracy of TB-SIX

AUC = 0.91 vs MRS 95% CI 0.84–0.97

AUC = 0.88 vs Xpert Ultra 95% CI 0.81–0.95

Cut-point / sub-group vs. MRS	Sensitivity, % (95% CI)	Specificity, % (95% CI)
Max-accuracy cut-point	96.7 (83.3–99.4)	73.6 (60.4–83.6)
≥90% sensitivity cut-point	90.0 (73.5–97.9)	77.4 (63.8–87.7)
PLHIV	75.0 (19.4–99.4)	53.3 (26.6–78.7)
HIV-negative	92.3 (74.9–99.1)	86.8 (71.9–95.6)
Diabetes	85.7 (42.1–99.6)	72.7 (39.0–94.0)
Xpert med/high	95.2 (76.2–99.9)	—
Xpert trace–low	100 (47.8–100)	—

Concordance between TB-SIX and research-grade RISK6

r = 0.95 Pearson correlation p < 0.001

ρ = 0.96 Spearman correlation p < 0.001

Conclusions

TB-SIX approached WHO minimum accuracy targets for a high-sensitivity TB screening test. Further assessment is needed among populations recommended for TB screening

- **Strong concordance with RISK6**: Enables standardised implementation of the RISK6 gene signature.
- May be offered as an alternative to symptom screen and Chest X-Ray in the TB screening pathway

Future directions

- Larger multi-country validation studies
- Evaluation in children and TB screening populations
- Integration into TB screening pathways with near point-of-care deployment
- Evaluations among inpatient populations

Acknowledgements

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