THE LANCET
Infectious Diseases

Supplementary appendix

Supplementary Appendix

Targeted next-generation sequencing to diagnose drug-resistant tuberculosis: systematic review and test accuracy meta-analysis

Tiana Carina Schwab, MSc [1], Lisa Perrig, MD [1], Pauline Carlotta Göller, PhD [1], Freddy Fernando Guebely De la Hoz, MD [1], Adrien Philippe Lahousse, MD [1], Beatrice Minder, MSc [2], Gunar Günther, MD [3 4], Orestis Efthimiou, PhD [1 5], Shaheed Vally Omar, PhD [6], Prof. Matthias Egger, MD [1 7 8], Prof. Lukas Fenner, MD [1 *]

1 Institute of Social and Preventive Medicine, University of Bern, Switzerland

2 Public Health & Primary Care Library, University Library of Bern, University of Bern, Switzerland

3 Department of Pulmonology and Allergology, Inselspital, Bern University Hospital, University of Bern, Switzerland

4 Department of Medicine, Faculty of Health Sciences, University of Namibia, Windhoek, Namibia

5 Institute of Primary Health Care (BIHAM), University of Bern, Switzerland

6 Centre for Tuberculosis, National & WHO Supranational TB Reference Laboratory, National Institute for Communicable Diseases, a division of the National Health Laboratory Services, Johannesburg, South Africa

7 Centre for Infectious Disease Epidemiology & Research, School of Public Health & Family Medicine, University of Cape Town, South Africa

8 Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK

Supplementary Material

Supplementary Figures

Supplementary Tables

SUPPLEMENTARY MATERIALS

Supplementary Material 1: Search strategies. Last date searched: 14 October 2022. From this date until 13 February 2024, search alerts were set and checked weekly for Embase.com, PubMed (Medline strategy translated accordingly) and Google Scholar to identify more recent studies for inclusion. Clinical trials were also monitored.

Embase.com

('drug resistant tuberculosis'/exp OR 'Mycobacterium tuberculosis'/de OR 'Mycobacterium tuberculosis complex'/de OR 'tuberculosis'/de OR (tubercul* OR TB OR TBC OR DR-TB OR MDR-TB OR MTBC OR RR-TB OR XDR-TB OR XDRTB OR (tubercle NEAR/3 bacill*)):ab,ti,kw) AND ('high throughput sequencing'/exp OR 'targeted sequencing'/de OR 'high throughput sequencer'/de OR 'deep sequencing'/de OR 'massively parallel sequencing'/de OR 'illumina'/de OR 'minion'/de OR (tNGS OR ((target* OR high-through-put OR high-throughput OR nanopore* OR next-generation* OR next-gen OR NGS OR ion-torrent OR ion-proton OR semiconductor OR semi-conductor OR massively-parallel OR mate-pair OR paired-end OR pair-end OR pairwise-end OR long-read OR shotgun OR shot-gun OR single-end OR single-read OR deep OR massively-parallel OR ONT) NEAR/3 (sequenc* OR resequen* OR re-sequenc* OR analys* OR technolog*)) OR (target* NEAR/2 (assay* OR resequenc*)) OR (molecul* NEAR/2 target*) OR "NGS analys*" OR line-probe-assay* OR pyrosequenc* OR pyro-sequenc* OR Deeplex-Myc-TB OR Deeplex-MycTB OR DeepChek OR "MDR-TB assay" OR "Tuberculosis IVD" OR Illumina OR MinION OR MiniSeq):ti,ab,kw) AND (targeted OR point-of-care OR portab* OR amplif* OR multiplex* OR multi-plex* OR specimen* OR sputum OR smear OR isolates OR rapid):ab,ti,kw NOT ([animals]/lim NOT [humans]/lim) NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim) AND [2005-2022]/py

---

Medline ALL (Ovid)

(exp Tuberculosis, Multidrug-Resistant/ OR Mycobacterium tuberculosis/ OR tuberculosis/ OR (tubercul* OR TB OR TBC OR DR-TB OR MDR-TB OR MTBC OR RR-TB OR XDR-TB OR XDRTB OR (tubercle ADJ3 bacill*)).ab,ti,kf.) AND (exp High-Throughput Nucleotide Sequencing/ OR (tNGS OR ((target* OR high-through-put OR high-throughput OR nanopore* OR next-generation* OR next-gen OR NGS OR ion-torrent OR ion-proton OR semiconductor OR semi-conductor OR massively-parallel OR mate-pair OR paired-end OR pair-end OR pairwise-end OR long-read OR shotgun OR shot-gun OR single-end OR single-read OR deep OR massively-parallel OR ONT) ADJ3 (sequenc* OR resequen* OR re-sequenc* OR analys* OR technolog*)) OR (target* ADJ2 (assay* OR resequenc*)) OR (molecul* ADJ2 target*) OR "NGS analys*" OR line-probe-assay* OR pyrosequenc* OR pyro-sequenc* OR Deeplex-Myc-TB OR Deeplex-MycTB OR DeepChek OR "MDR-TB assay" OR "Tuberculosis IVD" OR Illumina OR MinION OR MiniSeq).ab,ti,kf.) AND (targeted OR point-of-care OR portab* OR amplif* OR multiplex* OR multi-plex* OR specimen* OR sputum OR smear OR isolates OR rapid).ab,ti,kf NOT (exp animals/ NOT humans/) NOT (letter OR news OR comment OR editorial OR congress).pt. limit to yr="2005 -Current"

Cochrane Library (via Wiley) (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials)

((urban NEXT setting* OR urban NEXT context* OR city OR cities OR metropolitan NEXT area* OR superblock* OR town OR towns OR municipal*):ab,ti,kw) AND (((((urban or health) NEAR/3 govern*) or ((state* or health* or public or environment*) NEAR/3 polic*) or "health in all policy" OR "health in all policies" or "healthy public policy" or "healthy public policies"):ab,ti,kw) OR ((((community or public or citizen or civic or resident* or private or social or political) NEAR/3 (particip* OR empower* OR involv* OR collaborat* OR engagement* OR implement* or partnership*)) or (participatory NEAR/2 (approach* or framework*)) or "participatory spaces" or ((multisector* or multi-sector* or intersector* or inter-sector*) NEAR/3 (action* or collaborat*)) or "social citizenship" or stakeholder*):ab,ti,kw)) AND ((wellbeing OR well-being OR health NEXT equit* OR urban NEXT health* OR "quality of life" OR community NEXT health* OR healthy NEXT cit* OR "Urban HEART" OR health NEXT impact NEXT assess* OR SDG11 OR "SDG 11" OR SDG3 OR "SDG 3" OR "sustainable development goal" OR "sustainable development goals" OR population NEXT health* OR residents NEXT health* OR "healthy life" OR "healthy lives" OR liveabil* OR livabil* OR ((city or cities or settlement*) AND (inclusive or safe or resilient or sustainab*))):ab,ti,kw)

---

*Web of Science Core Collection

TS=(((tubercul* OR TB OR TBC OR DR-TB OR MDR-TB OR MTBC OR RR-TB OR XDR-TB OR XDRTB OR (tubercle NEAR/2 bacill*))) AND ((tNGS OR ((target* OR "high through put" OR high-throughput OR nanopore* OR "next generation" OR "next-gen" OR NGS OR ion-torrent OR ion-proton OR semiconductor OR semi-conductor OR massively-parallel OR mate-pair OR paired-end OR pair-end OR pairwise-end OR long-read OR shotgun OR shot-gun OR single-end OR single-read OR deep OR massively-parallel OR ONT) NEAR/2 (sequenc* OR resequen* OR analys* OR technolog*)) OR (target* NEAR/1 (assay* OR resequenc*)) OR (molecul* NEAR/1 target*) OR NGS-

analys* OR line-probe-assay* OR pyrosequenc* OR pyro-sequenc* OR Deeplex-Myc-TB OR Deeplex-MycTB OR DeepChek OR "MDR-TB assay" OR "Tuberculosis IVD" OR Illumina OR MinION OR MiniSeq))) AND TS=(targeted OR point-of-care OR portab* OR amplif* OR multiplex* OR multi-plex* OR specimen* OR sputum OR smear OR isolates OR rapid) NOT TS=((animal* OR plant* OR rat OR rats OR murine OR mouse OR mice OR pigs) NOT (human* OR patient*)) AND PY=(2005-2023)

Exclude: Document types: (editorial material OR book chapters OR letter OR meeting abstract OR proceeding paper)

* Science Citation Index Expanded (1900-present) ; Social Sciences Citation Index (1900-present) ; Arts & Humanities Citation Index (1975-present) ; Conference Proceedings Citation Index- Science (1990-present) ; Conference Proceedings Citation Index- Social Science & Humanities (1990-present) ; Emerging Sources Citation Index (2017-present)

Global Index Medicus (via https://www.globalindexmedicus.net/en Advanced search)

tw:((tw:(tubercul* OR tubercle OR tb OR tbc OR dr-tb OR mdr-tb OR mtbc OR rr-tb OR xdr-tb OR xdrtb)) AND (tw:(tngs OR target* OR "high through put" OR high-throughput OR nanopore* OR next-generation* OR next-gen OR ngs OR deep OR ont)) AND (tw:(sequenc* OR resequen* OR technolog*)))
OR
tw:((tw:(tubercul* OR tubercle OR tb OR tbc OR dr-tb OR mdr-tb OR mtbc OR rr-tb OR xdr-tb OR xdrtb)) AND (tw:(NGS-analys* OR line-probe-assay* OR pyrosequenc* OR pyro-sequenc* OR deeplex-myc-tb OR deeplex-myctb OR deepchek OR "MDR-TB assay" OR "Tuberculosis IVD" OR illumina OR minion OR miniseq)))

Google Scholar (first 200 most relevant results, 2005-2022)

tuberculosis|tuberculous|tubercle tNGS|"next generation"|"next-gen"|NGS|nanopore|"Deeplex Myc-TB"|"Deeplex-MycTB"|DeepChek|"MDR-TB"|"Tuberculosis IVD"|Illumina|MinION|MiniSeq|"high through put"|"high-throughput"|deep assay|assays|sequencing|sequencer

---

ClinicalTrials.gov (via Expert Search)

((tuberculosis OR tuberculous OR tubercle OR TB OR TBC OR DR-TB OR MDR-TB OR MTBC OR RR-TB OR XDR-TB OR XDRTB) AND (tNGS OR "high through put" OR high-throughput OR nanopore OR "next generation" OR "next-gen" OR NGS OR ion-torrent OR ion-proton OR semiconductor OR semi-conductor OR massively-parallel OR mate-pair OR paired-end OR pair-end OR pairwise-end OR long-read OR shotgun OR shot-gun OR single-end OR single-read OR deep OR massively-parallel OR ONT OR Deeplex OR DeepChek OR "MDR-TB assay" OR "Tuberculosis IVD" OR Illumina OR MinION OR MiniSeq))

WHO International Clinical Trials Registriy Platform (Search Portal) https://trialsearch.who.int

(tuberculosis AND tNGS) OR (tuberculosis AND high through put) OR (tuberculosis AND high-throughput) OR (tuberculosis AND nanopore) OR (tuberculosis AND next-generation) OR (tuberculosis AND next-gen) OR (tuberculosis AND Deeplex) OR (tuberculosis AND DeepChek) OR (tuberculosis AND MDR-TB assay) OR (tuberculosis AND Tuberculosis IVD) OR (tuberculosis AND Illumina) OR (tuberculosis AND MinION) OR (tuberculosis AND MiniSeq) OR (tb AND tNGS) OR (tb AND high through put) OR (tb AND high-throughput) OR (tb AND nanopore) OR (tb AND next-generation) OR (tb AND next-gen) OR (tb AND Deeplex) OR (tb AND DeepChek) OR (tb AND MDR-TB assay) OR (tb AND Tb IVD) OR (tb AND Illumina) OR (tb AND MinION) OR (tb AND MiniSeq)

Supplementary Material 2: Data Extraction Form

Details about Extractor

1. Name of Extractor
2. Date

Details about Publication

3. Title
4. First author (Last name, First name)
5. Publication year
6. PMID (if n/a DOI)
7. Type of article
   a. Journal article
   b. Review article
   c. Viewpoint
   d. Research note
   e. Conference abstract
   f. Registered clinical trial
8. Publication status (published / unpublished)

Review-specific questions

9. Type of review
10. Specific TB-tNGS assays mentioned
11. NGS technology mentioned
12. Referenced

Observational studies or clinical trials
[Study setting and methods]

13. Type of study
14. Setting
15. Country of specimen
16. Country of sequencing and analysis
17. Type of sample (e.g. sputum, culture isolate, smear content, etc.)
18. Number of included samples
19. TB-tNGS target panel

20. Gene targets
21. Number of targets
22. Breadth of coverage
23. DNA extraction method
24. DNA library preparation kit
25. NGS platform
26. NGS data analysis

[Results and performance]

27. Depth of coverage
28. Reference test
29. Percentage (%) agreement
30. True positives
31. True negatives
32. False positives
33. False negatives
34. Sensitivity
35. Specificity
36. Negative predictive value
37. Positive predicative value
38. Turn-around time
39. Cost
40. Advantages mentioned
41. Disadvantages mentioned
42. Any other comments

Supplementary Material 3: Priors used for Bayesian meta-analyses.

For the Bayesian analyses, we used the default prior distributions of MetaBayesDTA, as recommended by Cerullo et al.[1] For the pooled logit sensitivity and logit specificity, we used a normal distribution N(0, 1.5), which is equivalent to a 95% prior interval of [0.05; 0.95]. For the between-study standard deviations we used the truncated positive part of a standard normal distribution N≥0(0, 1). Finally, for the between-study correlation we used an LKJ (Lewandowski-Kurowicka-Joe) prior with shape parameter of 2 (LKJ(2)), which gives a 95% prior interval of (−0.8, 0.8)".[2]

SUPPLEMENTARY FIGURES

Supplementary Figure 1: The movement of samples from countries where samples were collected (left) and to where TB-tNGS done (right). The thickness of ribbons is proportional to the number of studies.
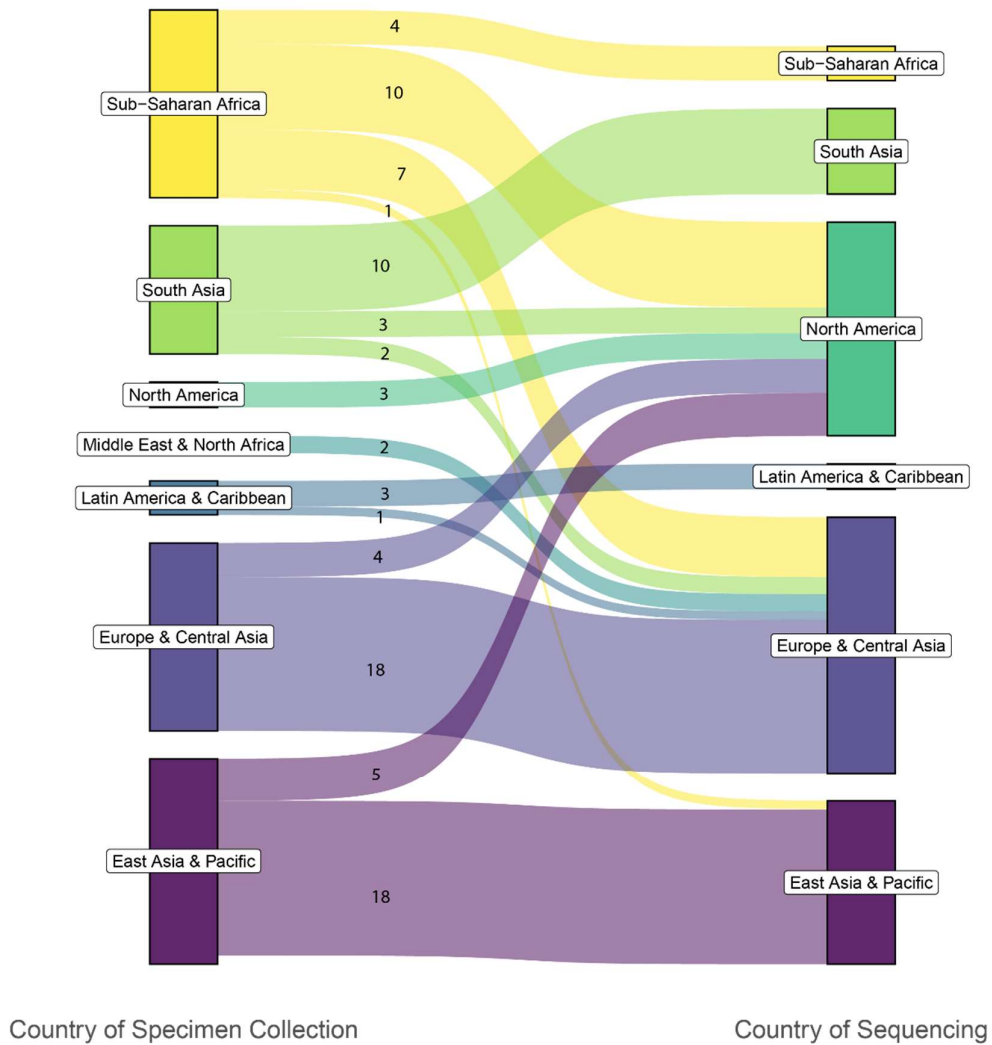
Supplementary Figure 2: Summary Receiver Operating Curve (SROC) plots derived from a meta-analysis of tuberculosis targeted Next Generation Sequencing (TB-tNGS) assays to phenotypic or genotypic drug susceptibility testing. Curves were generated using a Bayesian bivariate model. Circles represent estimates from the individual diagnostic accuracy studies, coloured by TB-tNGS assay used. Dotted lines represent the 95% prediction region from the bivariate model; the greyed-out areas represent the 95% credible region from the bivariate model.

Overall – data combined for all drugs in a given study, RIF – rifampicin, INH – isoniazid, EMB – ethambutol, PZA – pyrazinamide, STM – streptomycin, AMK – amikacin, CAP – capreomycin, KAN – kanamycin, MFX – moxifloxacin, FQs – fluoroquinolones.
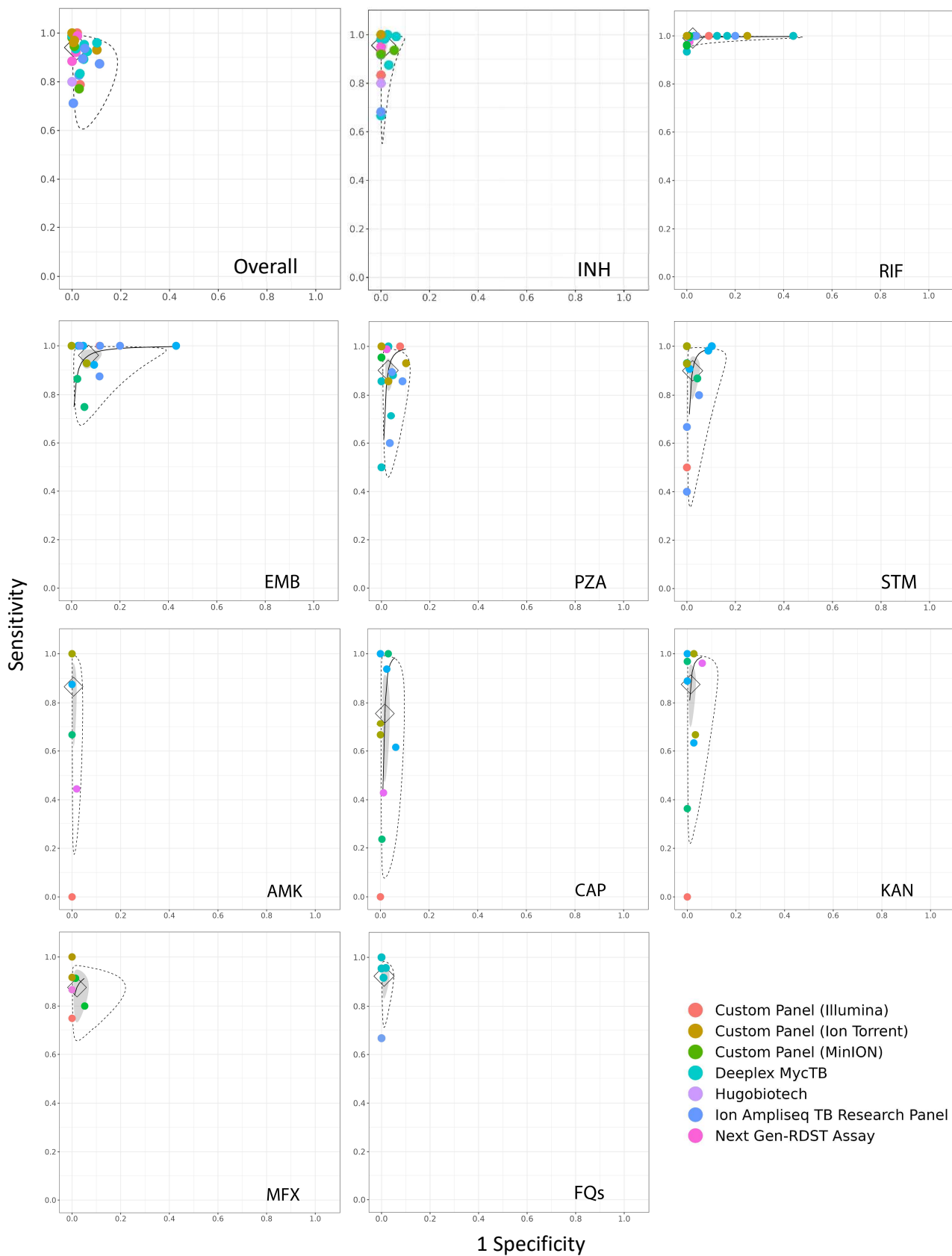
Supplementary Figure 3: Hierarchical Summary Receiver Operating Curve (HSROC) plots curves derived from a meta-analysis of studies evaluating tuberculosis-targeted next-generation sequencing (TB-tNGS) assays compared to phenotypic or genotypic drug susceptibility testing. Curves were generated using a frequentist random effects model. Each point on the curve represents a single study (Data), with the size of the point proportional to the study's weight in the meta-analysis. Points are colored by the type of TB-tNGS test. The curve represents the summary estimate of test performance across all included studies, depicting the trade-off between sensitivity and specificity.
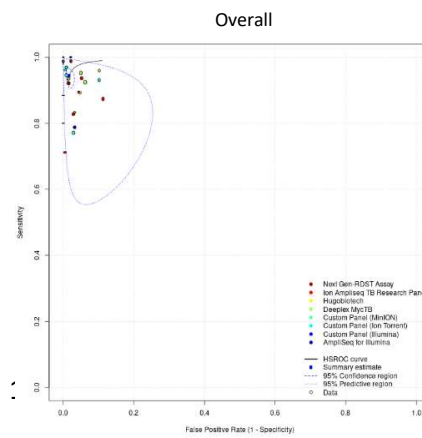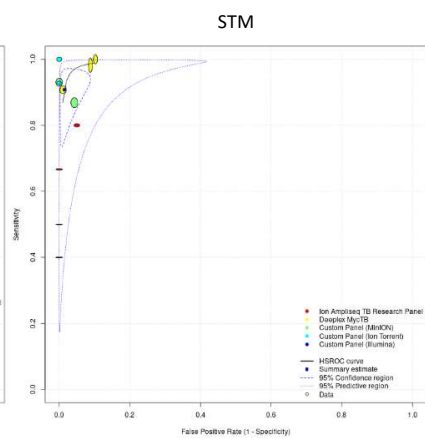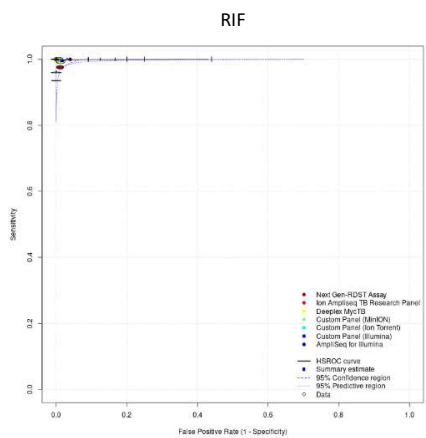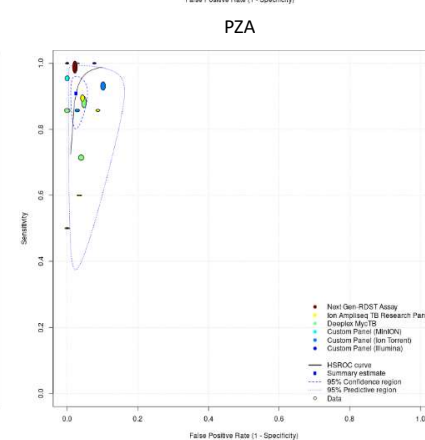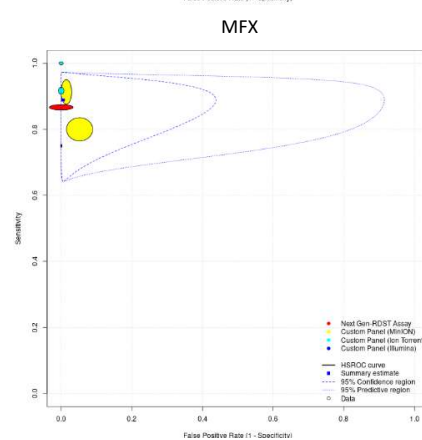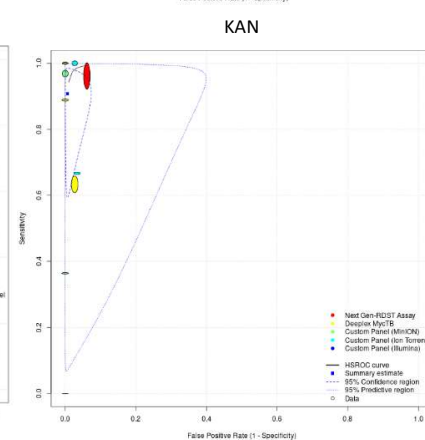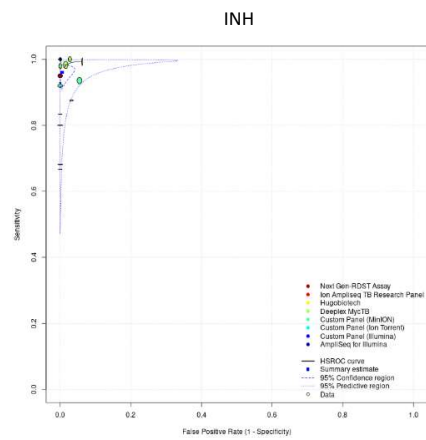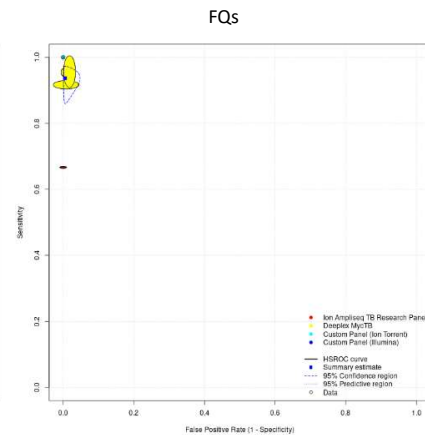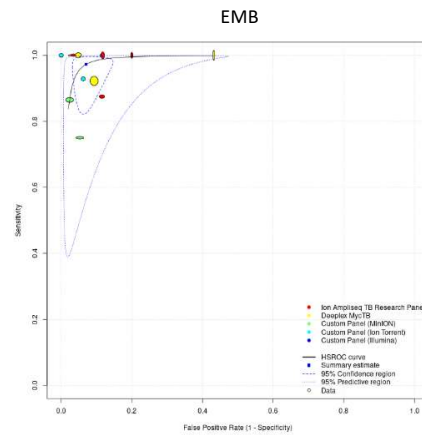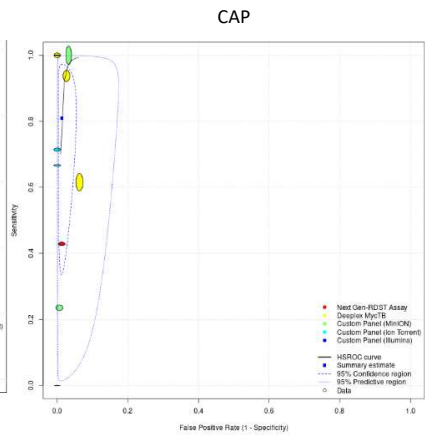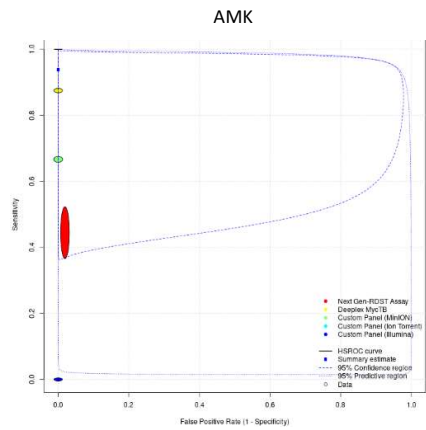
SUPPLEMENTARY TABLES

Supplementary Table 1: Inclusion and Exclusion criteria for Systematic Review and meta-analysis. TB-tNGS – targeted Next-Generation Sequencing for tuberculosis drug resistance testing.

	Inclusion criteria	Exclusion criteria
Systematic Review		
Population (P) and setting	Individuals of any age group with presumed or confirmed tuberculosis (TB) All settings Primary samples, culture isolates or reference strains	
Index test (I)	Targeted next-generation sequencing (tNGS), i.e. PCR amplification of selected gene targets and subsequent sequencing.	Not next-generation sequencing (e.g. only Sanger sequencing) Only whole-genome sequencing
Reference standard (R)		
Target condition (T)	Drug resistance detection in *Mycobacterium tuberculosis*	Not *Mycobacterium tuberculosis* No drug-resistance detection (e.g. detecting mixed infections or detecting presence of heteroresistance)
Record type and study design	Published and unpublished records of completed, planned and ongoing studies. Includes, not limited to, narrative and systematic reviews, observational studies, methodological studies, published study protocols, and interventional studies.	Method protocols
Other	No language restriction for search *	Excluding studies published <2005
Meta-analysis (in addition to systematic review)		
Index test (I)		Pyrosequencing assay
Reference standard (R)	Any phenotypic or genotypic reference standard	
Record type and study design	Test accuracy studies with results for any TB drug or drug groups.	Cross sectional studies other than test accuracy studies Methodological studies Case reports Study protocol
Other		No drug-level information available (drug resistance only reported in categories such as muti-drug resistant, extensively drug-resistant)

* During data extraction we excluded studies published in Chinese (10), Korean (1), Spanish (1) and Russian (1) due to language limitations of the reviewers.

13

Supplementary Table 2: Study Characteristics of 109 included studies in the systematic review. TB – clinically or bacteriologically diagnosed tuberculosis patients; DR-TB – drug resistant tuberculosis; TB-tNGS – tuberculosis drug resistance prediction using targeted Next-Generation Sequencing; NGS – Next-Generation Sequencing; PSQ – pyrosequencing; NA – not applicable.

STUDY	TYPE OF STUDY	COUNTRY OF SPECIMEN	COUNTRY OF SEQUENCING	STUDY SETTING	ENROLLMENT CATEGORY	TB-TNGS	NGS TECHNOLOGY	GENE TARGETS	NUMBER OF TARGETS	PSQ/NGS
AFFOLABI (2017)[3]	Diagnostic test accuracy study (unpublished)	Belgium (unclear); Benin; Cameroon; The Democratic Republic of the Congo; Ethiopia; Guinea; Mali; Nigeria; Rwanda; Senegal	Benin & Rwanda	Government and Public Health Department	TB and DR-TB	Deeplex Myc-TB	Not reported	rpoB, ahpC, fabG1, katG, inhA, pncA, embB, gyrA, gyrB, rrs, eis, tlyA, gidB, rpsL, ethA, rv0678, rrl, rplC	18	NGS
AJBANI ET AL (2015)[4]	Diagnostic test accuracy study	South Africa; Moldova; India; Philippines	USA	Research Institute	TB	Lin, 2014, PMID: 24478476	Not reported	rpoB, katG, gyrA, rrs, inhA promoter, ahpC promoter	6	PSQ
AJBANI ET AL (2018)[5]	Diagnostic test accuracy study	India	India	Hospital and Medical Research Center	TB and DR-TB	Custom target panel	PyroMark Q96 ID	katG, inhA, gyrA, rrs, eis, IS6110, rpoB1, rpoB2	8 (incl. IS6110)	PSQ
AJBANI ET AL (2018)[6]	Case Report	India	India	Hospital and Medical Research Center	TB	not reported	Not reported	rpoB	1	PSQ
AJBANI ET AL (2021)[7]	Diagnostic test accuracy study	India	India	Hospital and Medical Research Center	Presumptive TB	Lin, 2014, PMID: 24478476	PyroMark Q96 ID	rpoB, katG, gyrA, rrs, eis, inhA promoter, ahpC promoter	7	PSQ
ARNOLD ET AL (2005)[8]	Methodological study	United Kingdom	United Kingdom*	Government and Public Health Department	Presumptive DR-TB	Custom target panel	Pyrosequencing	rpoB, katG, gyrA, rnpB	7	PSQ

STUDY	TYPE OF STUDY	COUNTRY OF SPECIMEN	COUNTRY OF SEQUENCING	STUDY SETTING	ENROLLMENT CATEGORY	TB-TNGS	NGS TECHNOLOGY	GENE TARGETS	NUMBER OF TARGETS	PSQ/NGS
AUBRY (2020)[9]	Diagnostic test accuracy study (unpublished)	France	France	Government and Public Health Department	DR-TB	Deeplex Myc-TB	Not reported	rpoB, ahpC, fabG1, katG, inhA, pncA, embB, gyrA, gyrB, rrs, eis, tlyA, gidB, rpsL, ethA, rv0678, rrl, rplC	18	NGS
BARBOSA-AMEZCUA ET AL (2022)[10]	Diagnostic test accuracy study	Mexico	Mexico	Research Institute	Not reported	Custom target panel	Illumina MiSeq, Illumina NextSeq 500	Table S1	73	NGS
BEVIERE ET AL (2023)[11]	Narrative review	NA	NA	NA	NA	Not reported	Illumina Miseq, Illumina MiniSeq, Illumina HiSeq, Illumina iSeq, Illumina NextSeq, Illumina NovaSeq; IonTorrent PGM, IonTorrent Proton, Ion Torrent S5; Pacific Biosciences: PacBio RSII, Sequel; MinION, GridION, PromethION	NA	NA	NGS
BONNET ET AL (2021)[12]	Diagnostic test accuracy study	France	France	Government and Public Health Department	presumptive DR-TB	Deeplex Myc-TB	Illumina NextSeq 500	rpoB, ahpC, fabG1, katG, inhA, pncA, embB, gyrA, gyrB, rrs, eis, tlyA, gidB, rpsL, ethA, rv0678, rrl, rplC	18	NGS

STUDY	TYPE OF STUDY	COUNTRY OF SPECIMEN	COUNTRY OF SEQUENCING	STUDY SETTING	ENROLLMENT CATEGORY	TB-TNGS	NGS TECHNOLOGY	GENE TARGETS	NUMBER OF TARGETS	PSQ/NGS
BOUZIANE ET AL (2019)[13]	Cross-sectional study	Algeria	France	Government and Public Health Department	DR-TB	Custom target panel	454-GS Junior	rpoB, katG, inhA, pncA, embB, gyrA, gyrB, rrs, tlyA, gidB, rpsL, ethA, rplC, inhA promoter, ethR	15	NGS
BRANIGAN ET AL (2023)[14]	Pipeline Report	NA	NA	NA	NA	Deeplex Myc-TB; DeepCheck-TB; NanoTB; TBSeq; Clemedi Tuberculini; CleanPlex	Illumina iSeq, ONT MinION	NA	NA	NGS
BRAVO ET AL (2009)[15]	Diagnostic test accuracy study	Philippines	USA	Hospital and Medical Research Center	TB	Custom target panel	PSQ 96MA	rpoB, katG, gyrA	3	PSQ
BRAVO ET AL (2010)[16]	Methodological study	Not reported	USA *	Hospital and Medical Research Center	TB and DR-TB	Zhao, 2005b, PMID: 15786899	NA	rpoB	1	PSQ
CABIBBE AND CIRILLO (2016)[17]	Abstract	NA	NA	NA	NA	not reported	NA	NA	NA	NGS
CABIBBE ET AL (2020)[18]	Diagnostic test accuracy study	Italy	not reported	Unclear / not specified	TB	Deeplex Myc-TB	ONT MinION, Illumina MiniSeq	rpoB, ahpC, fabG1, katG, inhA, pncA, embB, gyrA, gyrB, rrs, eis, tlyA, gidB, rpsL, ethA, rv0678, rrl, rplC	18	NGS
CATANZARO ET AL (2015)[19]	Diagnostic test accuracy study	South Africa; Moldova; India	South Africa; Moldova; India	Unclear / not specified	presumptive DR-TB	Custom target panel	PyroMark Q96 ID	rpoB, katG, gyrA, rrs, inhA promoter, ahpC promoter, IS6110	7 (incl. IS6110)	PSQ
CATTAMANCHI (2021)[20]	Diagnostic test accuracy study (unpublished)	South Africa; India; Philippines; Georgia; Uganda; Vietnam	USA	Unclear / not specified	TB and DR-TB	not reported	NA	NA	NA	NGS

STUDY	TYPE OF STUDY	COUNTRY OF SPECIMEN	COUNTRY OF SEQUENCING	STUDY SETTING	ENROLLMENT CATEGORY	TB-TNGS	NGS TECHNOLOGY	GENE TARGETS	NUMBER OF TARGETS	PSQ/NGS
CHAN ET AL (2020)[21]	Methodological study	Hong Kong *	Hong Kong	Unclear / not specified	DR-TB	Custom target panel	ONT MinION, Illumina MiSeq	rpoB, katG, pncA, embB, gyrA, rrs, tlyA, rpsL, inhA promoter, eis promoter	10	NGS
CHANG ET AL (2010)[22]	Systematic Review (and meta-analysis)	NA	NA	NA	NA	Bravo, 2009, PMID: 19846642	Pyrosequencing	NA	NA	PSQ
CHANG ET AL (2011)[23]	Systematic Review (and meta-analysis)	NA	NA	NA	NA	not reported	NA	NA	NA	Unclear
CHENG ET AL (2014)[24]	Systematic Review (and meta-analysis)	NA	NA	NA	NA	Isola, 2005, PMID: 15823399; Zhao, 2005a, PMID: 15698720; Engström, 2012, PMID: 22461677	Pyrosequencing	NA	NA	PSQ
CHOERUNNISA ET AL (2020)[25]	Diagnostic test accuracy study	Indonesia	Indonesia	Government and Public Health Department	DR-TB	Custom target panel	Pyrosequencing	rpoB, katG, inhA, gyrA, rrs, eis	6	PSQ
COLMAN ET AL (2016)[26]	Diagnostic test accuracy study	Moldova	USA	Unclear / not specified	DR-TB	Next Gen-RDST assay	Illumina MiSeq	rpoB, katG, gyrA, rrs, inhA promoter, eis promoter	6	NGS
COLMAN ET AL (2019)[27]	Diagnostic test accuracy study	Archive collection	USA	Research Institute	DR-TB	Next Gen-RDST assay	Illumina MiSeq, Illumina iSeq100	rpoB, katG, gyrA, rrs, inhA promoter, eis promoter	6	NGS
CUEVAS-CORDOBA ET AL (2021)[28]	Methodological study	Mexico	Mexico	Unclear / not specified	TB	Custom target panel	Illumina NextSeq	NA	174	NGS
DAUM ET AL (2012)[29]	Diagnostic test accuracy study	South Africa	USA	Unclear / not specified	TB and DR-TB	Custom target panel	IonTorrent PGM	rpoB, katG, pncA, gyrA, rrs	6	NGS
DAUM ET AL (2013)[30]	Case Report	United States	USA	Diagnostic Company	NA	Custom target panel	IonTorrent PGM	rpoB, katG, inhA, pncA, gyrA, rrs, rpsL	7	NGS

STUDY	TYPE OF STUDY	COUNTRY OF SPECIMEN	COUNTRY OF SEQUENCING	STUDY SETTING	ENROLLMENT CATEGORY	TB-TNGS	NGS TECHNOLOGY	GENE TARGETS	NUMBER OF TARGETS	PSQ/NGS
DAUM ET AL (2019)[31]	Cross-sectional study	Ukraine	not reported	Diagnostic Company	TB	Custom target panel	Illumina MiSeq	pncA	1	NGS
DE ARAUJO ET AL (2023)[32]	Implementation model	Namibia	Namibia	Research Institute	NA	Not reported	Illumina iSeq	not mentioned	NA	NGS
DHEDA (2021)[33]	Interventional Study (unpublished)	South Africa	not reported	Unclear / not specified	TB and DR-TB	Deeplex Myc-TB	NA	rpoB, ahpC, fabG1, katG, inhA, pncA, embB, gyrA, gyrB, rrs, eis, tlyA, gidB, rpsL, ethA, rv0678, rrl, rplC	18	NGS
DIPPENAAR ET AL (2022)[34]	Mini-review	NA	NA	NA	NA	Deeplex Myc-TB; Tafess, 2020, PMID: 32402055; Chan, 2020, PMID: 32948225	ONT MinION, Illumina MiSeq, Illumina MiniSeq	NA	NA	NGS
DOLINGER ET AL (2016)[35]	Abstract	NA	NA	NA	NA	not reported	NA	NA	NA	NGS
DOMINGUEZ ET AL (2023)[36]	Consensus document	NA	NA	NA	NA	Deeplex Myc TB; Next Gen-RDST; Ion Ampliseq TB Research Panel	Not reported	rpoB, katG, inhA, ahpC, fabG1, gyrA, gyrB, Rv0678, rplc, rrl, embB, pncA, rrs, rpsl, ethA, eis (from Table 2)	16	NGS
DOOKIE ET AL (2022)[37]	Narrative review	NA	NA	NA	NA	Deeplex Myc-TB; Next Gen-RDST assay	ONT MinION, Illumina MiSeq, IonTorrent PGM (ThermoFisher), PacBio RSII	NA	NA	NGS
EL ACHKAR ET AL (2019)[38]	Cross-sectional study	Lebanon	not reported	Unclear / not specified	TB	Deeplex Myc-TB	Not reported	rpoB, ahpC, fabG1, katG, inhA, pncA, embB, gyrA, gyrB, rrs, eis, tlyA, gidB, rpsL, ethA, rv0678, rrl, rplC	18	NGS

18

STUDY	TYPE OF STUDY	COUNTRY OF SPECIMEN	COUNTRY OF SEQUENCING	STUDY SETTING	ENROLLMENT CATEGORY	TB-TNGS	NGS TECHNOLOGY	GENE TARGETS	NUMBER OF TARGETS	PSQ/NGS
ENGSTRÖM ET AL (2012)[39]	Diagnostic test accuracy study	Reference isolate collection	not reported	Research Institute	TB	Custom target panel	PSQ 96MA	rpoB, katG, embB, gyrA, rrs, inhA promoter, eis promoter	7	PSQ
FEUERRIEGEL ET AL (2021)[40]	Diagnostic test accuracy study	Germany; Sierra Leone	Germany	Research Institute	Not reported	Deeplex Myc-TB	Illumina NextSeq 500, Illumina MiniSeq	rpoB, ahpC, fabG1, katG, inhA, pncA, embB, gyrA, gyrB, rrs, eis, tlyA, gidB, rpsL, ethA, rv0678, rrl, rplC	18	NGS
FOUNDATION FOR INNOVATIVE NEW DIAGNOSTICS (2020)[41]	Diagnostic test accuracy study (unpublished)	South Africa; India; Georgia	not reported	Unclear / not specified	TB and presumptive DR-TB	not reported	NA	NA	NA	NGS
GARCIA-SIERRA ET AL (2011)[42]	Diagnostic test accuracy study	Spain *	Spain *	Unclear / not specified	TB	Custom target panel	PSQ 96MA	rpoB, katG, inhA	3	PSQ
GARZA-GONZALEZ ET AL (2010)[43]	Diagnostic test accuracy study	Mexico	Mexico	Research Institute	TB	Custom target panel	Pyrosequencer PSQ 96	rpoB, ahpC, inhA	3	PSQ
GEORGHIOU ET AL (2016)[44]	Cross-sectional study	South Africa; Moldova; India	not reported	Unclear / not specified	presumptive DR-TB	Custom target panel	PyroMark Q96 ID	rpoB, ahpC, katG, inhA, gyrA, rrs, eis	7	PSQ
GEORGHIOU ET AL (2016)[45]	Diagnostic test accuracy study	South Africa; Moldova; India	South Africa; Moldova; India + USA (eis from Moldova and South Africa)	Unclear / not specified	TB and presumptive DR-TB	Custom target panel	PyroMark Q96 ID	rpoB, katG, gyrA, rrs, inhA promoter, eis promoter, ahpC promoter	9 (incl. IS6110)	PSQ
GEORGHIOU ET AL (2016)[46]	Diagnostic test accuracy study	India	India	Hospital and Medical Research Center	TB	Lin, 2014, PMID: 24478476	PyroMark Q96 ID	rpoB, katG, gyrA, rrs, inhA promoter, ahpC promoter	6	PSQ
GEORGHIOU ET AL (2023)[47]	Narrative review	NA	NA	NA	NA	Deeplex Myc-TB	NA	NA	NA	NGS

STUDY	TYPE OF STUDY	COUNTRY OF SPECIMEN	COUNTRY OF SEQUENCING	STUDY SETTING	ENROLLMENT CATEGORY	TB-TNGS	NGS TECHNOLOGY	GENE TARGETS	NUMBER OF TARGETS	PSQ/NGS
GETACHEW ET AL (2021)[48]	Systematic Review (and meta-analysis)	NA	NA	NA	NA	Ajbani, 2015, PMID: 25367911; Lin, 2014, PMID: 24478476; Bravo, 2009, PMID: 19846642; Catanzaro, 2015, PMID: 26322781; EngstrÃ¶m, 2012, PMID: 22461677; Georghiou, 2016, PMID: 27576542; Govindaswamy, 2018, PMID: 30028665	Pyrosequencing	NA	NA	PSQ
GLIDDON ET AL (2021)[49]	Diagnostic test accuracy study	South Africa	United Kingdom *	Unclear / not specified	TB and DR-TB	Custom target panel	ONT MinION	rpoB, katG, inhA	3	NGS
GOPALASWAMY ET AL (2022)[50]	Editorial	NA	NA	NA	NA	Deeplex Myc-TB; Next Gen-RDST assay	ONT MinION, Illumina MiSeq, Illumina NextSeq, Illumina MiniSeq, Illumina iSeq	NA	NA	NGS
GOVINDASWAMY ET AL (2018)[51]	Diagnostic test accuracy study	India	India	Hospital and Medical Research Center	TB and DR-TB	Lin, 2014, PMID: 24478476	PyroMark Q24ID	rpoB, gyrA, rrs, eis promoter	4	PSQ

STUDY	TYPE OF STUDY	COUNTRY OF SPECIMEN	COUNTRY OF SEQUENCING	STUDY SETTING	ENROLLMENT CATEGORY	TB-TNGS	NGS TECHNOLOGY	GENE TARGETS	NUMBER OF TARGETS	PSQ/NGS
					NA					
GRACIAA ET AL (2023)[52]	Narrative review	NA	NA	NA		Not reported	Not reported	not mentioned	NA	NGS
					NA					
GUHA ET AL (2024)[53]	Narrative review	NA	NA	NA		Deeplex Myc-TB; Next Gen-RDST	ONT MinION	not mentioned	NA	NGS
GUO ET AL (2013)[54]	Systematic Review (and meta-analysis)	NA	NA	NA	NA	Zhao, 2005b, PMID: 15786899; Arnold, 2005, PMID: 15679486; Jureen, 2006, PMID: 16757581; Bravo, 2009, PMID: 19846642; Martilla, 2009, PMID:	PSQ 96 MA (pyrosequencing)	NA	NA	PSQ

21

STUDY	TYPE OF STUDY	COUNTRY OF SPECIMEN	COUNTRY OF SEQUENCING	STUDY SETTING	ENROLLMENT CATEGORY	TB-TNGS	NGS TECHNOLOGY	GENE TARGETS	NUMBER OF TARGETS	PSQ/NGS
						18719956; Halse, 2010, PMID: 20107097; Garza-Gonzalez, 2010, PMID: 19673965; Garcia-Sierra, 2011, PMID: 21813715; Engström, 2012, PMID: 22461677; [Zheng, 2007]; [Zheng, 2008]; [Zheng, 2011]				
HALSE ET AL (2010)[55]	Diagnostic test accuracy study	United States	USA	Government and Public Health Department	Presumptive DR-TB	Custom target panel	PyroMark Q96 ID	rpoB	1	PSQ
HILLERY ET AL (2014)[56]	Published Study Protocol	South Africa (Catanzaro); Moldova (Catanzaro); India (Catanzaro)	South Africa (Catanzaro); Moldova (Catanzaro); India (Catanzaro)	Unclear / not specified	DR-TB	Bravo, 2009, PMID: 19846642	PyroMark 96ID	rpoB, ahpC, katG, gyrA, rrs, inhA promoter	7 (incl. IS6110)	PSQ
HORITA ET AL (2022)[57]	Systematic Review (and meta-analysis) (unpublished)	NA	NA	NA	NA	Not reported	Not reported	Not reported	NA	NGS
HTIKE ET AL (2014)[58]	Diagnostic test accuracy study	Thailand	Thailand	Unclear / not specified	DR-TB	Custom target panel	PyroMark Q24	rpoB	1	PSQ
ISOLA ET AL (2005)[59]	Diagnostic test accuracy study	Georgia	Italy	Unclear / not specified	TB	Custom target panel	Pyrosequencer PSQ 96	embB	1	PSQ
JOUET ET AL (2021)[60]	Diagnostic test accuracy study	DR Congo (Kayomo); Djibouti (Tagliani); Reference isolate collection	Belgium (Kayomo); Italy (Tagliani); France *	Unclear / not specified	TB and DR-TB	Deeplex Myc-TB	Illumina MiSeq, Illumina NextSeq	rpoB, ahpC, fabG1, katG, inhA, pncA, embB, gyrA, gyrB, rrs, eis, tlyA, gidB, rpsL, ethA, rv0678, rrl, rplC	18	NGS

STUDY	TYPE OF STUDY	COUNTRY OF SPECIMEN	COUNTRY OF SEQUENCING	STUDY SETTING	ENROLLMENT CATEGORY	TB-TNGS	NGS TECHNOLOGY	GENE TARGETS	NUMBER OF TARGETS	PSQ/NGS
JUREEN ET AL (2006)[61]	Diagnostic test accuracy study	Reference isolate collection	Sweden	Unclear / not specified	DR-TB	Custom target panel	Pyrosequencing	rpoB	1	PSQ
KALOKHE ET AL (2013)[62]	Narrative review	NA	NA	NA	NA	Arnold, 2005, PMID: 15679486; Bravo, 2009, PMID: 19846642; Zhao, 2005a, PMID: 15698720; Martilla, 2009, PMID: 18719956; Zhao, 2005b, PMID: 15786899; Jureen, 2006, PMID: 16757581; Halse, 2010, PMID: 20107097	Pyrosequencing	NA	NA	PSQ
KAMBLI ET AL (2021)[63]	Diagnostic test accuracy study	India	India	Hospital and Medical Research Center	TB and DR-TB	Deeplex Myc-TB	Illumina iSeq100	rpoB, ahpC, fabG1, katG, inhA, pncA, embB, gyrA, gyrB, rrs, eis, tlyA, gidB, ethA, rv0678, rrl, rplC, rpsL	18	NGS
KAYOMO ET AL (2020)[64]	Cross-sectional study	DR Congo	Belgium	Research Institute	TB	Deeplex Myc-TB	Illumina MiSeq	rpoB, ahpC, fabG1, katG, inhA, pncA, embB, gyrA, gyrB, rrs, eis, tlyA, gidB, rpsL, ethA, rv0678, rrl, rplC	18	NGS

STUDY	TYPE OF STUDY	COUNTRY OF SPECIMEN	COUNTRY OF SEQUENCING	STUDY SETTING	ENROLLMENT CATEGORY	TB-TNGS	NGS TECHNOLOGY	GENE TARGETS	NUMBER OF TARGETS	PSQ/NGS
KLOTOE ET AL (2018)[65]	Diagnostic test accuracy study	Brazil; Kazakhstan; Spain; Lithuania; Pakistan	France	Unclear / not specified	TB	Custom target panel	NA	embB, gyrA, rrs, eis	4	PSQ
KO ET AL (2019)[66]	Diagnostic test accuracy study	South Korea	South Korea	Research Institute	TB	Ion AmpliSeq TB Research panel	IonS5 XL system	rpoB, katG, inhA, pncA, embB, gyrA, eis, rpsL	8	NGS
KONTSEVAYA ET AL (2011)[67]	Diagnostic test accuracy study	Russia	not reported	Government and Public Health Department	TB	Custom target panel	PyroMarkID	gyrA, gyrB	2	PSQ
KONTSEVAYA ET AL (2023)[68]	Narrative review	NA	NA	NA	NA	Deeplex Myc-TB	Not reported	not mentioned	NA	NGS
KUMAR AND KON (2021)[69]	Narrative review	NA	NA	NA	NA	Deeplex Myc-TB	NA	NA	NA	NGS
LACOMA ET AL (2015)[70]	Diagnostic test accuracy study	Spain; Lithuania	not reported	Unclear / not specified	TB	Custom target panel	PSQ 96MA	embB, gyrA, rrs, eis promoter	4	PSQ
LANGE ET AL (2018)[71]	Narrative review	NA	NA	NA	NA	Ajbani, 2015, PMID: 25367911	Pyrosequencing	NA	NA	PSQ
LEUNG ET AL (2022)[72]	Diagnostic test accuracy study	Hong Kong	Hong Kong	Hospital and Medical Research Center	TB	Custom target panel	Illumina MiSeq	rpoB, katG, inhA, pncA, embB, gyrA, gyrB, rrs, tlyA, rpsL, rrl, rplC, inhA promoter, eis promoter, rpsA, katG-furA, ubiA	17	NGS
LIN AND DESMOND (2014)[73]	Narrative review	NA	NA	NA	TB and DR-TB	pyrosequencing; daum, 2012, pmid: 22972833	Illumina MiSeq, PyroMark	NA	NA	Both
LIN ET AL (2014)[74]	Diagnostic test accuracy study	United States	USA	Government and Public Health Department	NA	Custom target panel	PyroMark Q96 ID	rpoB, katG, gyrA, rrs, inhA promoter, ahpC promoter	6	PSQ

STUDY	TYPE OF STUDY	COUNTRY OF SPECIMEN	COUNTRY OF SEQUENCING	STUDY SETTING	ENROLLMENT CATEGORY	TB-TNGS	NGS TECHNOLOGY	GENE TARGETS	NUMBER OF TARGETS	PSQ/NGS
LIU (2023)[75]	Diagnostic test accuracy study (unpublished)	China *	Not reported	Unclear / not specified	Presumptive TB	Not reported	Not reported	Not reported	NA	NGS
MACLEAN ET AL (2020)[76]	Mini-review	NA	NA	NA	NA	Deeplex Myc-TB; DeepCheck-TB	ONT MinION, Illumina iSeq	NA	NA	NGS
MAKHADO ET AL (2018)[77]	Cross-sectional study	South Africa; eSwatini	Belgium	Government and Public Health Department	TB	Deeplex Myc-TB	Illumina MiSeq	rpoB, ahpC, fabG1, katG, inhA, pncA, embB, gyrA, gyrB, rrs, eis, tlyA, gidB, rpsL, ethA, rv0678, rrl, rplC	18	NGS
MANINGI ET AL (2015)[78]	Diagnostic test accuracy study	South Africa	USA	Research Institute	TB	Custom target panel	IonTorrent PGM	pncA	1	NGS
MANSOOR ET AL (2023)[79]	Diagnostic test accuracy study	India	India	Hospital and Medical Research Center	Presumptive TB	Deeplex Myc-TB	Illumina MiSeq	rpoB, ahpC, fabG1, katG, inhA, pncA, embB, gyrA, gyrB, rrs, eis, tlyA, gidB, rpsL, ethA, rv0678, rrl, rplC	18	NGS
MARINER-LLICER ET AL (2021)[80]	Methodological study	Spain	not reported	Unclear / not specified	TB	Custom target panel	ONT MinION	rpoB, katG, inhA, pncA, embB, gyrA, gyrB, rrs, eis	9	NGS
MARTTILA ET AL (2009)[81]	Diagnostic test accuracy study	Russia; Finland	Finland	Government and Public Health Department	DR-TB	Custom target panel	PSQ 96MA	rpoB, katG	2	PSQ
MESFIN ET AL (2021)[82]	Cross-sectional study	Eritrea	Italy	Government and Public Health Department	TB	Deeplex Myc-TB	Illumina MiniSeq	rpoB, ahpC, fabG1, katG, inhA, pncA, embB, gyrA, gyrB, rrs, eis, tlyA, gidB, rpsL, ethA, rv0678, rrl, rplC	18	NGS

STUDY	TYPE OF STUDY	COUNTRY OF SPECIMEN	COUNTRY OF SEQUENCING	STUDY SETTING	ENROLLMENT CATEGORY	TB-TNGS	NGS TECHNOLOGY	GENE TARGETS	NUMBER OF TARGETS	PSQ/NGS
MESSAH AND PAWITAN (2020)[83]	Narrative review	NA	NA	NA	NA	not reported	IonTorrent PGM (ThermoFisher), Pyrosequencing (Roche 454), ABI SOLiD, Illumina (not further specified), Nanopore sequencing (not further specified)	NA	NA	NGS
METCALF (2022)[84]	Interventional Study (unpublished)	South Africa	South Africa *	Unclear / not specified	TB and DR-TB	not reported	NA	NA	NA	NGS
MOHAMED ET AL (2021)[85]	Editorial	NA	NA	NA	NA	Deeplex Myc-TB; DeepCheck-TB; Clemedi Tuberculini; Next Gen-RDST assay	Illumina (not further specified)	NA	NA	NGS
MUKHERJEE ET AL (2023)[86]	Narrative review	NA	NA	NA	NA	Daum, 2012, PMID: 22972833	ONT MinION	NA	NA	NGS
MURPHY ET AL (2023)[87]	Diagnostic test accuracy study	Not reported	USA	Government and Public Health Department	TB and DR-TB	Custom target panel	ONT MinION, ONT GridION	rpoB, katG, inhA, pncA, embB, gyrA, rrs, rpsL, ethA, eis promoter, embA, embC, mabA-inhA, pncA promoter, mabA, aphC-oxyR	16	NGS

STUDY	TYPE OF STUDY	COUNTRY OF SPECIMEN	COUNTRY OF SEQUENCING	STUDY SETTING	ENROLLMENT CATEGORY	TB-TNGS	NGS TECHNOLOGY	GENE TARGETS	NUMBER OF TARGETS	PSQ/NGS
					NA			rpoB, katG, inhA, ahpC, fabG1, gyrA, gyrB, Rv0678, rplc, rrl, embB, pncA, rrs, rpsl, ethA, eis, gidB, ethA		
NAIDOO ET AL (2023)[88]	Narrative review	NA	NA	NA		Deeplex Myc-TB; Ion Ampliseq TB Research Panel	Not reported		18	NGS
NAMBIAR ET AL (2018)[89]	Diagnostic test accuracy study	India	India	Hospital and Medical Research Center	presumptive DR-TB	Lin, 2014, PMID: 24478476	PyroMark Q96 ID	rpoB, katG, gyrA, rrs, inhA promoter, eis promoter	6	PSQ
NESS ET AL (2022)[90]	Narrative review	NA	NA	NA	NA	Deeplex Myc-TB; Next Gen-RDST assay	ONT MinION, ONT GridION, Illumina MiSeq, Illumina HiSeq, IonTorrent PGM (ThermoFisher), PacBio RSII, Illumina NextSeq, Illumina MiniSeq, Illumina iSeq, Illumina Nova Seq, PromethION (ONT)	NA	NA	NGS
NGUYEN ET AL (2019)[91]	Narrative review	NA	NA	NA	NA	AmpliSEq for Illumina TB Research Panel; Daum, 2012, PMID: 22972833	ONT MinION, IonTorrent PGM (ThermoFisher), PacBio RSII	NA	NA	NGS
NOVAIS AND THORSTENSON ET AL (2011)[92]	Narrative review	NA	NA	NA	NA	Arnold, 2005, PMID: 15679486; Jureen, 2006, PMID: 16757581;	Pyrosequencing (Roche 454), Pyrosequencing (QIAGEN)	NA	NA	PSQ

STUDY	TYPE OF STUDY	COUNTRY OF SPECIMEN	COUNTRY OF SEQUENCING	STUDY SETTING	ENROLLMENT CATEGORY	TB-TNGS	NGS TECHNOLOGY	GENE TARGETS	NUMBER OF TARGETS	PSQ/NGS
						Zhao, 2005a, PMID: 15698720; Zhao, 2005b, PMID: 15786899; Isola, 2005, PMID: 15823399				
PARK ET AL (2018A)[93]	Diagnostic test accuracy study	South Korea	South Korea	Research Institute	TB	Ion AmpliSeq TB Research panel	Ion Torrent PROTON	rpoB, katG, inhA, pncA, embB, gyrA, eis, rpsL	8	NGS
PARK ET AL (2018B)[94]	Diagnostic test accuracy study	South Korea	South Korea	Research Institute	DR-TB	Ion AmpliSeq TB Research panel	Ion Torrent Proton	rpoB, katG, inhA, pncA, embB, gyrA, eis, rpsL	8	NGS
RAHMO ET AL (2012)[95]	Cross-sectional study	Iraq; Lebanon; Syria	not reported	Unclear / not specified	Presumptive TB	Bravo, 2009, PMID: 19846642	PyroMark Q96 ID	rpoB	1	PSQ
RAMASAMY ET AL (2021)[96]	Narrative review	NA	NA	NA	DR-TB	Daum, 2012, PMID: 22972833	ONT MinION, Illumina MiSeq, IonTorrent PGM (ThermoFisher), Illumina iSeq	NA	NA	NGS
RANSOM ET AL (2020)[97]	Narrative review	NA	NA	NA	NA	not reported	ONT MinION, PacBio RSII, Illumina (not further specified)	NA	NA	NGS
RODRIGUES (2019)[98]	Diagnostic test accuracy study (unpublished)	South Africa; India; Georgia	not reported	Unclear / not specified	NA	not reported	NA	NA	NA	NGS
RODRIGUES & SINGHAL (2024)[99]	Narrative review	NA	NA	NA	NA	Deeplex Myc-TB, DeepChek-TB, NanoTB	Not reported	not mentioned	NA	PSQ/NGS
ROWLINSON AND MUSSER (2022)[100]	Narrative review	NA	NA	NA	NA	not reported	Oxford Nanopore and Illumina in general	NA	NA	NGS

STUDY	TYPE OF STUDY	COUNTRY OF SPECIMEN	COUNTRY OF SEQUENCING	STUDY SETTING	ENROLLMENT CATEGORY	TB-TNGS	NGS TECHNOLOGY	GENE TARGETS	NUMBER OF TARGETS	PSQ/NGS
ROWNEKI ET AL (2020)[101]	Methodological study	Ghana; Uganda; Kenya; Zambia	USA	Research Institute	TB	Custom target panel	Illumina MiSeq	rpoB, katG, pncA, embB, gyrA, gyrB, rrs, eis, rpsL, inhA promoter	17	NGS
SCHLANDERER ET AL (2023)[102]	Proof-of-concept (incl. diagnostic test accuracy evaluation)	Nepal	Germany	Research and Development company	TB	Ampliseq for Illumina TB Research Panel	Illumina	rif, inh	2	NGS
SHRESTHA (2007)[103]	Narrative review	NA	NA	NA	NA	Pyrosequencing	PyroMarkTM ID, MicroSeq Microbial Identification System (Applied Biosystems, CA, USA);	NA	NA	PSQ
SIBANDZE ET AL (2022)[104]	Diagnostic test accuracy study	Germany; eSwatini	Germany	Research Institute	TB	Deeplex Myc-TB	Illumina NextSeq 500	rpoB, ahpC, fabG1, katG, inhA, pncA, embB, gyrA, gyrB, rrs, eis, tlyA, gidB, rpsL, ethA, rv0678, rrl, rplC	18	NGS
SODJA ET AL (2019)[105]	Diagnostic test accuracy study	North Macedonia; Slovenia	Slovenia *	Research Institute	TB	Ion AmpliSeq TB Research panel	Ion S5 System, Ion Chef	rpoB, katG, inhA, pncA, embB, gyrA, eis, rpsL	8	NGS
SODJA ET AL (2022)[106]	Diagnostic test accuracy study	North Macedonia; Slovenia	Slovenia *	Research Institute	DR-TB	Ion AmpliSeq TB Research panel	Ion S5 System, Ion Chef	rpoB, katG, inhA, pncA, embB, gyrA, eis, rpsL	8	NGS
SONG ET AL (2022)[107]	Diagnostic test accuracy study	China	China	Hospital and Medical Research Center	DR-TB	Custom target panel	Ion Proton Sequencer	rpoB, katG, inhA, embB, gyrA, gyrB, rrs, tlyA, rpsL, eis promoter, inhA-fabG promoter	11 (9 drugs)	NGS

STUDY	TYPE OF STUDY	COUNTRY OF SPECIMEN	COUNTRY OF SEQUENCING	STUDY SETTING	ENROLLMENT CATEGORY	TB-TNGS	NGS TECHNOLOGY	GENE TARGETS	NUMBER OF TARGETS	PSQ/NGS
SYAFIRA ET AL (2020)[108]	Diagnostic test accuracy study	Indonesia	Indonesia *	Research Institute	DR-TB	not reported	PyroMark 48 Autoprep	rpoB, katG, gyrA, rrs, inhA promoter, eis promoter	7	PSQ
TAFESS ET AL (2020)[109]	Diagnostic test accuracy study	Ethiopia; Hong Kong	Hong Kong	Research Institute	TB	Custom target panel	ONT MinION, Illumina MiSeq	rpoB, katG, pncA, embB, gyrA, gyrB, rrs, eis, tlyA, rpsL, rv0678, rrl, rplC, rpsA, ubiA, atpE, mabA-inhA, whiB7, furA-katG	19	NGS
TAGLIANI ET AL (2017)[110]	Cross-sectional study	Djibouti	Italy	Government and Public Health Department	TB	Deeplex Myc-TB	Illumina MiniSeq	rpoB, ahpC, fabG1, katG, inhA, pncA, embB, gyrA, gyrB, rrs, eis, tlyA, gidB, rpsL, ethA, rv0678, rrl, rplC	18	NGS
TORRES ET AL (2015)[111]	Cross-sectional study	South Africa; Moldova; India; Philippines	USA	Research Institute	DR-TB	Custom target panel	PyroMark Q96 ID	katG, inhA	2	PSQ
WANG ET AL (2019)[112]	Diagnostic test accuracy study	Botswana	not reported	Unclear / not specified	TB	Next Gen-RDST assay	Illumina MiSeq	rpoB, katG, inhA promoter	3	NGS
WHITFIELD ET AL (2022)[113]	Diagnostic test accuracy study	South Africa	not reported	Unclear / not specified	DR-TB	Next Gen-RDST assay	Illumina MiSeq	pncA, pncA promoter	4 amplicons (1 drug)	NGS

STUDY	TYPE OF STUDY	COUNTRY OF SPECIMEN	COUNTRY OF SEQUENCING	STUDY SETTING	ENROLLMENT CATEGORY	TB-TNGS	NGS TECHNOLOGY	GENE TARGETS	NUMBER OF TARGETS	PSQ/NGS
WORLD HEALTH ORGANIZATION (2018)[114]	Technical Guide	NA	NA	NA	NA	Deeplex Myc-TB; Next Gen-RDST assay	ONT MinION, ONT GridION, Illumina MiSeq, Illumina HiSeq, IonTorrent PGM (ThermoFisher), PacBio RSII, Illumina NextSeq, Illumina MiniSeq, Proton (Thermo Fisher), Illumina Nova Seq, Sequel (Pacific Biosciences), PromethION (ONT), GeneReader NGS System	NA	NA	NGS
				NA						
WORLD HEALTH ORGANISATION (2023)[115]	Rapid communication	NA	NA	NA		Deeplex Myc-TB, NanoTB , TBseq	Not reported	no specified	NA	NGS
WU ET AL (2022)[116]	Diagnostic test accuracy study	Archive collection	Taiwan	Government and Public Health Department		Custom target panel	Ion GeneStudio S5 Prime	rpoB, katG, fabG1, inhA, embB, pncA, gyrA, gyrB, rrs, eis, rpsL, atpE, Rv0678, pepQ, Rv1979c, rrl, rplC, ddn, fgd1, fbiA, fbiB, fbiC	22	NGS

31

STUDY	TYPE OF STUDY	COUNTRY OF SPECIMEN	COUNTRY OF SEQUENCING	STUDY SETTING	ENROLLMENT CATEGORY	TB-TNGS	NGS TECHNOLOGY	GENE TARGETS	NUMBER OF TARGETS	PSQ/NGS
					TB					
WU ET AL (2023)[117]	Diagnostic test accuracy study	China	China	Unclear / not specified		Hugobiotech. Co., Ltd. (Beijing, China)	Not reported	rpoB, katG, inhA	3	NGS
ZHANG ET AL (2015)[118]	Diagnostic test accuracy study	China	China *	Government and Public Health Department	TB	Custom target panel	PyroMark Q96 ID	embB	1	PSQ
ZHANG (2018)[119]	Interventional Study (unpublished)	China	not reported	Unclear / not specified	TB and DR-TB	not reported	NA	NA	NA	NGS
ZHANG ET AL (2023)[120]	Diagnostic test accuracy study	China	China	Hospital and Medical Research Center	Presumptive TB	Hugobiotech. Co., Ltd. (Beijing, China)	Not reported	rpoB, katG, inhA, ethA, rpsL, embB, thyA, rpoB, gyrA, rrs	10	NGS
ZHAO ET AL (2005)[121]	Diagnostic test accuracy study	China	China	Hospital and Medical Research Center	TB and DR-TB	Custom target panel	Pyrosequencer PSQ 96	rpoB	1	PSQ
ZHAO ET AL (2005)[122]	Methodological study	China	China *	Unclear / not specified	TB	Custom target panel	Pyrosequencer PSQ 96	rpoB, katG, embB	3	PSQ
ZHAO ET AL (2022)[123]	Methodological study	China	China	Research Institute	TB	Custom target panel	ONT GridION	rpoB, katG, inhA, gyrA, gyrB, rrs, eis	7	NGS
ZHENG ET AL (2014)[124]	Diagnostic test accuracy study	China	China	Unclear / not specified	TB	Custom target panel	PyroMark 96MA	rpoB, katG, embB, gyrA, rrs, rpsL	6	PSQ
ZHENG ET AL (2023)[125]	Diagnostic test accuracy study	China	China	Hospital and Medical Research Center	Presumptive TB	Hugobiotech. Co., Ltd. (Beijing, China)	Illumina NextSeq	Not reported	NA	NGS
ZIGNOL ET AL (2016)[126]	Cross-sectional study	South Africa; Pakistan; Bangladesh;	Unclear	Government and Public Health Department	TB and DR-TB	not reported	Illumina MiSeq, Illumina HiSeq, IonTorrent PGM	pncA, pncA promoter	2	NGS

STUDY	TYPE OF STUDY	COUNTRY OF SPECIMEN	COUNTRY OF SEQUENCING	STUDY SETTING	ENROLLMENT CATEGORY	TB-TNGS	NGS TECHNOLOGY	GENE TARGETS	NUMBER OF TARGETS	PSQ/NGS
		Azerbaijan; Belarus								

Supplementary Table 3: Types of samples used for tuberculosis drug resistance testing using targeted next-generation sequencing (TB-tNGS) in studies included in meta-analysis.

Sample type used for TB-tNGS	Sample category	No. sample sets
Culture isolates	Culture isolates	12
Culture isolates and reference isolates	Culture isolates	2
Reference isolates	Culture isolates	2
Clinical samples	Primary samples	3
Formalin-fixed and paraffin-embedded (FFPE) tissues	Primary samples	1
Unprocessed sputum	Primary samples	4
Decontaminated sputum	Primary samples	3
Stool	Primary samples	2
Sputum and culture isolates	Combined	1

Supplementary Table 4: Study characteristics of the 24 studies included in the meta-analysis. **TB-tNGS** – tuberculosis drug resistance prediction using targeted Next-Generation Sequencing; **No. recruited** – number of patients or samples selected and recruited for study; **no. included** – number of samples included in contingency table; **rob_patient** – risk of bias assessment for patient selection; **app_patient** – applicability concerns for patient selection; **rob_index** – risk of bias assessment for index test; **app_index** – applicability concerns for index test; **rob_ref** – risk of bias assessment for reference test; **app_rob** – applicability concerns for reference test; **rob_flow** – risk of bias assessment for flow and timing; **rob_total** – combined risk of bias assessment across patient selection, index test and flow and timing domain; **L** – low risk of bias; **H** – high risk of bias; **U** – unclear risk of bias.

Study	Sample set	Sample category	Sample type	TB-tNGS	Reference test	TB drug or drug group	No. Recruited	True positives	False negatives	False positives	True negatives	No. Included	Sensitivity [95% confidence interval]	Specificity [95% confidence interval]	rob_patient	app_patient	rob_index	app_index	rob_ref	app_ref	rob_flow	rob_total
Barboza-Amezcua et al (2022)[10]	2	Direct	Sputum	Custom Panel (Illumina)	pDST (MGIT 960)	CAP	46	0	1	0	10	11	0.00 [0.00,0.79]	1.00 [0.72,1.00]	L	L	L	L	L	L	H	H
Barboza-Amezcua et al (2022)[10]	2	Direct	Sputum	Custom Panel (Illumina)	pDST (MGIT 960)	MFX	46	3	1	0	7	11	0.75 [0.30,0.95]	1.00 [0.65,1.00]	L	L	L	L	L	L	H	H
Barboza-Amezcua et al (2022)[10]	2	Direct	Sputum	Custom Panel (Illumina)	pDST (MGIT 960)	ETH+PTH	46	3	4	0	11	18	0.43 [0.16,0.75]	1.00 [0.74,1.00]	L	L	L	L	L	L	H	H
Barboza-Amezcua et al (2022)[10]	2	Direct	Sputum	Custom Panel (Illumina)	pDST (MGIT 960)	OFX+LFX	46	3	1	0	14	18	0.75 [0.30,0.95]	1.00 [0.78,1.00]	L	L	L	L	L	L	H	H
Barboza-Amezcua et al (2022)[10]	2	Direct	Sputum	Custom Panel (Illumina)	pDST (MGIT 960)	AMK	46	0	1	0	18	19	0.00 [0.00,0.79]	1.00 [0.82,1.00]	L	L	L	L	L	L	H	H
Barboza-Amezcua et al (2022)[10]	2	Direct	Sputum	Custom Panel (Illumina)	pDST (MGIT 960)	KAN	46	0	1	0	18	19	0.00 [0.00,0.79]	1.00 [0.82,1.00]	L	L	L	L	L	L	H	H
Barboza-Amezcua et al (2022)[10]	2	Direct	Sputum	Custom Panel (Illumina)	pDST (MGIT 960)	RIF	46	20	0	1	10	31	1.00 [0.84,1.00]	0.91 [0.62,0.98]	L	L	L	L	L	L	L	L
Barboza-Amezcua et al (2022)[10]	2	Direct	Sputum	Custom Panel (Illumina)	pDST (MGIT 960)	INH	46	10	2	0	19	31	0.83 [0.55,0.95]	1.00 [0.83,1.00]	L	L	L	L	L	L	L	L
Barboza-Amezcua et al (2022)[10]	2	Direct	Sputum	Custom Panel (Illumina)	pDST (MGIT 960)	STM	46	3	3	0	25	31	0.50 [0.19,0.81]	1.00 [0.87,1.00]	L	L	L	L	L	L	L	L
Barboza-Amezcua et al (2022)[10]	2	Direct	Sputum	Custom Panel (Illumina)	pDST (MGIT 960)	EMB	46	5	0	3	23	31	1.00 [0.57,1.00]	0.88 [0.71,0.96]	L	L	L	L	L	H	L	L
Barboza-Amezcua et al (2022)[10]	2	Direct	Sputum	Custom Panel (Illumina)	pDST (MGIT 960)	PZA	46	5	0	2	24	31	1.00 [0.57,1.00]	0.92 [0.76,0.98]	L	L	L	L	L	H	L	L
Barboza-Amezcua et al (2022)[10]	1	Indirect	Reference isolates	Custom Panel (Illumina)	pDST (MGIT 960)	AMK+KAN+CAP	20	7	0	0	13	20	1.00 [0.65,1.00]	1.00 [0.77,1.00]	U	L	L	L	L	L	L	L
Barboza-Amezcua et al (2022)[10]	1	Indirect	Reference isolates	Custom Panel (Illumina)	pDST (MGIT 960)	ETH+PTH	20	3	0	0	17	20	1.00 [0.44,1.00]	1.00 [0.82,1.00]	U	L	L	L	L	L	L	L
Barboza-Amezcua et al (2022)[10]	1	Indirect	Reference isolates	Custom Panel (Illumina)	pDST (MGIT 960)	FQ	20	7	0	0	13	20	1.00 [0.65,1.00]	1.00 [0.77,1.00]	U	L	L	L	L	L	L	L
Barboza-Amezcua et al (2022)[10]	1	Indirect	Reference isolates	Custom Panel (Illumina)	pDST (MGIT 960)	INH	20	13	1	0	6	20	0.93 [0.69,0.99]	1.00 [0.61,1.00]	U	L	L	L	L	L	L	L
Barboza-Amezcua et al (2022)[10]	1	Indirect	Reference isolates	Custom Panel (Illumina)	pDST (MGIT 960)	STM	20	9	0	0	11	20	1.00 [0.70,1.00]	1.00 [0.74,1.00]	U	L	L	L	L	L	L	L
Barboza-Amezcua et al (2022)[10]	1	Indirect	Reference isolates	Custom Panel (Illumina)	pDST (MGIT 960)	RIF	20	13	0	0	7	20	1.00 [0.77,1.00]	1.00 [0.65,1.00]	U	L	L	L	L	L	L	L
Barboza-Amezcua et al (2022)[10]	1	Indirect	Reference isolates	Custom Panel (Illumina)	pDST (MGIT 960)	EMB	20	11	0	0	9	20	1.00 [0.74,1.00]	1.00 [0.70,1.00]	U	L	L	L	L	L	H	L
Barboza-Amezcua et al (2022)[10]	1	Indirect	Reference isolates	Custom Panel (Illumina)	pDST (MGIT 960)	PZA	20	9	0	0	11	20	1.00 [0.70,1.00]	1.00 [0.74,1.00]	U	L	L	L	L	L	H	L
Bonnet et al (2021)[11]	1	Combined	Clinical samples; Culture isolates	Deeplex MycTB	pDST (LJ)	INH	140	96	2	0	26	124	0.98 [0.93,0.99]	1.00 [0.87,1.00]	L	H	L	L	L	L	L	L
Bonnet et al (2021)[11]	1	Indirect	Culture isolates	Deeplex MycTB	pDST (LJ)	RIF	94	54	0	0	28	82	1.00 [0.93,1.00]	1.00 [0.88,1.00]	L	H	L	L	L	L	L	L
Bonnet et al (2021)[11]	1	Direct	Clinical samples	Deeplex MycTB	pDST (LJ)	RIF	46	24	0	0	13	37	1.00 [0.86,1.00]	1.00 [0.77,1.00]	L	H	L	L	L	L	L	L
Colman et al (2016)[26]	1	Direct	Sputum	Next Gen-RDST Assay	pDST (MGIT 960)	AMK	254	4	5	3	154	166	0.44 [0.19,0.73]	0.98 [0.95,0.99]	L	L	L	L	L	L	L	L
Colman et al (2016)[26]	1	Direct	Sputum	Next Gen-RDST Assay	pDST (MGIT 960)	CAP	254	3	4	2	157	166	0.43 [0.16,0.75]	0.99 [0.96,1.00]	L	L	L	L	L	L	L	L
Colman et al (2016)[26]	1	Direct	Sputum	Next Gen-RDST Assay	pDST (MGIT 960)	KAN	254	50	2	7	107	166	0.96 [0.87,0.99]	0.94 [0.88,0.97]	L	L	L	L	L	L	L	L
Colman et al (2016)[26]	1	Direct	Sputum	Next Gen-RDST Assay	pDST (MGIT 960)	INH	254	95	5	0	71	171	0.95 [0.89,0.98]	1.00 [0.95,1.00]	L	L	L	L	L	L	L	L
Colman et al (2016)[26]	1	Direct	Sputum	Next Gen-RDST Assay	pDST (MGIT 960)	RIF	254	81	2	1	88	172	0.98 [0.92,0.99]	0.99 [0.94,1.00]	L	L	L	L	L	L	L	L
Colman et al (2016)[26]	1	Direct	Sputum	Next Gen-RDST Assay	pDST (MGIT 960)	MFX	254	13	2	0	157	172	0.87 [0.62,0.96]	1.00 [0.98,1.00]	L	L	L	L	L	L	L	L
Colman et al (2016)[26]	1	Direct	Sputum	Next Gen-RDST Assay	pDST (MGIT 960)	OFX	254	12	2	1	157	172	0.86 [0.60,0.96]	0.99 [0.97,1.00]	L	L	L	L	L	L	L	L
Daum et al (2012)[29]	1	Indirect	Culture isolates	Custom Panel (Ion Torrent)	pDST (MGIT 960)	FQ	26	10	0	0	16	26	1.00 [0.72,1.00]	1.00 [0.81,1.00]	L	L	H	L	L	L	L	H
Daum et al (2012)[29]	1	Indirect	Culture isolates	Custom Panel (Ion Torrent)	pDST (MGIT 960)	INH	26	16	0	0	10	26	1.00 [0.81,1.00]	1.00 [0.72,1.00]	L	L	H	L	L	L	L	H
Daum et al (2012)[29]	1	Indirect	Culture isolates	Custom Panel (Ion Torrent)	pDST (MGIT 960)	KAN	26	7	0	0	19	26	1.00 [0.65,1.00]	1.00 [0.83,1.00]	L	L	H	L	L	L	L	H
Daum et al (2012)[29]	1	Indirect	Culture isolates	Custom Panel (Ion Torrent)	pDST (MGIT 960)	RIF	26	21	0	0	5	26	1.00 [0.85,1.00]	1.00 [0.57,1.00]	L	L	H	L	L	L	L	H
Daum et al (2012)[29]	1	Indirect	Culture isolates	Custom Panel (Ion Torrent)	pDST (MGIT 960)	PZA	26	9	0	0	17	26	1.00 [0.70,1.00]	1.00 [0.82,1.00]	L	L	H	L	L	H	L	H
Feuerriegel et al (2021)[40]	1	Direct	Clinical samples	Deeplex MycTB	pDST (not further specified)	BDQ+CFZ	50	0	0	0	2	2	NaN [NaN,NaN]	1.00 [0.34,1.00]	H	L	L	L	L	L	H	H
Feuerriegel et al (2021)[40]	1	Direct	Clinical samples	Deeplex MycTB	pDST (not further specified)	LZD	50	0	0	0	2	2	NaN [NaN,NaN]	1.00 [0.34,1.00]	H	L	L	L	L	L	H	H
Feuerriegel et al (2021)[40]	1	Direct	Clinical samples	Deeplex MycTB	pDST (not further specified)	KAN	50	0	0	0	4	4	NaN [NaN,NaN]	1.00 [0.51,1.00]	H	L	L	L	L	L	H	H
Feuerriegel et al (2021)[40]	1	Direct	Clinical samples	Deeplex MycTB	pDST (not further specified)	CAP	50	0	0	0	5	5	NaN [NaN,NaN]	1.00 [0.57,1.00]	H	L	L	L	L	L	H	H
Feuerriegel et al (2021)[40]	1	Direct	Clinical samples	Deeplex MycTB	pDST (not further specified)	ETH+PTH	50	3	2	0	3	8	0.60 [0.23,0.88]	1.00 [0.44,1.00]	H	L	L	L	L	L	H	H
Feuerriegel et al (2021)[40]	1	Direct	Clinical samples	Deeplex MycTB	pDST (not further specified)	AMK+KAN+CAP	50	1	0	0	7	8	1.00 [0.21,1.00]	1.00 [0.65,1.00]	H	L	L	L	L	L	H	H
Feuerriegel et al (2021)[40]	1	Direct	Clinical samples	Deeplex MycTB	pDST (not further specified)	FQ	50	0	0	4	8	12	NaN [NaN,NaN]	0.67 [0.39,0.86]	H	L	L	L	L	L	H	H
Feuerriegel et al (2021)[40]	1	Direct	Clinical samples	Deeplex MycTB	pDST (not further specified)	RIF	50	7	0	1	31	39	1.00 [0.65,1.00]	0.97 [0.84,0.99]	H	L	L	L	L	L	L	L
Feuerriegel et al (2021)[40]	1	Direct	Clinical samples	Deeplex MycTB	pDST (not further specified)	INH	50	7	1	1	30	39	0.88 [0.53,0.98]	0.97 [0.84,0.99]	H	L	L	L	L	L	L	L
Feuerriegel et al (2021)[40]	1	Direct	Clinical samples	Deeplex MycTB	pDST (not further specified)	EMB	50	3	0	1	35	39	1.00 [0.44,1.00]	0.97 [0.86,1.00]	H	L	L	L	L	H	L	L
Feuerriegel et al (2021)[40]	1	Direct	Clinical samples	Deeplex MycTB	pDST (not further specified)	PZA	50	4	0	1	34	39	1.00 [0.51,1.00]	0.97 [0.85,0.99]	H	L	L	L	L	H	L	L
Gliddon et al (2021)[49]	1	Indirect	Culture isolates	Custom Panel (MinION)	pDST (MGIT)	INH	29	25	0	0	4	29	1.00 [0.87,1.00]	1.00 [0.51,1.00]	U	H	L	L	L	L	L	L

Study	Sample set	Sample category	Sample type	TB-tNGS	Reference test	TB drug or drug group	No. Recruited	True positives	False negatives	False positives	True negatives	No. Included	Sensitivity [95% confidence interval]	Specificity [95% confidence interval]	rob_patient	app_patient	rob_index	app_index	rob_ref	app_ref	rob_flow	rob_total
Gliddon et al (2021)[49]	1	Indirect	Culture isolates	Custom Panel (MinION)	pDST (MGIT)	RIF	29	26	1	0	2	29	0.96 [0.82,0.99]	1.00 [0.34,1.00]	U	H	L	L	L	L	L	L
Jouet et al (2021)[60]	1	Indirect	Reference isolates	Deeplex MycTB	pDST (MGIT 460)	LZD	429	0	0	0	20	20	NaN [NaN,NaN]	1.00 [0.84,1.00]	H	L	L	L	L	L	H	H
Jouet et al (2021)[60]	1	Indirect	Reference isolates	Deeplex MycTB	pDST (Middlebrook 7H11) + MGIT 460	AMK	429	9	0	0	54	63	1.00 [0.70,1.00]	1.00 [0.93,1.00]	H	L	L	L	L	L	H	H
Jouet et al (2021)[60]	1	Indirect	Reference isolates	Deeplex MycTB	pDST (Middlebrook 7H11) + MGIT 460	KAN	429	8	1	0	72	81	0.89 [0.57,0.98]	1.00 [0.95,1.00]	H	L	L	L	L	L	H	H
Jouet et al (2021)[60]	1	Indirect	Reference isolates	Deeplex MycTB	pDST (Middlebrook 7H11) + MGIT 460	ETH	429	25	2	33	70	130	0.93 [0.77,0.98]	0.68 [0.58,0.76]	H	L	L	L	L	L	H	H
Jouet et al (2021)[60]	1	Indirect	Reference isolates	Deeplex MycTB	pDST (Middlebrook 7H11) + MGIT 460	CAP	429	15	1	3	112	131	0.94 [0.72,0.99]	0.97 [0.93,0.99]	H	L	L	L	L	L	H	H
Jouet et al (2021)[60]	1	Indirect	Reference isolates	Deeplex MycTB	pDST (Middlebrook 7H11) + MGIT 460	FQ	429	22	2	1	120	145	0.92 [0.74,0.98]	0.99 [0.95,1.00]	H	L	L	L	L	L	H	H
Jouet et al (2021)[60]	1	Indirect	Reference isolates	Deeplex MycTB	pDST (LJ) + MGIT 960	STM	429	49	5	1	91	146	0.91 [0.80,0.96]	0.99 [0.94,1.00]	H	L	L	L	L	L	H	H
Jouet et al (2021)[60]	1	Indirect	Reference isolates	Deeplex MycTB	pDST (LJ) + MGIT 960	PZA	429	42	7	0	135	184	0.86 [0.73,0.93]	1.00 [0.97,1.00]	H	L	L	L	H	L	H	H
Jouet et al (2021)[60]	1	Indirect	Reference isolates	Deeplex MycTB	pDST (LJ) + MGIT 960	INH	429	176	3	3	190	372	0.98 [0.95,0.99]	0.98 [0.96,0.99]	H	L	L	L	L	L	L	L
Jouet et al (2021)[60]	2	Direct	Sputum	Deeplex MycTB	Illumina+MTBSeq	STM	109	14	0	4	35	53	1.00 [0.78,1.00]	0.90 [0.76,0.96]	L	L	L	L	L	L	H	H
Jouet et al (2021)[60]	2	Direct	Sputum	Deeplex MycTB	Illumina+MTBSeq	CAP	109	12	0	0	59	71	1.00 [0.76,1.00]	1.00 [0.94,1.00]	L	L	L	L	L	L	L	L
Jouet et al (2021)[60]	2	Direct	Sputum	Deeplex MycTB	Illumina+MTBSeq	KAN	109	5	0	0	66	71	1.00 [0.57,1.00]	1.00 [0.94,1.00]	L	L	L	L	L	L	L	L
Jouet et al (2021)[60]	2	Direct	Sputum	Deeplex MycTB	Illumina+MTBSeq	AMK	109	5	0	0	67	72	1.00 [0.57,1.00]	1.00 [0.95,1.00]	L	L	L	L	L	L	L	L
Jouet et al (2021)[60]	2	Direct	Sputum	Deeplex MycTB	Illumina+MTBSeq	ETH	109	7	0	1	66	74	1.00 [0.65,1.00]	0.99 [0.92,1.00]	L	L	L	L	L	L	L	L
Jouet et al (2021)[60]	1	Indirect	Reference isolates	Deeplex MycTB	pDST (LJ) + MGIT 960	RIF	429	159	1	3	241	404	0.99 [0.97,1.00]	0.99 [0.96,1.00]	H	L	L	L	L	L	L	H
Jouet et al (2021)[60]	1	Indirect	Reference isolates	Deeplex MycTB	pDST (LJ) + MGIT 960	EMB	429	95	8	28	273	404	0.92 [0.85,0.96]	0.91 [0.87,0.93]	H	L	L	L	H	L	L	H
Jouet et al (2021)[60]	2	Direct	Sputum	Deeplex MycTB	Illumina+MTBSeq	LZD	109	0	0	0	87	87	NaN [NaN,NaN]	1.00 [0.96,1.00]	L	L	L	L	L	L	L	L
Jouet et al (2021)[60]	2	Direct	Sputum	Deeplex MycTB	Illumina+MTBSeq	BDQ	109	0	0	0	99	99	NaN [NaN,NaN]	1.00 [0.96,1.00]	L	L	L	L	L	L	L	L
Jouet et al (2021)[60]	2	Direct	Sputum	Deeplex MycTB	Illumina+MTBSeq	CFZ	109	0	0	0	99	99	NaN [NaN,NaN]	1.00 [0.96,1.00]	L	L	L	L	L	L	L	L
Jouet et al (2021)[60]	2	Direct	Sputum	Deeplex MycTB	Illumina+MTBSeq	INH	109	31	0	2	71	104	1.00 [0.89,1.00]	0.97 [0.91,0.99]	L	L	L	L	L	L	L	L
Jouet et al (2021)[60]	2	Direct	Sputum	Deeplex MycTB	Illumina+MTBSeq	PZA	109	20	8	3	73	104	0.71 [0.53,0.85]	0.96 [0.89,0.99]	L	L	L	L	L	L	L	L
Jouet et al (2021)[60]	2	Direct	Sputum	Deeplex MycTB	Illumina+MTBSeq	EMB	109	22	0	4	79	105	1.00 [0.85,1.00]	0.95 [0.88,0.98]	L	L	L	L	L	L	L	L
Jouet et al (2021)[60]	2	Direct	Sputum	Deeplex MycTB	Illumina+MTBSeq	FQ	109	0	0	1	104	105	NaN [NaN,NaN]	0.99 [0.95,1.00]	L	L	L	L	L	L	L	L
Jouet et al (2021)[60]	2	Direct	Sputum	Deeplex MycTB	Illumina+MTBSeq	RIF	109	29	2	0	75	106	0.94 [0.79,0.98]	1.00 [0.95,1.00]	L	L	L	L	L	L	L	L
Kambli et al (2021)[63]	1	Indirect	Culture isolates	Deeplex MycTB	pDST (MGIT 960)	INH	40	29	0	0	2	31	1.00 [0.88,1.00]	1.00 [0.34,1.00]	L	H	L	L	L	L	L	L
Kambli et al (2021)[63]	2	Direct	Sediment	Deeplex MycTB	pDST (MGIT 960)	INH	40	29	0	0	2	31	1.00 [0.88,1.00]	1.00 [0.34,1.00]	L	H	L	L	L	L	L	L
Kambli et al (2021)[63]	1	Indirect	Culture isolates	Deeplex MycTB	pDST (inhouse)	AMK	40	0	0	0	33	33	NaN [NaN,NaN]	1.00 [0.90,1.00]	L	H	L	L	L	L	L	L
Kambli et al (2021)[63]	1	Indirect	Culture isolates	Deeplex MycTB	pDST (inhouse)	CAP	40	1	0	0	32	33	1.00 [0.21,1.00]	1.00 [0.89,1.00]	L	H	L	L	L	L	L	L
Kambli et al (2021)[63]	1	Indirect	Culture isolates	Deeplex MycTB	pDST (inhouse)	KAN	40	4	0	0	29	33	1.00 [0.51,1.00]	1.00 [0.88,1.00]	L	H	L	L	L	L	L	L
Kambli et al (2021)[63]	2	Direct	Sediment	Deeplex MycTB	pDST (inhouse)	AMK	40	0	0	0	33	33	NaN [NaN,NaN]	1.00 [0.90,1.00]	L	H	L	L	L	L	L	L
Kambli et al (2021)[63]	2	Direct	Sediment	Deeplex MycTB	pDST (inhouse)	CAP	40	1	0	0	32	33	1.00 [0.21,1.00]	1.00 [0.89,1.00]	L	H	L	L	L	L	L	L
Kambli et al (2021)[63]	2	Direct	Sediment	Deeplex MycTB	pDST (inhouse)	KAN	40	4	0	0	29	33	1.00 [0.51,1.00]	1.00 [0.88,1.00]	L	H	L	L	L	L	L	L
Kambli et al (2021)[63]	1	Indirect	Culture isolates	Deeplex MycTB	pDST (MGIT 960)	RIF	40	31	0	0	6	37	1.00 [0.89,1.00]	1.00 [0.61,1.00]	L	H	L	L	L	L	L	L
Kambli et al (2021)[63]	2	Direct	Sediment	Deeplex MycTB	pDST (MGIT 960)	RIF	40	31	0	0	6	37	1.00 [0.89,1.00]	1.00 [0.61,1.00]	L	H	L	L	L	L	L	L
Kambli et al (2021)[63]	1	Indirect	Culture isolates	Deeplex MycTB	pDST (inhouse)	FQ	40	21	1	0	17	39	0.95 [0.78,0.99]	1.00 [0.82,1.00]	L	H	L	L	L	L	L	L
Kambli et al (2021)[63]	2	Direct	Sediment	Deeplex MycTB	pDST (inhouse)	FQ	40	21	1	0	17	39	0.95 [0.78,0.99]	1.00 [0.82,1.00]	L	H	L	L	L	L	L	L
Ko et al (2019)[66]	1	Indirect	Culture isolates	Ion Ampliseq TB Research Panel	Pyrazinamidase activity test	PZA	36	4	4	0	28	36	0.50 [0.22,0.78]	1.00 [0.88,1.00]	H	H	H	L	H	L	L	H
Ko et al (2019)[66]	1	Indirect	Culture isolates	Ion Ampliseq TB Research Panel	pDST (LJ absolute conc.)	FQ	36	4	2	0	30	36	0.67 [0.30,0.90]	1.00 [0.89,1.00]	H	H	H	L	L	L	L	H
Ko et al (2019)[66]	1	Indirect	Culture isolates	Ion Ampliseq TB Research Panel	pDST (LJ absolute conc.)	INH	36	12	3	0	21	36	0.80 [0.55,0.93]	1.00 [0.85,1.00]	H	H	H	L	L	L	L	H
Ko et al (2019)[66]	1	Indirect	Culture isolates	Ion Ampliseq TB Research Panel	pDST (LJ absolute conc.)	STM	36	4	6	0	26	36	0.40 [0.17,0.69]	1.00 [0.87,1.00]	H	H	H	L	L	L	L	H
Ko et al (2019)[66]	1	Indirect	Culture isolates	Ion Ampliseq TB Research Panel	pDST (LJ absolute conc.)	AMK+KAN	36	0	2	0	34	36	0.00 [0.00,0.66]	1.00 [0.90,1.00]	H	H	H	L	L	L	L	H
Ko et al (2019)[66]	1	Indirect	Culture isolates	Ion Ampliseq TB Research Panel	pDST (LJ absolute conc.)	RIF	36	11	0	0	25	36	1.00 [0.74,1.00]	1.00 [0.87,1.00]	H	H	H	L	L	L	L	H
Ko et al (2019)[66]	1	Indirect	Culture isolates	Ion Ampliseq TB Research Panel	pDST (LJ absolute conc.)	EMB	36	7	0	1	28	36	1.00 [0.65,1.00]	0.97 [0.83,0.99]	H	H	H	L	H	L	L	H
Leung et al (2022)[72]	1	Direct	Sediment	Custom Panel (Illumina)	pDST (MGIT 960)	RIF	92	12	0	2	48	62	1.00 [0.76,1.00]	0.96 [0.87,0.99]	H	H	L	L	L	L	L	L
Leung et al (2022)[72]	1	Direct	Sediment	Custom Panel (Illumina)	pDST (MGIT 960)	INH	92	17	0	0	45	62	1.00 [0.82,1.00]	1.00 [0.92,1.00]	H	H	L	L	L	L	L	L
Maningi et al (2015)[77]	1	Indirect	Culture isolates	Custom Panel (Ion Torrent)	pDST (MGIT 960)	PZA	179	27	2	6	53	88	0.93 [0.78,0.98]	0.90 [0.80,0.95]	L	H	H	L	H	L	H	H
Mansoor et al (2023)[79]	1	Combined	Sputum; Culture isolates	Deeplex MycTB	pDST (MGIT)	ETH	161	49	16	3	64	132	0.75 [0.64,0.84]	0.96 [0.88,0.98]	U	H	L	L	L	L	L	L
Mansoor et al (2023)[79]	1	Combined	Sputum; Culture isolates	Deeplex MycTB	pDST (MGIT)	EMB	161	89	0	19	25	133	1.00 [0.96,1.00]	0.57 [0.42,0.70]	U	H	L	L	H	L	L	H
Mansoor et al (2023)[79]	1	Combined	Sputum; Culture isolates	Deeplex MycTB	pDST (MGIT)	CAP	161	8	5	8	119	140	0.62 [0.36,0.82]	0.94 [0.88,0.97]	U	H	L	L	L	L	L	L
Mansoor et al (2023)[79]	1	Combined	Sputum; Culture isolates	Deeplex MycTB	pDST (MGIT)	KAN	161	19	11	3	109	142	0.63 [0.46,0.78]	0.97 [0.92,0.99]	U	H	L	L	L	L	L	L
Mansoor et al (2023)[79]	1	Combined	Sputum; Culture isolates	Deeplex MycTB	pDST (MGIT)	PZA	161	90	12	2	40	144	0.88 [0.81,0.93]	0.95 [0.84,0.99]	U	H	L	L	L	L	H	L
Mansoor et al (2023)[79]	1	Combined	Sputum; Culture isolates	Deeplex MycTB	pDST (MGIT)	AMK	161	14	2	0	129	145	0.88 [0.64,0.97]	1.00 [0.97,1.00]	U	H	L	L	L	L	L	L
Mansoor et al (2023)[79]	1	Combined	Sputum; Culture isolates	Deeplex MycTB	pDST (MGIT)	CFZ	161	2	4	6	134	146	0.33 [0.10,0.70]	0.96 [0.91,0.98]	U	H	L	L	L	L	L	L
Mansoor et al (2023)[79]	1	Combined	Sputum; Culture isolates	Deeplex MycTB	pDST (MGIT)	STM	161	110	2	3	31	146	0.98 [0.94,1.00]	0.91 [0.77,0.97]	U	H	L	L	L	L	L	L
Mansoor et al (2023)[79]	1	Combined	Sputum; Culture isolates	Deeplex MycTB	pDST (MGIT)	INH	161	130	1	1	15	147	0.99 [0.96,1.00]	0.94 [0.72,0.99]	U	H	L	L	L	L	L	L
Mansoor et al (2023)[79]	1	Combined	Sputum; Culture isolates	Deeplex MycTB	pDST (MGIT)	LZD	161	2	2	0	143	147	0.50 [0.15,0.85]	1.00 [0.96,1.00]	U	H	L	L	L	L	L	L
Mansoor et al (2023)[79]	1	Combined	Sputum; Culture isolates	Deeplex MycTB	pDST (MGIT)	RIF	161	123	0	11	14	148	1.00 [0.97,1.00]	0.56 [0.37,0.73]	U	H	L	L	L	L	L	L
Mansoor et al (2023)[79]	1	Combined	Sputum; Culture isolates	Deeplex MycTB	pDST (MGIT)	FQ	161	88	4	1	55	148	0.96 [0.89,0.98]	0.98 [0.91,1.00]	U	H	L	L	L	L	L	L
Park et al (2018a)[93]	1	Direct	Sediment	Ion Ampliseq TB Research Panel	pDST (LJ absolute conc.)	INH	34	22	2	0	4	28	0.92 [0.74,0.98]	1.00 [0.51,1.00]	L	H	L	L	L	L	H	H

Study	Sample set	Sample category	Sample type	TB-tNGS	Reference test	TB drug or drug group	No. Recruited	True positives	False negatives	False positives	True negatives	No. Included	Sensitivity [95% confidence interval]	Specificity [95% confidence interval]	rob_patient	app_patient	rob_index	app_index	rob_ref	app_ref	rob_flow	rob_total
Park et al (2018a)[93]	1	Direct	Sediment	Ion Ampliseq TB Research Panel	Pyrazinamidase activity test	PZA	34	3	2	1	28	34	0.60 [0.23,0.88]	0.97 [0.83,0.99]	L	H	L	L	H	L	H	H
Park et al (2018a)[93]	1	Direct	Sediment	Ion Ampliseq TB Research Panel	pDST (LJ absolute conc.)	EMB	34	7	1	3	23	34	0.88 [0.53,0.98]	0.88 [0.71,0.96]	L	H	L	L	H	L	H	H
Park et al (2018a)[93]	1	Direct	Sediment	Ion Ampliseq TB Research Panel	pDST (LJ absolute conc.)	RIF	34	8	0	1	25	34	1.00 [0.68,1.00]	0.96 [0.81,0.99]	L	H	L	L	L	L	L	L
Park et al (2018a)[93]	1	Direct	Sediment	Ion Ampliseq TB Research Panel	pDST (LJ absolute conc.)	AMK+KAN	34	0	1	0	33	34	0.00 [0.00,0.79]	1.00 [0.90,1.00]	L	H	L	L	L	L	L	L
Park et al (2018a)[93]	1	Direct	Sediment	Ion Ampliseq TB Research Panel	pDST (LJ absolute conc.)	FQ	34	2	1	0	31	34	0.67 [0.21,0.94]	1.00 [0.89,1.00]	L	H	L	L	L	L	L	L
Park et al (2018a)[93]	1	Direct	Sediment	Ion Ampliseq TB Research Panel	pDST (LJ absolute conc.)	STM	34	6	3	0	25	34	0.67 [0.35,0.88]	1.00 [0.87,1.00]	L	H	L	L	L	L	L	L
Park et al (2018b)[94]	1	Indirect	Culture isolates	Ion Ampliseq TB Research Panel	Pyrazinamidase activity test	PZA	30	6	1	2	21	30	0.86 [0.49,0.97]	0.91 [0.73,0.98]	L	H	L	L	H	L	L	H
Park et al (2018b)[94]	1	Indirect	Culture isolates	Ion Ampliseq TB Research Panel	pDST (LJ absolute conc.)	FQ	30	2	1	0	27	30	0.67 [0.21,0.94]	1.00 [0.88,1.00]	L	H	L	L	L	L	L	L
Park et al (2018b)[94]	1	Indirect	Culture isolates	Ion Ampliseq TB Research Panel	pDST (LJ absolute conc.)	INH	30	29	1	0	0	30	0.97 [0.83,0.99]	NaN [NaN,NaN]	L	H	L	L	L	L	L	L
Park et al (2018b)[94]	1	Indirect	Culture isolates	Ion Ampliseq TB Research Panel	pDST (LJ absolute conc.)	STM	30	8	2	1	19	30	0.80 [0.49,0.94]	0.95 [0.76,0.99]	L	H	L	L	L	L	L	L
Park et al (2018b)[94]	1	Indirect	Culture isolates	Ion Ampliseq TB Research Panel	pDST (LJ absolute conc.)	AMK+KAN	30	0	0	0	30	30	NaN [NaN,NaN]	1.00 [0.89,1.00]	L	H	L	L	L	L	L	L
Park et al (2018b)[94]	1	Indirect	Culture isolates	Ion Ampliseq TB Research Panel	pDST (LJ absolute conc.)	RIF	30	29	1	0	0	30	0.97 [0.83,0.99]	NaN [NaN,NaN]	L	H	L	L	L	L	L	L
Park et al (2018b)[94]	1	Indirect	Culture isolates	Ion Ampliseq TB Research Panel	pDST (LJ absolute conc.)	EMB	30	15	0	3	12	30	1.00 [0.80,1.00]	0.80 [0.55,0.93]	L	H	L	L	H	L	L	L
Schlanderer (2023)[102]	1	Direct	Sputum	Custom Panel (Ion Torrent)	Xpert MTB/RIF and Genotype MTBDRplus	RIF	35	1	0	0	16	17	1.00 [0.21,1.00]	1.00 [0.81,1.00]	L	L	L	L	L	U	H	H
Schlanderer (2023)[102]	1	Direct	Sputum	Custom Panel (Ion Torrent)	Genotype MTBDRplus	INH	35	2	0	0	15	17	1.00 [0.34,1.00]	1.00 [0.80,1.00]	L	L	L	L	L	U	H	H
Sibanze et al (2020)[104]	1	Direct	Stool	Deeplex MycTB	pDST (MGIT 960)	PZA	66	1	1	0	7	9	0.50 [0.09,0.91]	1.00 [0.65,1.00]	H	L	L	L	H	L	H	H
Sibanze et al (2020)[104]	1	Direct	Stool	Deeplex MycTB	pDST (MGIT 960)	STM	66	4	0	0	13	17	1.00 [0.51,1.00]	1.00 [0.77,1.00]	H	L	L	L	L	L	H	H
Sibanze et al (2020)[104]	1	Direct	Stool	Deeplex MycTB	pDST (MGIT 960)	RIF	66	2	0	2	14	18	1.00 [0.34,1.00]	0.88 [0.64,0.97]	H	L	L	L	L	L	H	H
Sibanze et al (2020)[104]	1	Direct	Stool	Deeplex MycTB	pDST (MGIT 960)	INH	66	4	2	0	12	18	0.67 [0.30,0.90]	1.00 [0.76,1.00]	H	L	L	L	L	L	H	H
Sibanze et al (2020)[104]	1	Direct	Stool	Deeplex MycTB	pDST (MGIT 960)	EMB	66	4	0	0	14	18	1.00 [0.51,1.00]	1.00 [0.78,1.00]	H	L	L	L	H	L	H	H
Sibanze et al (2020)[104]	2	Direct	Stool	Deeplex MycTB	pDST (MGIT 960)	TH	21	1	0	4	1	6	1.00 [0.21,1.00]	0.20 [0.04,0.62]	H	L	L	L	L	L	H	H
Sibanze et al (2020)[104]	2	Direct	Stool	Deeplex MycTB	pDST (MGIT 960)	BDQ	21	1	0	0	6	7	1.00 [0.21,1.00]	1.00 [0.61,1.00]	H	L	L	L	L	L	H	H
Sibanze et al (2020)[104]	2	Direct	Stool	Deeplex MycTB	pDST (MGIT 960)	FQ	21	2	0	0	5	7	1.00 [0.34,1.00]	1.00 [0.57,1.00]	H	L	L	L	L	L	H	H
Sibanze et al (2020)[104]	2	Direct	Stool	Deeplex MycTB	pDST (MGIT 960)	CFZ	21	1	1	0	5	7	0.50 [0.09,0.91]	1.00 [0.57,1.00]	H	L	L	L	L	L	H	H
Sibanze et al (2020)[104]	2	Direct	Stool	Deeplex MycTB	pDST (MGIT 960 + LJ)	PZA	21	2	0	0	9	11	1.00 [0.34,1.00]	1.00 [0.70,1.00]	H	L	L	L	H	L	H	H
Sibanze et al (2020)[104]	2	Direct	Stool	Deeplex MycTB	pDST (MGIT 960 + LJ)	RIF	21	6	0	1	5	12	1.00 [0.61,1.00]	0.83 [0.44,0.97]	H	L	L	L	L	L	H	H
Sibanze et al (2020)[104]	2	Direct	Stool	Deeplex MycTB	pDST (MGIT 960 + LJ)	INH	21	6	0	0	6	12	1.00 [0.61,1.00]	1.00 [0.61,1.00]	H	L	L	L	L	L	H	H
Sibanze et al (2020)[104]	2	Direct	Stool	Deeplex MycTB	pDST (MGIT 960 + LJ)	EMB	21	5	0	0	7	12	1.00 [0.57,1.00]	1.00 [0.65,1.00]	H	L	L	L	H	L	H	H
Sodja et al (2019)[105]	1	Indirect	Culture isolates	Ion Ampliseq TB Research Panel	pDST (MGIT 960)	EMB	61	26	0	4	30	60	1.00 [0.87,1.00]	0.88 [0.73,0.95]	L	L	L	L	H	L	L	H
Sodja et al (2019)[105]	1	Indirect	Culture isolates	Ion Ampliseq TB Research Panel	pDST (MGIT 960)	INH	61	30	14	0	17	61	0.68 [0.53,0.80]	1.00 [0.82,1.00]	L	L	L	L	L	L	L	L
Sodja et al (2019)[105]	1	Indirect	Culture isolates	Ion Ampliseq TB Research Panel	pDST (MGIT 960)	RIF	61	41	0	4	16	61	1.00 [0.91,1.00]	0.80 [0.58,0.92]	L	L	L	L	L	L	L	L
Sodja et al (2021)[106]	1	Indirect	Culture isolates	Ion Ampliseq TB Research Panel	pDST (MGIT 960)	PZA	61	34	4	1	22	61	0.89 [0.76,0.96]	0.96 [0.79,0.99]	L	L	L	L	H	L	L	H
Song et al (2022)[107]	1	Direct	FFPE	Custom Panel (MinION)	pDST (Encode Medical Engineering)	RIF	178	24	1	0	153	178	0.96 [0.80,0.99]	1.00 [0.98,1.00]	L	L	H	L	L	L	H	H
Song et al (2022)[107]	1	Direct	FFPE	Custom Panel (MinION)	pDST (Encode Medical Engineering)	AMK	178	4	2	0	172	178	0.67 [0.30,0.90]	1.00 [0.98,1.00]	L	L	H	L	L	L	H	H
Song et al (2022)[107]	1	Direct	FFPE	Custom Panel (MinION)	pDST (Encode Medical Engineering)	CAP	178	4	13	1	160	178	0.24 [0.10,0.47]	0.99 [0.97,1.00]	L	L	H	L	L	L	H	H
Song et al (2022)[107]	1	Direct	FFPE	Custom Panel (MinION)	pDST (Encode Medical Engineering)	EMB	178	6	2	9	161	178	0.75 [0.41,0.93]	0.95 [0.90,0.97]	L	L	H	L	H	L	H	H
Song et al (2022)[107]	1	Direct	FFPE	Custom Panel (MinION)	pDST (Encode Medical Engineering)	INH	178	29	2	8	139	178	0.94 [0.79,0.98]	0.95 [0.90,0.97]	L	L	H	L	L	L	H	H
Song et al (2022)[107]	1	Direct	FFPE	Custom Panel (MinION)	pDST (Encode Medical Engineering)	KAN	178	4	7	0	167	178	0.36 [0.15,0.65]	1.00 [0.98,1.00]	L	L	H	L	L	L	H	H
Song et al (2022)[107]	1	Direct	FFPE	Custom Panel (MinION)	pDST (Encode Medical Engineering)	LFX	178	10	2	9	157	178	0.83 [0.55,0.95]	0.95 [0.90,0.97]	L	L	H	L	L	L	H	H
Song et al (2022)[107]	1	Direct	FFPE	Custom Panel (MinION)	pDST (Encode Medical Engineering)	MFX	178	4	1	9	164	178	0.80 [0.38,0.96]	0.95 [0.90,0.97]	L	L	H	L	L	L	H	H
Song et al (2022)[107]	1	Direct	FFPE	Custom Panel (MinION)	pDST (Encode Medical Engineering)	STM	178	33	5	6	134	178	0.87 [0.73,0.94]	0.96 [0.91,0.98]	L	L	H	L	L	L	H	H
Tafess et al (2020)[109]	1	Indirect	Culture isolates	Custom Panel (MinION)	pDST (agar proportion)	CAP	163	28	0	2	60	90	1.00 [0.88,1.00]	0.97 [0.89,0.99]	U	L	L	L	L	L	L	L
Tafess et al (2020)[109]	1	Indirect	Culture isolates	Custom Panel (MinION)	pDST (agar proportion)	MFX	163	21	2	1	68	92	0.91 [0.73,0.98]	0.99 [0.92,1.00]	U	L	L	L	L	L	L	L
Tafess et al (2020)[109]	1	Indirect	Culture isolates	Custom Panel (MinION)	pDST (agar proportion)	AMK	163	31	0	0	62	93	1.00 [0.89,1.00]	1.00 [0.94,1.00]	U	L	L	L	L	L	L	L
Tafess et al (2020)[109]	1	Indirect	Culture isolates	Custom Panel (MinION)	pDST (agar proportion)	KAN	163	31	1	0	61	93	0.97 [0.84,0.99]	1.00 [0.94,1.00]	U	L	L	L	L	L	L	L
Tafess et al (2020)[109]	1	Indirect	Culture isolates	Custom Panel (MinION)	pDST (agar proportion)	OFX	163	23	2	0	68	93	0.92 [0.75,0.98]	1.00 [0.95,1.00]	U	L	L	L	L	L	L	L
Tafess et al (2020)[109]	1	Indirect	Culture isolates	Custom Panel (MinION)	pDST (MGIT 960)	PZA	163	42	2	0	49	93	0.95 [0.85,0.99]	1.00 [0.93,1.00]	U	L	L	L	H	L	L	L
Tafess et al (2020)[109]	1	Indirect	Culture isolates	Custom Panel (MinION)	pDST (MGIT 960)	INH	163	80	7	0	76	163	0.92 [0.84,0.96]	1.00 [0.95,1.00]	U	L	L	L	L	L	L	L
Tafess et al (2020)[109]	1	Indirect	Culture isolates	Custom Panel (MinION)	pDST (MGIT 960)	STM	163	67	5	0	91	163	0.93 [0.85,0.97]	1.00 [0.96,1.00]	U	L	L	L	L	L	L	L
Tafess et al (2020)[109]	1	Indirect	Culture isolates	Custom Panel (MinION)	pDST (MGIT 960)	RIF	163	65	0	1	97	163	1.00 [0.94,1.00]	0.99 [0.94,1.00]	U	L	L	L	L	L	L	L
Tafess et al (2020)[109]	1	Indirect	Culture isolates	Custom Panel (MinION)	pDST (MGIT 960)	EMB	163	32	5	3	123	163	0.86 [0.72,0.94]	0.98 [0.93,0.99]	U	L	L	L	H	L	L	L
Wang et al (2019)[112]	1	Indirect	Culture isolates	Next Gen-RDST Assay	pDST (MGIT 960)	RIF	241	11	0	0	211	222	1.00 [0.74,1.00]	1.00 [0.98,1.00]	U	L	L	L	L	L	H	H
Wang et al (2019)[112]	1	Indirect	Culture isolates	Next Gen-RDST Assay	pDST (MGIT 960)	INH	241	12	3	0	226	241	0.80 [0.55,0.93]	1.00 [0.98,1.00]	U	L	L	L	L	L	L	L
Whitfield (2019)[113]	1	Indirect	Culture isolates	Next Gen-RDST Assay	pDST (MGIT 960)	PZA	358	170	2	4	179	355	0.99 [0.96,1.00]	0.98 [0.95,0.99]	L	H	L	L	H	L	L	L
Wu et al (2022)[116]	1	Indirect	Culture isolates; Reference isolates	Custom Panel (Ion Torrent)	pDST (7H10/7H11 agar proportion method)	DLM	50	0	0	0	33	33	NaN [NaN,NaN]	1.00 [0.90,1.00]	U	H	L	L	L	L	L	L
Wu et al (2022)[116]	1	Indirect	Culture isolates; Reference isolates	Custom Panel (Ion Torrent)	pDST (7H10/7H11 agar proportion method)	CFZ	50	0	0	0	37	37	NaN [NaN,NaN]	1.00 [0.91,1.00]	U	H	L	L	L	L	L	L
Wu et al (2022)[116]	1	Indirect	Culture isolates; Reference isolates	Custom Panel (Ion Torrent)	pDST (7H10/7H11 agar proportion method)	EMB	50	16	0	0	23	39	1.00 [0.81,1.00]	1.00 [0.86,1.00]	U	H	L	L	H	L	L	L
Wu et al (2022)[116]	1	Indirect	Culture isolates; Reference isolates	Custom Panel (Ion Torrent)	pDST (7H10/7H11 agar proportion method)	BDQ	50	1	0	0	39	40	1.00 [0.21,1.00]	1.00 [0.91,1.00]	U	H	L	L	L	L	L	L
Wu et al (2022)[116]	1	Indirect	Culture isolates; Reference isolates	Custom Panel (Ion Torrent)	pDST (7H10/7H11 agar proportion method)	LZD	50	1	0	0	39	40	1.00 [0.21,1.00]	1.00 [0.91,1.00]	U	H	L	L	L	L	L	L
Wu et al (2022)[116]	1	Indirect	Culture isolates; Reference isolates	Custom Panel (Ion Torrent)	pDST (7H10/7H11 agar proportion method)	AMK	50	5	0	0	38	43	1.00 [0.57,1.00]	1.00 [0.91,1.00]	U	H	L	L	L	L	L	L

Study	Sample set	Sample category	Sample type	TB-tNGS	Reference test	TB drug or drug group	No. Recruited	True positives	False negatives	False positives	True negatives	No. Included	Sensitivity [95% confidence interval]	Specificity [95% confidence interval]	rob_patient	app_patient	rob_index	app_index	rob_ref	app_ref	rob_flow	rob_total
Wu et al (2022)[116]	1	Indirect	Culture isolates; Reference isolates	Custom Panel (Ion Torrent)	pDST (7H10/7H11 agar proportion method)	CAP	50	5	2	0	36	43	0.71 [0.36,0.92]	1.00 [0.90,1.00]	U	H	L	L	L	L	L	L
Wu et al (2022)[116]	1	Indirect	Culture isolates; Reference isolates	Custom Panel (Ion Torrent)	pDST (7H10/7H11 agar proportion method)	KAN	50	6	0	1	36	43	1.00 [0.61,1.00]	0.97 [0.86,1.00]	U	H	L	L	L	L	L	L
Wu et al (2022)[116]	2	Indirect	Culture isolates; Reference isolates	Custom Panel (Ion Torrent)	pDST (7H10/7H11 agar proportion method)	INH	35	24	0	0	4	28	1.00 [0.86,1.00]	1.00 [0.51,1.00]	H	H	L	L	L	L	L	H
Wu et al (2022)[116]	2	Indirect	Culture isolates; Reference isolates	Custom Panel (Ion Torrent)	pDST (7H10/7H11 agar proportion method)	CFZ	35	0	0	0	29	29	NaN [NaN,NaN]	1.00 [0.88,1.00]	H	H	L	L	L	L	L	H
Wu et al (2022)[116]	1	Indirect	Culture isolates; Reference isolates	Custom Panel (Ion Torrent)	pDST (7H10/7H11 agar proportion method)	INH	50	35	0	0	10	45	1.00 [0.90,1.00]	1.00 [0.72,1.00]	U	H	L	L	L	L	L	L
Wu et al (2022)[116]	1	Indirect	Culture isolates; Reference isolates	Custom Panel (Ion Torrent)	pDST (7H10/7H11 agar proportion method)	STM	50	15	0	0	30	45	1.00 [0.80,1.00]	1.00 [0.89,1.00]	U	H	L	L	L	L	L	L
Wu et al (2022)[116]	2	Indirect	Culture isolates; Reference isolates	Custom Panel (Ion Torrent)	pDST (7H10/7H11 agar proportion method)	BDQ	35	1	0	0	29	30	1.00 [0.21,1.00]	1.00 [0.88,1.00]	H	H	L	L	L	L	L	H
Wu et al (2022)[116]	2	Indirect	Culture isolates; Reference isolates	Custom Panel (Ion Torrent)	pDST (7H10/7H11 agar proportion method)	EMB	35	13	1	1	15	30	0.93 [0.69,0.99]	0.94 [0.72,0.99]	H	H	L	L	H	L	L	H
Wu et al (2022)[116]	2	Indirect	Culture isolates; Reference isolates	Custom Panel (Ion Torrent)	pDST (7H10/7H11 agar proportion method)	LZD	35	2	0	0	28	30	1.00 [0.34,1.00]	1.00 [0.88,1.00]	H	H	L	L	L	L	L	H
Wu et al (2022)[116]	2	Indirect	Culture isolates; Reference isolates	Custom Panel (Ion Torrent)	pDST (7H10/7H11 agar proportion method)	LFX	35	4	0	0	27	31	1.00 [0.51,1.00]	1.00 [0.88,1.00]	H	H	L	L	L	L	L	H
Wu et al (2022)[116]	2	Indirect	Culture isolates; Reference isolates	Custom Panel (Ion Torrent)	pDST (7H10/7H11 agar proportion method)	MFX	35	4	0	0	27	31	1.00 [0.51,1.00]	1.00 [0.88,1.00]	H	H	L	L	L	L	L	H
Wu et al (2022)[116]	2	Indirect	Culture isolates; Reference isolates	Custom Panel (Ion Torrent)	pDST (7H10/7H11 agar proportion method)	DLM	35	0	0	0	31	31	NaN [NaN,NaN]	1.00 [0.88,1.00]	H	H	L	L	L	L	L	H
Wu et al (2022)[116]	2	Indirect	Culture isolates; Reference isolates	Custom Panel (Ion Torrent)	pDST (7H10/7H11 agar proportion method)	PZA	35	5	0	0	27	32	1.00 [0.57,1.00]	1.00 [0.88,1.00]	H	H	L	L	H	L	L	H
Wu et al (2022)[116]	1	Indirect	Culture isolates; Reference isolates	Custom Panel (Ion Torrent)	pDST (7H10/7H11 agar proportion method)	LFX	50	11	0	0	37	48	1.00 [0.74,1.00]	1.00 [0.91,1.00]	U	H	L	L	L	L	L	L
Wu et al (2022)[116]	1	Indirect	Culture isolates; Reference isolates	Custom Panel (Ion Torrent)	pDST (7H10/7H11 agar proportion method)	MFX	50	11	1	0	36	48	0.92 [0.65,0.99]	1.00 [0.90,1.00]	U	H	L	L	L	L	L	L
Wu et al (2022)[116]	2	Indirect	Culture isolates; Reference isolates	Custom Panel (Ion Torrent)	pDST (7H10/7H11 agar proportion method)	AMK	35	2	0	0	31	33	1.00 [0.34,1.00]	1.00 [0.89,1.00]	H	H	L	L	L	L	L	H
Wu et al (2022)[116]	2	Indirect	Culture isolates; Reference isolates	Custom Panel (Ion Torrent)	pDST (7H10/7H11 agar proportion method)	CAP	35	2	1	0	30	33	0.67 [0.21,0.94]	1.00 [0.89,1.00]	H	H	L	L	L	L	L	H
Wu et al (2022)[116]	2	Indirect	Culture isolates; Reference isolates	Custom Panel (Ion Torrent)	pDST (7H10/7H11 agar proportion method)	KAN	35	2	0	0	31	33	0.67 [0.21,0.94]	0.97 [0.83,0.99]	H	H	L	L	L	L	L	H
Wu et al (2022)[116]	2	Indirect	Culture isolates; Reference isolates	Custom Panel (Ion Torrent)	pDST (7H10/7H11 agar proportion method)	RIF	35	28	0	0	5	33	1.00 [0.88,1.00]	1.00 [0.57,1.00]	H	H	L	L	L	L	L	H
Wu et al (2022)[116]	1	Indirect	Culture isolates; Reference isolates	Custom Panel (Ion Torrent)	pDST (7H10/7H11 agar proportion method)	PZA	50	12	2	1	34	49	0.86 [0.60,0.96]	0.97 [0.85,0.99]	U	H	L	L	H	L	L	L
Wu et al (2022)[116]	2	Indirect	Culture isolates; Reference isolates	Custom Panel (Ion Torrent)	pDST (7H10/7H11 agar proportion method)	STM	35	13	1	0	20	34	0.93 [0.69,0.99]	1.00 [0.84,1.00]	H	H	L	L	L	L	L	H
Wu et al (2022)[116]	1	Indirect	Culture isolates; Reference isolates	Custom Panel (Ion Torrent)	pDST (7H10/7H11 agar proportion method)	RIF	50	42	0	2	6	50	1.00 [0.92,1.00]	0.75 [0.41,0.93]	U	H	L	L	L	L	L	L
Wu et al (2023b)[117]	1	Direct	Clinical samples	Hugobiotech	pDST (MGIT 960)	INH	130	8	2	0	41	51	0.80 [0.49,0.94]	1.00 [0.91,1.00]	L	L	U	L	L	L	H	H

Supplementary Table 5: Test accuracy data for tuberculosis (TB) drugs and drug groups which were not meta-analysed on a drug level.

TB-tNGS – tuberculosis drug resistance prediction using targeted Next-Generation Sequencing; **No. recruited** – number of patients or samples selected and recruited for study; **no. included** – number of samples included in contingency table; **rob_total** – combined risk of bias assessment across patient selection, index test and flow and timing domain; **L** – low risk of bias; **H** – high risk of bias; **U** – unclear risk of bias.

Study	Sample set	Sample category	Sample type	TB-tNGS	Reference Test	TB drug or drug group	No. recruited	True Positives	False Negative	False Positive	True Negative	No. included	Sensitivity [95% confidence interval]	Specificity [95% confidence interval]	rob_total
Kambli et al (2021)	1	Indirect	Culture isolates	Deeplex MycTB	pDST (inhouse)	AMK	40	0	0	0	33	33	NaN [NaN,NaN]	1.00 [0.90,1.00]	L
Kambli et al (2021)	2	Direct	Sediment	Deeplex MycTB	pDST (inhouse)	AMK	40	0	0	0	33	33	NaN [NaN,NaN]	1.00 [0.90,1.00]	L
Park et al (2018b)	1	Indirect	Culture isolates	Ion Ampliseq TB Research Panel	pDST (LJ absolute conc.)	AMK+KAN	30	0	0	0	30	30	NaN [NaN,NaN]	1.00 [0.89,1.00]	L
Ko et al (2019)	1	Indirect	Culture isolates	Ion Ampliseq TB Research Panel	pDST (LJ absolute conc.)	AMK+KAN	36	0	2	0	34	36	0.00 [0.00,0.66]	1.00 [0.90,1.00]	H
Park et al (2018a)	1	Direct	Sediment	Ion Ampliseq TB Research Panel	pDST (LJ absolute conc.)	AMK+KAN	34	0	1	0	33	34	0.00 [0.00,0.79]	1.00 [0.90,1.00]	L
Feuerriegel et al (2021)	1	Direct	Clinical samples	Deeplex MycTB	pDST (not further specified)	AMK+KAN+CAP	50	1	0	0	7	8	1.00 [0.21,1.00]	1.00 [0.65,1.00]	H
Barboza-Amezcua et al (2022)	1	Indirect	Reference isolates	Custom Panel (Illumina)	pDST (MGIT 960)	AMK+KAN+CAP	20	7	0	0	13	20	1.00 [0.65,1.00]	1.00 [0.77,1.00]	L
Jouet et al (2021)	2	Direct	Sputum	Deeplex MycTB	Illumina+MTBSeq	BDQ	109	0	0	0	99	99	NaN [NaN,NaN]	1.00 [0.96,1.00]	L
Sibanze et al (2020)	2	Direct	Stool	Deeplex MycTB	pDST (MGIT 960)	BDQ	21	1	0	0	6	7	1.00 [0.21,1.00]	1.00 [0.61,1.00]	H
Wu et al (2022)	1	Indirect	Culture isolates; Reference isolates	Custom Panel (Ion Torrent)	pDST (7H10/7H11 agar proportion method)	BDQ	50	1	0	0	39	40	1.00 [0.21,1.00]	1.00 [0.91,1.00]	L
Wu et al (2022)	2	Indirect	Culture isolates; Reference isolates	Custom Panel (Ion Torrent)	pDST (7H10/7H11 agar proportion method)	BDQ	35	1	0	0	29	30	1.00 [0.21,1.00]	1.00 [0.88,1.00]	H
Feuerriegel et al (2021)	1	Direct	Clinical samples	Deeplex MycTB	pDST (not further specified)	BDQ+CFZ	50	0	0	0	2	2	NaN [NaN,NaN]	1.00 [0.34,1.00]	H
Feuerriegel et al (2021)	1	Direct	Clinical samples	Deeplex MycTB	pDST (not further specified)	CAP	50	0	0	0	5	5	NaN [NaN,NaN]	1.00 [0.57,1.00]	H
Wu et al (2022)	1	Indirect	Culture isolates; Reference isolates	Custom Panel (Ion Torrent)	pDST (7H10/7H11 agar proportion method)	CFZ	50	0	0	0	37	37	NaN [NaN,NaN]	1.00 [0.91,1.00]	L
Jouet et al (2021)	2	Direct	Sputum	Deeplex MycTB	Illumina+MTBSeq	CFZ	109	0	0	0	99	99	NaN [NaN,NaN]	1.00 [0.96,1.00]	L
Wu et al (2022)	2	Indirect	Culture isolates; Reference isolates	Custom Panel (Ion Torrent)	pDST (7H10/7H11 agar proportion method)	CFZ	35	0	0	0	29	29	NaN [NaN,NaN]	1.00 [0.88,1.00]	H
Mansoor et al (2023)	1	Combined	Sputum; Culture isolates	Deeplex MycTB	pDST (MGIT)	CFZ	161	2	4	6	134	146	0.33 [0.10,0.70]	0.96 [0.91,0.98]	L
Sibanze et al (2020)	2	Direct	Stool	Deeplex MycTB	pDST (MGIT 960)	CFZ	21	1	1	0	5	7	0.50 [0.09,0.91]	1.00 [0.57,1.00]	H
Wu et al (2022)	1	Indirect	Culture isolates; Reference isolates	Custom Panel (Ion Torrent)	pDST (7H10/7H11 agar proportion method)	DLM	50	0	0	0	33	33	NaN [NaN,NaN]	1.00 [0.90,1.00]	L
Wu et al (2022)	2	Indirect	Culture isolates; Reference isolates	Custom Panel (Ion Torrent)	pDST (7H10/7H11 agar proportion method)	DLM	35	0	0	0	31	31	NaN [NaN,NaN]	1.00 [0.89,1.00]	H
Jouet et al (2021)	1	Indirect	Reference isolates	Deeplex MycTB	pDST (Middlebrook 7H11) + MGIT 460	ETH	429	25	2	33	70	130	0.93 [0.77,0.98]	0.68 [0.58,0.76]	H
Jouet et al (2021)	2	Direct	Sputum	Deeplex MycTB	Illumina+MTBSeq	ETH	109	7	0	1	66	74	1.00 [0.65,1.00]	0.99 [0.92,1.00]	L
Mansoor et al (2023)	1	Combined	Sputum; Culture isolates	Deeplex MycTB	pDST (MGIT)	ETH	161	49	16	3	64	132	0.75 [0.64,0.84]	0.96 [0.88,0.98]	L
Feuerriegel et al (2021)	1	Direct	Clinical samples	Deeplex MycTB	pDST (not further specified)	ETH+PTH	50	3	2	0	3	8	0.60 [0.23,0.88]	1.00 [0.44,1.00]	H

Study	Sample set	Sample category	Sample type	TB-tNGS	Reference Test	TB drug or drug group	No. recruited	True Positives	False Negative	False Positive	True Negative	No. included	Sensitivity [95% confidence interval]	Specificity [95% confidence interval]	rob_total
Barboza-Amezcua et al (2022)	2	Direct	Sputum	Custom Panel (Illumina)	pDST (MGIT 960)	ETH+PTH	46	3	4	0	11	18	0.43 [0.16,0.75]	1.00 [0.74,1.00]	H
Barboza-Amezcua et al (2022)	1	Indirect	Reference isolates	Custom Panel (Illumina)	pDST (MGIT 960)	ETH+PTH	20	3	0	0	17	20	1.00 [0.44,1.00]	1.00 [0.82,1.00]	L
Feuerriegel et al (2021)	1	Direct	Clinical samples	Deeplex MycTB	pDST (not further specified)	FQ	50	0	0	4	8	12	NaN [NaN,NaN]	0.67 [0.39,0.86]	H
Jouet et al (2021)	2	Direct	Sputum	Deeplex MycTB	Illumina+MTBSeq	FQ	109	0	0	1	104	105	NaN [NaN,NaN]	0.99 [0.95,1.00]	L
Park et al (2018b)	1	Indirect	Culture isolates	Ion Ampliseq TB Research Panel	pDST (LJ absolute conc.)	INH	30	29	1	0	0	30	0.97 [0.83,0.99]	NaN [NaN,NaN]	L
Feuerriegel et al (2021)	1	Direct	Clinical samples	Deeplex MycTB	pDST (not further specified)	KAN	50	0	0	0	4	4	NaN [NaN,NaN]	1.00 [0.51,1.00]	H
Wu et al (2022)	2	Indirect	Culture isolates; Reference isolates	Custom Panel (Ion Torrent)	pDST (7H10/7H11 agar proportion method)	LFX	35	4	0	0	27	31	1.00 [0.51,1.00]	1.00 [0.88,1.00]	H
Wu et al (2022)	1	Indirect	Culture isolates; Reference isolates	Custom Panel (Ion Torrent)	pDST (7H10/7H11 agar proportion method)	LFX	50	11	0	0	37	48	1.00 [0.74,1.00]	1.00 [0.91,1.00]	L
Song et al (2022)	1	Direct	FFPE	Custom Panel (MinION)	pDST (Encode Medical Engineering)	LFX	178	10	2	9	157	178	0.83 [0.55,0.95]	0.95 [0.90,0.97]	H
Jouet et al (2021)	1	Indirect	Reference isolates	Deeplex MycTB	pDST (MGIT 460)	LZD	429	0	0	0	20	20	NaN [NaN,NaN]	1.00 [0.84,1.00]	H
Feuerriegel et al (2021)	1	Direct	Clinical samples	Deeplex MycTB	pDST (not further specified)	LZD	50	0	0	0	2	2	NaN [NaN,NaN]	1.00 [0.34,1.00]	H
Jouet et al (2021)	2	Direct	Sputum	Deeplex MycTB	Illumina+MTBSeq	LZD	109	0	0	0	87	87	NaN [NaN,NaN]	1.00 [0.96,1.00]	L
Mansoor et al (2023)	1	Combined	Sputum; Culture isolates	Deeplex MycTB	pDST (MGIT)	LZD	161	2	2	1	142	147	0.50 [0.15,0.85]	0.99 [0.96,1.00]	L
Wu et al (2022)	1	Indirect	Culture isolates; Reference isolates	Custom Panel (Ion Torrent)	pDST (7H10/7H11 agar proportion method)	LZD	50	1	0	0	39	40	1.00 [0.21,1.00]	1.00 [0.91,1.00]	L
Wu et al (2022)	2	Indirect	Culture isolates; Reference isolates	Custom Panel (Ion Torrent)	pDST (7H10/7H11 agar proportion method)	LZD	35	2	0	0	28	30	1.00 [0.34,1.00]	1.00 [0.88,1.00]	H
Colman et al (2016)	1	Direct	Sputum	Next Gen-RDST Assay	pDST (MGIT 960)	OFX	254	12	2	1	157	172	0.86 [0.60,0.96]	0.99 [0.97,1.00]	L
Tafess et al (2020)	1	Indirect	Culture isolates	Custom Panel (MinION)	pDST (agar proportion)	OFX	163	23	2	0	68	93	0.92 [0.75,0.98]	1.00 [0.95,1.00]	L
Barboza-Amezcua et al (2022)	2	Direct	Sputum	Custom Panel (Illumina)	pDST (MGIT 960)	OFX+LFX	46	3	1	0	14	18	0.75 [0.30,0.95]	1.00 [0.78,1.00]	H
Park et al (2018b)	1	Indirect	Culture isolates	Ion Ampliseq TB Research Panel	pDST (LJ absolute conc.)	RIF	30	29	1	0	0	30	0.97 [0.83,0.99]	NaN [NaN,NaN]	L
Sibanze et al (2020)	2	Direct	Stool	Deeplex MycTB	pDST (MGIT 960)	TH	21	1	0	4	1	6	1.00 [0.21,1.00]	0.20 [0.04,0.62]	H

Supplementary Table 6: Combined sensitivity and specificity estimates using a frequentist meta-analysis: overall, per drug, and excluding any studies at high-risk of bias.

RIF – rifampicin, INH – isoniazid, EMB – ethambutol, PZA – pyrazinamide, STM – streptomycin, AMK – amikacin, CAP – capreomycin, KAN – kanamycin, MFX – moxifloxacin, FQs – fluoroquinolones, n – total number of compared datasets.

	All studies				Excluding studies at high-risk of bias		
Sensitivity - n (datasets), n (observations), Combined Estimate (95% Confidence Interval)								
Overall	29	13639	0.95	(0.92, 0.96)	15	7749	0.96	(0.93, 0.97)
INH	25	2065	0.96	(0.93, 0.98)	12	1137	0.98	(0.94, 0.99)
RIF	24	2054	1.00	(0.98, 1.00)	12	946	1.00	(0.97, 1.00)
EMB	16	1332	0.97	(0.89, 0.99)	7	521	1.00	(0.00, 1.00)
PZA	18	1346	0.91	(0.84, 0.95)	7	796	0.94	(0.84, 0.98)
STM	13	933	0.91	(0.80, 0.96)	7	469	0.92	(0.78, 0.97)
KAN	12	918	0.91	(0.73, 0.97)	7	581	0.97	(0.78, 1.00)
AMK	9	812	0.94	(0.65, 0.99)	5	519	0.97	(0.37, 1.00)
CAP	11	929	0.81	(0.5, 0.95)	7	576	0.93	(0.49, 0.99)
FQs	10	524	0.94	(0.89, 0.96)	6	310	0.95	(0.90, 0.97)
MFX	6	532	0.89	(0.78, 0.95)	3	312	0.90	(0.78, 0.96)
Specificity - n (datasets), n (observations), Combined Estimate (95% Confidence Interval)								
Overall	29	13639	0.98	(0.97, 0.99)	15	7749	0.99	(0.98, 1.00)
INH	25	2065	0.99	(0.98, 1.00)	12	1137	1.00	(0.96, 1.00)
RIF	24	2054	0.98	(0.95, 0.99)	12	946	0.98	(0.92, 1.00)
EMB	16	1332	0.93	(0.88, 0.96)	7	521	0.92	(0.80, 0.97)
PZA	18	1346	0.98	(0.95, 0.99)	7	796	0.97	(0.95, 0.98)
STM	13	933	0.99	(0.95, 1.00)	7	469	0.99	(0.92, 1.00)
KAN	12	918	0.99	(0.96, 1.00)	7	581	0.99	(0.94, 1.00)
AMK	9	812	1.00	(0.71, 1.00)	5	519	1.00	(0.60, 1.00)
CAP	11	929	0.99	(0.97, 1.00)	7	576	0.99	(0.95, 1.00)
FQs	10	524	0.99	(0.98, 1.00)	6	310	0.99	(0.96, 1.00)
MFX	6	532	0.99	(0.93, 1.00)	3	312	1.00	(0.97, 1.00)

Supplementary Table 7: Subgroup analysis comparing combined sensitivity and specificity estimates in studies enrolling any TB patients and studies enrolling drug-resistant TB patients (DR-TB). Estimates were calculated using a frequentist meta-analysis for all data reported in a study (overall) and per drug.

RIF – rifampicin, INH – isoniazid, EMB – ethambutol, PZA – pyrazinamide, STM – streptomycin, AMK – amikacin, CAP – capreomycin, KAN – kanamycin, MFX – moxifloxacin, FQs – fluoroquinolones, n – total number of compared datasets.

	Any TB-patients enrolled				Only DR-TB patients enrolled				
Sensitivity - n (datasets), n (observations), Combined Estimate (95% Confidence Interval)									p-value
Overall	16	8906	0.92	(0.88, 0.95)	13	4733	0.96	(0.93, 0.98)	0.06
INH	15	1504	0.93	(0.87, 0.96)	10	561	0.99	(0.95, 1.00)	0.03
RIF	14	1469	0.99	(0.97, 1.00)	10	585	1.00	(0.84, 1.00)	0.45
EMB	10	1030	0.95	(0.77, 0.99)	6	302	0.98	(0.92, 1.00)	0.37
PZA	10	578	0.90	(0.80, 0.95)	8	768	0.90	(0.76, 0.96)	0.99
STM	7	608	0.91	(0.86, 0.94)	6	325	0.88	(0.66, 0.97)	0.69
KAN	7	634	0.89	(0.66, 0.97)	5	284	0.89	(0.42, 0.99)	0.95
AMK	6	591	0.93	(0.43, 1.00)	3	221	0.91	(0.71, 0.98)	0.87
CAP	6	647	0.84	(0.26, 0.99)	5	282	0.71	(0.46, 0.88)	0.61
FQs	4	198	0.95	(0.83, 0.99)	6	326	0.91	(0.78, 0.96)	0.42
MFX	4	453	0.87	(0.74, 0.94)	2	79	0.94	(0.66, 0.99)	0.48
Specificity - n (datasets), n (observations), Combined Estimate (95% Confidence Interval)									p-value
Overall	16	8906	0.98	(0.96, 0.99)	13	4733	0.99	(0.97, 0.99)	0.63
INH	15	1504	1.00	(0.97, 1.00)	10	561	1.00	(0.78, 1.00)	0.90
RIF	14	1469	0.99	(0.96, 1.00)	10	585	0.98	(0.84, 1.00)	0.64
EMB	10	1030	0.94	(0.91, 0.96)	6	302	0.90	(0.75, 0.97)	0.37
PZA	10	578	0.99	(0.95, 1.00)	8	768	0.96	(0.93, 0.98)	0.17
STM	7	608	0.96	(0.93, 1.00)	6	325	0.99	(0.90, 1.00)	0.91
KAN	7	634	1.00	(0.00, 1.00)	5	284	0.98	(0.94, 1.00)	0.42
AMK	6	591	1.00	(0.70, 1.00)	3	221	1.00	(0.00, 1.00)	1.00
CAP	6	647	0.99	(0.97, 0.99)	5	282	1.00	(0.04, 1.00)	0.55
FQs	4	198	0.99	(0.96, 1.00)	6	326	1.00	(0.83, 1.00)	0.68
MFX	4	453	0.99	(0.92, 1.00)	2	79	1.00	(0.00, 1.00)	1.00

Supplementary Table 8: Subgroup analysis comparing combined sensitivity and specificity estimates in studies using primary samples for targeted sequencing and studies using culture isolates. Estimates were calculated using a frequentist meta-analysis for all data reported in a study (overall) and per drug.

RIF – rifampicin, INH – isoniazid, EMB – ethambutol, PZA – pyrazinamide, STM – streptomycin, AMK – amikacin, CAP – capreomycin, KAN – kanamycin, MFX – moxifloxacin, FQs – fluoroquinolones, n – total number of compared datasets.

	Primary samples				Culture isolates				p-value
Sensitivity - n (datasets), n (observations), Combined Estimate (95% Confidence Interval)									
Overall	13	5223	0.91	(0.85, 0.95)	16	6574	0.96	(0.93, 0.98)	0.05
INH	12	742	0.94	(0.89, 0.97)	11	1052	0.96	(0.89, 0.99)	0.54
RIF	12	743	0.99	(0.94, 1.00)	12	1163	1.00	(0.98, 1.00)	0.34
EMB	7	417	0.96	(0.73, 1.00)	8	782	0.95	(0.81, 0.99)	0.81
PZA	6	228	0.76	(0.62, 0.86)	11	974	0.93	(0.86, 0.97)	0.01
STM	5	313	0.84	(0.84, 0.85)	7	474	0.91	(0.76, 0.97)	0.32
KAN	5	467	0.80	(0.41, 0.96)	6	309	0.95	(0.86, 0.98)	0.13
AMK	4	435	0.67	(0.34, 0.88)	4	232	NA*	(NA, NA)	NA
CAP	5	459	0.66	(0.13, 0.96)	5	330	0.92	(0.69, 0.98)	0.26
FQs	3	80	0.93	(0.75, 0.98)	6	296	0.92	(0.83, 0.96)	0.88
MFX	3	361	0.83	(0.61, 0.94)	3	171	0.92	(0.79, 0.98)	0.27
Specificity - n (datasets), n (observations), Combined Estimate (95% Confidence Interval)									
Overall	13	5223	0.98	(0.97, 0.99)	16	6574	0.99	(0.97, 1.00)	0.23
INH	12	742	0.99	(0.94, 1.00)	11	1052	1.00	(0.96, 1.00)	0.46
RIF	12	743	0.98	(0.95, 0.99)	12	1163	0.99	(0.93, 1.00)	0.46
EMB	7	417	0.95	(0.91, 0.97)	8	782	0.94	(0.88, 0.97)	0.67
PZA	6	228	0.96	(0.92, 0.98)	11	974	0.99	(0.95, 1.00)	0.18
STM	5	313	0.97	(0.97, 0.97)	7	474	0.99	(0.97, 1.00)	0.05
KAN	5	467	1.00	(0.06, 1.00)	6	309	0.99	(0.97, 1.00)	0.60
AMK	4	435	1.00	(0.89, 1.00)	4	232	NA	(NA, NA)	NA
CAP	5	459	1.00	(0.97, 1.00)	5	330	0.99	(0.94, 1.00)	0.45
FQs	3	80	1.00	(0.00, 1.00)	6	296	1.00	(0.97, 1.00)	1.00
MFX	3	361	0.99	(0.62, 1.00)	3	171	0.99	(0.95, 1.00)	0.91

* NA – not available. Meta-analysis was not possible since data contained no false positives and no false negatives.

REFERENCES

1   Cerullo E, Sutton AJ, Jones HE, Wu O, Quinn TJ, Cooper NJ. MetaBayesDTA: codeless Bayesian meta-analysis of test accuracy, with or without a gold standard. *BMC Medical Research Methodology* 2023; **23**: 127.

2   Lewandowski D, Kurowicka D, Joe H. Generating random correlation matrices based on vines and extended onion method. *Journal of Multivariate Analysis* 2009; **100**: 1989–2001.

3   Affolabi, Dissou. DIAgnostics for Multidrug Resistant Tuberculosis in Africa (DIAMA). clinicaltrials.gov, 2017 https://clinicaltrials.gov/study/NCT03303963 (accessed Jan 1, 2023).

4   Ajbani K, Lin SY, Rodrigues C, *et al.* Evaluation of pyrosequencing for detecting extensively drug-resistant Mycobacterium tuberculosis among clinical isolates from four high-burden countries. *Antimicrobial Agents & Chemotherapy* 2015; **59**: 414–20.

5   Ajbani K, Kazi M, Naik S, Soman R, Shetty A, Rodrigues C. Utility of pyrosequencing for rapid detection of tubercular meningitis (TBM) and associated susceptibility directly from CSF specimens. *Tuberculosis* 2018; **111**: 54–6.

6   Ajbani K, Kazi M, Tornheim J, *et al.* Pyrosequencing to resolve discrepant Xpert MTB/RIF and Mycobacterial Growth Indicator Tube 960. *Lung India* 2018; **35**: 168–70.

7   Ajbani K, Kazi M, Agrawal U, *et al.* Evaluation of CSF pyrosequencing to diagnose tuberculous meningitis: A retrospective diagnostic accuracy study. *Tuberculosis* 2021; **126**: 6.

8   Arnold C, Westland L, Mowat G, Underwood A, Magee J, Gharbia S. Single-nucleotide polymorphism-based differentiation and drug resistance detection in Mycobacterium tuberculosis from isolates or directly from sputum. *Clinical Microbiology and Infection* 2005; **11**: 122–30.

9   Aubry, Alexandra. New Genomic Techniques and Management of Multidrug-resistant Tuberculosis (GENO-MDR). clinicaltrials.gov, 2020 https://clinicaltrials.gov/study/NCT04397536 (accessed Jan 1, 2023).

10   Barbosa-Amezcua M, Cuevas-Cordoba B, Fresno C, *et al.* Rapid Identification of Drug Resistance and Phylogeny in M. tuberculosis, Directly from Sputum Samples. *Microbiology Spectrum* 2022; : e0125222.

11   Beviere M, Reissier S, Penven M, *et al.* The Role of Next-Generation Sequencing (NGS) in the Management of Tuberculosis: Practical Review for Implementation in Routine. *Pathogens* 2023; **12**: 978.

12   Bonnet I, Enouf V, Morel F, *et al.* A Comprehensive Evaluation of GeneLEAD VIII DNA Platform Combined to Deeplex Myc-TB [R] Assay to Detect in 8 Days Drug Resistance to 13 Antituberculous Drugs and Transmission of Mycobacterium tuberculosis Complex Directly From Clinical Samples. *Frontiers in Cellular & Infection Microbiology* 2021; **11**: 707244.

13   Bouziane F, Allem R, Sebaihia M, *et al.* First genetic characterisation of multidrug-resistant Mycobacterium tuberculosis isolates from Algeria. *J Glob Antimicrob Resist* 2012; **19**: 301–7.

14 Branigan D, Deborggraeve S, Denkinger C, *et al.* Tuberculosis Diagnostics. 2023.

15 Bravo LTC, Tuohy MJ, Ang C, *et al.* Pyrosequencing for rapid detection of Mycobacterium tuberculosis resistance to rifampin, isoniazid, and fluoroquinolones. *Journal of Clinical Microbiology* 2009; **47**: 3985–90.

16 Bravo LTC, Tuohy MJ, Shrestha NK. Successful Pyrosequencing of GC-rich DNA Sequences by Partial Substitution of Deoxyguanosine With Deoxyinosine. *Diagn Mol Pathol* 2010; **19**: 123–5.

17 Cabibbe AM, Cirillo DM. Best approaches to drug-resistance surveillance at the country level. *Int J Mycobacteriol* 2016; **5 Suppl 1**: S40–1.

18 Cabibbe AM, Spitaleri A, Battaglia S, *et al.* Application of Targeted Next-Generation Sequencing Assay on a Portable Sequencing Platform for Culture-Free Detection of Drug-Resistant Tuberculosis from Clinical Samples. *J Clin Microbiol* 2020; **58**: 22.

19 Catanzaro A, Rodwell TC, Catanzaro DG, *et al.* Performance Comparison of Three Rapid Tests for the Diagnosis of Drug-Resistant Tuberculosis. *PLoS ONE [Electronic Resource]* 2015; **10**: e0136861.

20 Cattamanchi, Adithya. Rapid Research in Diagnostics Development for TB Network (R2D2TB Network). clinicaltrials.gov, 2021 https://clinicaltrials.gov/study/NCT04923958 (accessed Jan 1, 2023).

21 Chan WS, Au CH, Chung Y, *et al.* Rapid and economical drug resistance profiling with Nanopore MinION for clinical specimens with low bacillary burden of Mycobacterium tuberculosis. *BMC Research Notes* 2020; **13**: 444.

22 Chang KC, Yew WW, Yeung Chan RC. Rapid assays for fluoroquinolone resistance in Mycobacterium tuberculosis: A systematic review and meta-analysis. *Journal of Antimicrobial Chemotherapy* 2010; **65**: 1551–61.

23 Chang KC, Yew WW, Zhang Y. Pyrazinamide susceptibility testing in mycobacterium tuberculosis: A systematic review with meta-analyses. *Antimicrobial Agents and Chemotherapy* 2011; **55**: 4499–505.

24 Cheng S, Cui Z, Li Y, Hu Z. Diagnostic accuracy of a molecular drug susceptibility testing method for the antituberculosis drug ethambutol: A systematic review and meta-analysis. *Journal of Clinical Microbiology* 2014; **52**: 2913–24.

25 Choerunnisa L, Rita C, Tjandrawati A, Chaidir L, Parwati I. Comparison of Interpretation between Pyrosequencing and Xpert MTB/RIF Assay in Multidrug-Resistant Tuberculosis. *Maj Kedokt Bdg-MKB* 2020; **52**: 238–42.

26 Colman RE, Anderson J, Lemmer D, *et al.* Rapid Drug Susceptibility Testing of Drug-Resistant Mycobacterium tuberculosis Isolates Directly from Clinical Samples by Use of Amplicon Sequencing: a Proof-of-Concept Study. *J Clin Microbiol* 2016; **54**: 2058–67.

27 Colman RE, Mace A, Seifert M, *et al.* Whole-genome and targeted sequencing of drug-resistant Mycobacterium tuberculosis on the iSeq100 and MiSeq: A performance, ease-of-use, and cost evaluation. *PLoS Med* 2019; **16**: e1002794.

28   Cuevas-Cordoba B, Fresno C, Haase-Hernandez JI, *et al.* A bioinformatics pipeline for Mycobacterium tuberculosis sequencing that cleans contaminant reads from sputum samples. *PLoS ONE* 2021; **16**: e0258774.

29   Daum LT, Rodriguez JD, Worthy SA, *et al.* Next-generation ion torrent sequencing of drug resistance mutations in Mycobacterium tuberculosis strains. *Journal of Clinical Microbiology* 2012; **50**: 3831–7.

30   Daum LT, Fischer GW, Sromek J, *et al.* Characterization of multi-drug resistant Mycobacterium tuberculosis from immigrants residing in the USA using Ion Torrent full-gene sequencing. *Epidemiology and Infection* 2014; **142**: 1328–33.

31   Daum LT, Konstantynovska OS, Solodiankin OS, *et al.* Characterization of novel Mycobacterium tuberculosis pncA gene mutations in clinical isolates from the Ukraine. *Diagn Microbiol Infect Dis* 2019; **93**: 334–8.

32   De Araujo L, Cabibbe AM, Mhuulu L, *et al.* Implementation of targeted next-generation sequencing for the diagnosis of drug-resistant tuberculosis in low-resource settings: a programmatic model, challenges, and initial outcomes. *Front Public Health* 2023; **11**: 1204064.

33   Dheda, Keertan. Test to Treat TB: Impact of Sputum Sequencing-guided Individualised Therapy on Outcomes in Drug-resistant Tuberculosis (T3-RCT). clinicaltrials.gov, 2021 https://clinicaltrials.gov/study/NCT05007795 (accessed Jan 1, 2023).

34   Dippenaar A, Goossens SN, Grobbelaar M, *et al.* Nanopore Sequencing for Mycobacterium tuberculosis: a Critical Review of the Literature, New Developments, and Future Opportunities. *J Clin Microbiol* 2022; **60**: e0064621.

35   Dolinger DL, Colman RE, Engelthaler DM, Rodwell TC. Next-generation sequencing-based user-friendly platforms for drug-resistant tuberculosis diagnosis: A promise for the near future. *The International Journal of Mycobacteriology* 2016; **5**: S27–8.

36   Domínguez J, Boeree MJ, Cambau E, *et al.* Clinical implications of molecular drug resistance testing for Mycobacterium tuberculosis: a 2023 TBnet/RESIST-TB consensus statement. *The Lancet Infectious Diseases* 2023; **23**: e122–37.

37   Dookie N, Khan A, Padayatchi N, Naidoo K. Application of Next Generation Sequencing for Diagnosis and Clinical Management of Drug-Resistant Tuberculosis: Updates on Recent Developments in the Field. *Front Microbiol* 2022; **13**: 775030.

38   El Achkar S, Demanche C, Osman M, *et al.* Drug-Resistant Tuberculosis, Lebanon, 2016 - 2017. *Emerg Infect Dis* 2019; **25**: 564–8.

39   Engström A, Morcillo N, Imperiale B, Hoffner SE, Juréen P. Detection of first- and second-line drug resistance in Mycobacterium tuberculosis clinical isolates by pyrosequencing. *Journal of Clinical Microbiology* 2012; **50**: 2026–33.

40   Feuerriegel S, Kohl T, Utpatel C, ... Rapid genomic first-and second-line drug resistance prediction from clinical Mycobacterium tuberculosis specimens using Deeplex-MycTB. *Eur Respir J* 2021. https://erj.ersjournals.com/content/57/1/2001796.abstract.

41 Foundation for Innovative New Diagnostics, Switzerland. Clinical Evaluation of tNGS for Diagnosis of DR-TB (Seq&Treat). clinicaltrials.gov, 2020 https://clinicaltrials.gov/study/NCT04239326 (accessed Jan 1, 2023).

42 García-Sierra N, Lacoma A, Prat C, *et al.* Pyrosequencing for rapid molecular detection of rifampin and isoniazid resistance in Mycobacterium tuberculosis strains and clinical specimens. *Journal of Clinical Microbiology* 2011; **49**: 3683–6.

43 Garza-González E, González GM, Rentería A, Cruz-Pulido W, Rivera G, Bocanegra-García V. A pyrosequencing method for molecular monitoring of regions in the inhA, ahpC and rpoB genes of Mycobacterium tuberculosis. *Clinical Microbiology and Infection* 2010; **16**: 607–12.

44 Georghiou SB, Seifert M, Catanzaro D, *et al.* Frequency and Distribution of Tuberculosis Resistance-Associated Mutations between Mumbai, Moldova, and Eastern Cape. *Antimicrob Agents Chemother* 2016; **60**: 3994–4004.

45 Georghiou SB, Seifert M, Lin SY, *et al.* Shedding light on the performance of a pyrosequencing assay for drug-resistant tuberculosis diagnosis. *BMC Infect Dis* 2016; **16**: 458.

46 Georghiou SB, Ajbani K, Rodrigues C, Rodwell TC. Performance of a pyrosequencing platform in diagnosing drug-resistant extra-pulmonary tuberculosis in India. *Int J Tuberc Lung Dis* 2016; **20**: 160–5.

47 Georghiou SB, de Vos M, Velen K, *et al.* Designing molecular diagnostics for current tuberculosis drug regimens. *Emerging Microbes & Infections* 2023; **12**: 2178243.

48 Getachew E, Adebeta T, Gebrie D, *et al.* Pyrosequencing for diagnosis of multidrug and extensively drug-resistant tuberculosis: A systemic review and meta-analysis. *J Clin Tuberc Other Mycobact Dis* 2021; **24**: 100254.

49 Gliddon HD, Frampton D, Munsamy V, *et al.* A Rapid Drug Resistance Genotyping Workflow for Mycobacterium tuberculosis, Using Targeted Isothermal Amplification and Nanopore Sequencing. *Microbiol* 2021; **9**: e0061021.

50 Gopalaswamy R, Subramanian B, Chandrasekaran P, Shanmugam SK. An odyssey from laboratory to field ? – Portable tNGS system for TB diagnosis in programmatic setting. *Indian Journal of Tuberculosis* 2022. DOI:10.1016/j.ijtb.2022.04.004.

51 Govindaswamy A, Sakthi D, Pai R, Jeyaseelan L, Michael JS. Pyrosequencing: a rapid and effective sequencing method to diagnose drug-resistant tuberculosis. *J Med Microbiol* 2018; **67**: 1212–6.

52 Graciaa DS, Schechter MC, Fetalvero KB, Cranmer LM, Kempker RR, Castro KG. Updated considerations in the diagnosis and management of tuberculosis infection and disease: integrating the latest evidence-based strategies. *Expert Review of Anti-infective Therapy* 2023; **21**: 595–616.

53 Guha P, Dutta S, Murti K, *et al.* The Integration of Omics: A Promising Approach to Personalized Tuberculosis Treatment. *Medicine in Omics* 2024; : 100033.

54 Guo Q, Zheng RJ, Zhu CT, *et al.* Pyrosequencing for the rapid detection of rifampicin resistance in Mycobacterium tuberculosis: A meta-analysis. *International Journal of Tuberculosis and Lung Disease* 2013; **17**: 1008–13.

55   Halse TA, Edwards J, Cunningham PL, *et al.* Combined real-time pcr and rpob gene pyrosequencing for rapid identification of mycobacterium tuberculosis and determination of rifampin resistance directly in clinical specimens. *Journal of Clinical Microbiology* 2010; **48**: 1182–8.

56   Hillery N, Groessl EJ, Trollip A, *et al.* The Global Consortium for Drug-resistant Tuberculosis Diagnostics (GCDD): Design of a multi-site, head-to-head study of three rapid tests to detect extensively drug-resistant tuberculosis. *Trials* 2014; **15**. DOI:10.1186/1745-6215-15-434.

57   Horita N. Next-generation sequencing to predict phenotypic drug sensitivity of tuberculosis: meta-analysis of diagnostic test accuracy. WHO Trial Registration. 2022. https://center6.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000056117 (accessed Feb 22, 2024).

58   Htike KPM, Pitaksajjakul P, Tipkrua N, Wongwit W, Jintaridh P, Ramasoota P. NOVEL MUTATION DETECTION IN RpoB OF RIFAMPICIN-RESISTANT MYCOBACTERIUM TUBERCULOSIS USING PYROSEQUENCING. *Southeast Asian J Trop Med Public Health* 2014; **45**: 843–52.

59   Isola D, Pardini M, Varaine F, *et al.* A Pyrosequencing assay for rapid recognition of SNPs in Mycobacterium tuberculosis embB306 region. *Journal of Microbiological Methods* 2005; **62**: 113–20.

60   Jouet A, Gaudin C, Badalato N, *et al.* Deep amplicon sequencing for culture-free prediction of susceptibility or resistance to 13 anti-tuberculous drugs. *Eur Respir J* 2020; **57**: 03.

61   Jureen P, Engstrand L, Eriksson S, Alderborn A, Krabbe M, Hoffner SE. Rapid detection of rifampin resistance in Mycobacterium tuberculosis by pyrosequencing technology. *Journal of Clinical Microbiology* 2006; **44**: 1925–9.

62   Kalokhe AS, Shafiq M, Lee JC, *et al.* Multidrug-resistant tuberculosis drug susceptibility and molecular diagnostic testing. *American Journal of the Medical Sciences* 2013; **345**: 143–8.

63   Kambli P, Ajbani K, Kazi M, *et al.* Targeted next generation sequencing directly from sputum for comprehensive genetic information on drug resistant Mycobacterium tuberculosis. *Tuberculosis (Edinb)* 2021; **127**: 102051.

64   Kayomo MK, Mbula VN, Aloni M, *et al.* Targeted next-generation sequencing of sputum for diagnosis of drug-resistant TB: results of a national survey in Democratic Republic of the Congo. *Sci* 2020; **10**: 10786.

65   Klotoe BJ, Molina-Moya B, Gomes HM, *et al.* TB-EFI, a novel 18-Plex microbead-based method for prediction of second-line drugs and ethambutol resistance in Mycobacterium tuberculosis complex. *J Microbiol Methods* 2018; **152**: 10–7.

66   Ko DH, Lee EJ, Lee SK, *et al.* Application of next-generation sequencing to detect variants of drug-resistant Mycobacterium tuberculosis: genotype-phenotype correlation. *Ann Clin Microbiol Antimicrob* 2019; **18**: 2.

67   Kontsevaya I, Mironova S, Nikolayevskyy V, Balabanova Y, Mitchell S, Drobniewski F. Evaluation of two molecular assays for rapid detection of Mycobacterium tuberculosis resistance to fluoroquinolones in high-tuberculosis and -multidrug-resistance settings. *Journal of Clinical Microbiology* 2011; **49**: 2832–7.

68 Kontsevaya I, Cabibbe AM, Cirillo DM, *et al.* Update on the diagnosis of tuberculosis. *Clinical Microbiology and Infection* 2023; : S1198743X23003403.

69 Kumar K, Kon OM. Personalised Medicine for Tuberculosis and Non-Tuberculous Mycobacterial Pulmonary Disease. *Microorganisms* 2021; **9**: 26.

70 Lacoma A, Molina-Moya B, Prat C, *et al.* Pyrosequencing for rapid detection of Mycobacterium tuberculosis second-line drugs and ethambutol resistance. *Diagn Microbiol Infect Dis* 2015; **83**: 263–9.

71 Lange C, Chesov D, Heyckendorf J, Leung C, ... Drug-resistant tuberculosis: an update on disease burden, diagnosis and treatment. ... 2018. https://onlinelibrary.wiley.com/doi/abs/10.1111/resp.13304.

72 Leung KS, Tam KK, Ng TT, *et al.* Clinical utility of target amplicon sequencing test for rapid diagnosis of drug-resistant Mycobacterium tuberculosis from respiratory specimens. *Front Microbiol* 2022; **13**: 974428.

73 Lin SYG, Desmond EP. Molecular diagnosis of tuberculosis and drug resistance. *Clinics in Laboratory Medicine* 2014; **34**: 297–314.

74 Lin SYG, Rodwell TC, Victor TC, *et al.* Pyrosequencing for rapid detection of extensively drug-resistant Mycobacterium tuberculosis in clinical isolates and clinical specimens. *Journal of Clinical Microbiology* 2014; **52**: 475–82.

75 Liu Q. A new tNGS technology applied in drug resistant tuberculosis diagnosis of prospective controlled study. WHO Trial Registration. https://www.chictr.org.cn/showproj.html?proj=214535 (accessed Feb 22, 2024).

76 MacLean E, Kohli M, Weber SF, *et al.* Advances in Molecular Diagnosis of Tuberculosis. *J Clin Microbiol* 2020; **58**: 22.

77 Makhado NA, Matabane E, Faccin M, *et al.* Outbreak of multidrug-resistant tuberculosis in South Africa undetected by WHO-endorsed commercial tests: an observational study. *Lancet Infect Dis* 2018; **18**: 1350–9.

78 Maningi NE, Daum LT, Rodriguez JD, *et al.* Improved Detection by Next-Generation Sequencing of Pyrazinamide Resistance in Mycobacterium tuberculosis Isolates. *J Clin Microbiol* 2015; **53**: 3779–83.

79 Mansoor H, Hirani N, Chavan V, *et al.* Clinical utility of target-based next-generation sequencing for drug-resistant TB. *The International Journal of Tuberculosis and Lung Disease* 2023; **27**: 41–8.

80 Mariner-Llicer C, Goig GA, Zaragoza-Infante L, *et al.* Accuracy of an amplicon-sequencing nanopore approach to identify variants in tuberculosis drug-resistance-associated genes. *Microb Genom* 2021; **7**: 12.

81 Marttila HJ, Mäkinen J, Marjamäki M, Soini H. Prospective evaluation of pyrosequencing for the rapid detection of isoniazid and rifampin resistance in clinical Mycobacterium tuberculosis isolates. *European Journal of Clinical Microbiology and Infectious Diseases* 2009; **28**: 33–8.

82 Mesfin AB, Araia ZZ, Beyene HN, *et al.* First molecular-based anti-TB drug resistance survey in Eritrea. *International Journal of Tuberculosis & Lung Disease* 2021; **25**: 43–51.

83 Messah ADV, Pawitan JA. Next Generation Sequencing as Rapid Diagnosis of Multidrug Resistance Tuberculosis. *Advan Life Sci* 2020; **8**: 30–7.

84 Metcalf, John. Pragmatic Use of Next-generation Sequencing for Management of Drug-resistant Tuberculosis (TSELiOT). clinicaltrials.gov, 2022 https://clinicaltrials.gov/study/NCT05553236 (accessed Jan 1, 2023).

85 Mohamed S, Köser CU, Salfinger M, Sougakoff W, Heysell SK. Targeted next-generation sequencing: a Swiss army knife for mycobacterial diagnostics? *European Respiratory Journal* 2021; **57**. DOI:10.1183/13993003.04077-2020.

86 Mukherjee S, Perveen S, Negi A, Sharma R. Evolution of tuberculosis diagnostics: From molecular strategies to nanodiagnostics. *Tuberculosis (Edinburgh, Scotland)* 2023; **140**: 102340.

87 Murphy SG, Smith C, Lapierre P, *et al.* Direct detection of drug-resistant Mycobacterium tuberculosis using targeted next generation sequencing. *Frontiers in Public Health* 2023; **11**. https://www.frontiersin.org/articles/10.3389/fpubh.2023.1206056 (accessed June 30, 2023).

88 Naidoo K, Perumal R, Ngema SL, Shunmugam L, Somboro AM. Rapid Diagnosis of Drug-Resistant Tuberculosis–Opportunities and Challenges. *Pathogens* 2023; **13**: 27.

89 Nambiar R, Shah D, Ajbani K, *et al.* Evaluation of pyrosequencing for extensive drug resistance-defining anti-tuberculosis drugs for use in public healthcare. *Tuberculosis (Edinb)* 2018; **110**: 86–90.

90 Ness TE, DiNardo A, Farhat MR. High Throughput Sequencing for Clinical Tuberculosis: An Overview. *Pathogens (Basel, Switzerland)* 2022; **11**: 1343.

91 Nguyen T, Berre VA-L, Bañuls A, ... Molecular diagnosis of drug-resistant tuberculosis; a literature review. *Frontiers in …* 2019. https://www.frontiersin.org/articles/10.3389/fmicb.2019.00794/full.

92 Novais RC, Thorstenson YR. The evolution of Pyrosequencing (R) for microbiology: From genes to genomes. *J Microbiol Methods* 2011; **86**: 1–7.

93 Park J, Jang W, Kim M, *et al.* Molecular drug resistance profiles of Mycobacterium tuberculosis from sputum specimens using ion semiconductor sequencing. *J Microbiol Methods* 2018; **145**: 1–6.

94 Park J, Shin SY, Kim K, Park K, Shin S, Ihm C. Determining Genotypic Drug Resistance by Ion Semiconductor Sequencing With the Ion AmpliSeq TM TB Panel in Multidrug-Resistant Mycobacterium tuberculosis Isolates. *Ann Lab Med* 2018; **38**: 316–23.

95 Rahmo A, Hamdar Z, Kasaa I, Dabboussi F, Hamze M. Genotypic detection of rifampicin-resistant M. tuberculosis strains in Syrian and Lebanese patients. *Journal of Infection and Public Health* 2012; **5**: 381–7.

96 Ramasamy P, Sounderrajan V, Vijayakumar KK, Harshavardhan S. Current perceptions on advanced molecular diagnostics for drug-resistant mycobacterium tuberculosis. *Biomedical and Pharmacology Journal* 2021; **14**: 1249–57.

97 Ransom EM, Potter RF, Dantas G, Burnham CD. Genomic Prediction of Antimicrobial Resistance: Ready or Not, Here It Comes! *Clin Chem* 2020; **66**: 1278–89.

98 Rodrigues C. Multi-centre Clinical Trial to Assess the Performance of Culture-free, End-to-end Targeted NGS (tNGS) Solutions for Diagnosis of Drug Resistant TB (DR-TB). https://ctri.nic.in/, 2019 https://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=37331 (accessed Oct 24, 2023).

99 Rodrigues C, Singhal T. What is New in the Diagnosis of Childhood Tuberculosis? *Indian J Pediatr* 2024; published online Jan 2. DOI:10.1007/s12098-023-04992-0.

100 Rowlinson MC, Musser KA. Current Methods and Role of Next-Generation Sequencing in the Diagnosis of Antimicrobial Resistance in Tuberculosis. *Clinical Microbiology Newsletter* 2022; **44**: 1–12.

101 Rowneki M, Aronson N, Du P, *et al.* Detection of drug resistant Mycobacterium tuberculosis by high-throughput sequencing of DNA isolated from acid fast bacilli smears. *PLoS ONE* 2020; **15**: e0232343.

102 Schlanderer J, Hoffmann H, Lüddecke J, *et al.* Two-stage tuberculosis diagnostics: combining centrifugal microfluidics to detect TB infection and Inh and Rif resistance at the point of care with subsequent antibiotic resistance profiling by targeted NGS. *Lab Chip* 2024; **24**: 74–84.

103 Shrestha NK. Rapid diagnostic testing for mycobacterial infections. *Future Microbiol* 2007; **2**: 397–408.

104 Sibandze DB, Kay A, Dreyer V, *et al.* Rapid molecular diagnostics of tuberculosis resistance by targeted stool sequencing. *Genome Med* 2022; **14**: 52.

105 Sodja E, Toplak N, Koren S, Kovač M, Truden S, Žolnir-Dovč M. Next-generation sequencing of drug resistant mycobacterium tuberculosis clinical isolates in low-incidence countries. *Russian Journal of Infection and Immunity* 2019; **9**: 773–8.

106 Sodja E, Koren S, Toplak N, Truden S, Zolnir-Dovc M. Next-generation sequencing to characterise pyrazinamide resistance in Mycobacterium tuberculosis isolates from two Balkan countries. *J Glob Antimicrob Resist* 2022; **29**: 507–12.

107 Song J, Du W, Liu Z, Che J, Li K, Che N. Application of Amplicon-Based Targeted NGS Technology for Diagnosis of Drug-Resistant Tuberculosis Using FFPE Specimens. *Microbiol* 2022; **10**: e0135821.

108 Syafira SZ, Zavitri NG, Yan S, Sribudiani Y, Lezhava A, Chaidir L. Positivity Rate of Pyrosequencing to Diagnose Drug-Resistant Tuberculosis Directly from Sputum with Different Bacterial Load. *Indones Biomed J* 2020; **12**: 313–9.

109 Tafess K, Ng TTL, Lao HY, *et al.* Targeted-Sequencing Workflows for Comprehensive Drug Resistance Profiling of Mycobacterium tuberculosis Cultures Using Two Commercial Sequencing Platforms: Comparison of Analytical and Diagnostic Performance, Turnaround Time, and Cost. *Clin Chem* 2020; **66**: 809–20.

110 Tagliani E, Hassan MO, Waberi Y, *et al.* Culture and Next-generation sequencing-based drug susceptibility testing unveil high levels of drug-resistant-TB in Djibouti: results from the first national survey. *Sci* 2017; **7**: 17672.

111 Torres JN, Paul LV, Rodwell TC, *et al.* Novel katG mutations causing isoniazid resistance in clinical M. tuberculosis isolates. *Emerg* 2015; **4**: e42.

112 Wang Q, Modongo C, Allender C, *et al.* Utility of Targeted, Amplicon-Based Deep Sequencing To Detect Resistance to First-Line Tuberculosis Drugs in Botswana. *Antimicrob Agents Chemother* 2019; **63**: 11.

113 Whitfield MG, Engelthaler DM, Allender C, *et al.* Comparative Performance of Genomic Methods for the Detection of Pyrazinamide Resistance and Heteroresistance in Mycobacterium tuberculosis. *J Clin Microbiol* 2022; **60**: e0190721.

114 World Health Organization. The use of next-generation sequencing technologies for the detection of mutations associated with drug resistance in Mycobacterium tuberculosis complex …. 2018. https://apps.who.int/iris/bitstream/handle/10665/274443/WHO-CDS-TB-2018.19-eng.pdf.

115 World Health Organization. Use of targeted next-generation sequencing to detect drug-resistant tuberculosis: rapid communcation, July 2023. 2023; published online July 23. https://www.who.int/publications/i/item/9789240076372 (accessed Dec 18, 2023).

116 Wu S-H, Xiao Y-X, Hsiao H-C, Jou R. Development and Assessment of a Novel Whole-Gene-Based Targeted Next-Generation Sequencing Assay for Detecting the Susceptibility of Mycobacterium tuberculosis to 14 Drugs. *Microbiology Spectrum* 2022; **10**: e02605-22.

117 Wu X, Liang R, Xiao Y, *et al.* Application of targeted next generation sequencing technology in the diagnosis of Mycobacterium Tuberculosis and first line drugs resistance directly from cell-free DNA of bronchoalveolar lavage fluid. *Journal of Infection* 2023; **86**: 399–401.

118 Zhang H, Chen X, Wang Z, *et al.* Pyrosequencing analysis for mutations in embB codon306 among clinical mycobacterium tuberculosis isolates from Qingdao, China. *Int J Clin Exp Med* 2015; **8**: 11276–82.

119 Zhang W. NGS-Guided(G) Regimens(R) of Anti-tuberculosis(A) Drugs for the Control(C) and Eradication(E) of MDR-TB (GRACE-TB). clinicaltrials.gov, 2018 https://clinicaltrials.gov/study/NCT03604848 (accessed Jan 1, 2023).

120 Zhang G, Zhang H, Zhang Y, Hu X, Tang M, Gao Q. Targeted next-generation sequencing technology showed great potential in identifying spinal tuberculosis and predicting the drug resistance. *Journal of Infection* 2023; **87**: e110–2.

121 Zhao JR, Bai YJ, Zhang QH, Wang Y, Luo M, Yan XJ. Pyrosequencing-based approach for rapid detection of rifampin-resistant Mycobacterium tuberculosis. *Diagnostic Microbiology and Infectious Disease* 2005; **51**: 135–7.

122 Zhao JR, Bai YJ, Wang Y, Zhang QH, Luo M, Yan XJ. Development of a pyrosequencing approach for rapid screening of rifampin, isoniazid and ethambutol-resistant Mycobacterium tuberculosis. *International Journal of Tuberculosis and Lung Disease* 2005; **9**: 328–32.

123 Zhao K, Tu C, Chen W, *et al.* Rapid Identification of Drug-Resistant Tuberculosis Genes Using Direct PCR Amplification and Oxford Nanopore Technology Sequencing. *Can* 2022; **2022**: 7588033.

124 Zheng R, Zhu C, Guo Q, *et al.* Pyrosequencing for rapid detection of Tuberculosis resistance in clinical isolates and Sputum samples from re-treatment Pulmonary Tuberculosis patients. *BMC Infectious Diseases* 2014; **14**. DOI:10.1186/1471-2334-14-200.

125 Zheng H, Yang H, Wang Y, *et al.* Diagnostic value of tNGS vs Xpert MTB/RIF in childhood TB. *Heliyon* 2024; **10**: e23217.

126 Zignol M, Dean AS, Alikhanova N, *et al.* Population-based resistance of Mycobacterium tuberculosis isolates to pyrazinamide and fluoroquinolones: results from a multicountry surveillance project. *The Lancet Infectious Diseases* 2016; **16**: 1185–92.