Biomarkers for diagnosis of childhood tuberculosis: a systematic review

Toyin Togun¹*, Emily MacLean¹, Beate Kampmann²,³, and Madhukar Pai¹,⁴
**Supplementary Information:**

Information extracted from each study comprised the following:

(i) biomarker: name, biomarker name, number of markers, category of biomarker, up or down regulation of biomarker;

(ii) index test: sample type needed, type of test, commercialization status, level of technical facilities required, blinding of test;

(iii) reference standard: reference standard employed and remarks;

(iv) participant information: descriptive study population information, age demographic, total number of participants, negative population, different populations included in study;

(v) study information: author-defined study design, sampling strategy, study location, study time period, place of sample testing, study location, study time period;

(vi) deployment information: place of sample testing, current level of evidence;

(vii) diagnostic performance data: numbers of true positives, true negatives, false positives, and false negatives, sensitivity and confidence intervals, specificity and confidence intervals, statistical significance, AUC, cut-off and explanation, positive and negative predictive values, number of TB cases assayed, number of reference standard negative controls

(viii) bibliographic information
Biomarker & primary study information

biomarker information and bibliographic info from primary studies

* Required

BIOMARKER & STUDY INFORMATION

1. Biomarker name? (001) *

2. Who completed this form?
   * Mark only one oval.
   - Emily (1)
   - Toyin (2)
   - Other:

3. Alternate biomarker name (002)
   * other names the biomarker is called, separate with ;

4. Number of markers (003) *

5. Title of publication (004) *

6. Year of publication (005) *

7. First author (006) *
   * i.e. First name Last name (e.g. Jacqueline M. Achkar)

8. Corresponding author name (007)
   * i.e. First name Last name (e.g. Jacqueline M. Achkar)
9. **Corresponding author country (008)**

10. **Corresponding author email (009)**

11. **Study design (016)**
    Cohort (group of individuals, initially defined and composed, with common characteristics (e.g., condition, birth year), who are examined or traced over a given time period) / Case-control (group of individuals with specific characteristics (e.g., conditions or exposures) compared to group(s) with different characteristics, but otherwise similar) usually not representative of the whole population / Cross-sectional: a cross-sectional study (also known as a cross-sectional analysis, transversal study, prevalence study) is a type of observational study that involves the analysis of data collected from a population, or a representative subset, at one specific point in time from: https://clinicaltrials.gov/ct2/home; Unclear requireds discussion; NR=Not reported

Mark only one oval.

- [ ] Cohort (1)
- [ ] Case control (2)
- [ ] Cross-sectional (3)
- [ ] NR (4)
- [ ] Unclear! (5)
- [ ] Other:

12. **Sampling (017)**
    Consecutive Sample=Sequential Sample: Sample in which the units are chosen on a strict first come first chosen basis. All subjects who are eligible should be included as they are seen. / Convenience Sample: Subjects or groups selected at the investigator's convenience or primarily because they were available at a convenient time or place. / Random Sample: A sample derived by selecting sampling units (eg, individualpatients) such that each unit has an independent and fixed (generally equal) chance ofselection. Whether a given unit is selected is determined by chance (eg, by a tablerandomly ordered numbers).

Mark only one oval.

- [ ] Convenience (1)
- [ ] Consecutive (2)
- [ ] Random (3)
- [ ] NR (4)
- [ ] Unclear! (5)
- [ ] Other:

13. **Study period (018)**
    month/year TO month/year; e.g. 3/2011-5/2013 (use 0/2011 if month unclear, no blanks)

14. **Sample/patient location (019)**
    Country only, separate with ;
15. **Type of sample for index test? (020)**
   *Check all that apply.*
   - Breath (2)
   - PBMCs
   - Plasma (9)
   - QFT supernatant
   - Saliva (4)
   - Serum (8)
   - Sputum (6)
   - Urine (7)
   - WBA Supernatant (10)
   - Whole blood (1)
   - Other:

16. **Type of biomarker (021)**
   *Check all that apply.*
   - Antibody (1)
   - Cell surface protein (2)
   - Cytokine (3)
   - Enzyme (4)
   - Hematological marker (5)
   - Metabolic activity marker (6)
   - Lipid (7)
   - microRNA (8)
   - mRNA expression/host transcription (9)
   - TB protein: antigenic (10)
   - TB protein: enzyme (11)
   - TB: lipid (12)
   - TB: mycolic acid (13)
   - TB: transcriptional marker (14)
   - VOC (15)
   - Whole bacili (16)
   - Unclear! (17)
   - Gene transcript
   - Other: __________________________
17. **Index test type (method of detection) (022)**
*Check all that apply.*

- Cell stimulation (1)
- Cytometry (FACS or otherwise) (2)
- Electronic nose (3)
- MS (6)
- Microarray (7)
- NMR (8)
- PCR (9)
- Multiplex
- ELISA
- Lateral flow assay
- Other immunoassays
- Other: __________

18. **Index method details (023)**
e.g. type of cells a cell marker is on; type of Ag used for cell stimulation; model used; etc

__________________________________________________________________________

__________________________________________________________________________

__________________________________________________________________________

19. **Was the index test interpreted in a blinded manner? (025)**
*Mark only one oval.*

- Yes (1)
- No (2)
- NR (3)
- Other: __________

20. **Study Population Section (027)**
Copy author defined study population section; include disease groups and controls

__________________________________________________________________________

__________________________________________________________________________

__________________________________________________________________________

__________________________________________________________________________

21. **Patient subgroup analysis [patient phenotype] (072)**
22. **Total no. enrolled patients (029)**
   after exclusion, (Largest number minus exclusions)

---

23. **Reference standard used (030)**
   to calculate diagnostic performance (e.g. Positive, Negative), multiple means composite
   *Check all that apply.*

   - Liquid culture (1)
   - Solid culture (2)
   - Culture (non specified) (3)
   - Smear microscopy (4)
   - Chest x-ray (5)
   - Xpert (6)
   - Molecular (not including Xpert, e.g. sequencing, LPA, qPCR, etc) (7)
   - Clinical signs (8)
   - Outcome (9)
   - TB treatment regimen initiated (10)
   - Cytometry (flow or other) (11)
   - NR (12)
   - Other: ________________________________

---

24. **Remarks on Reference standard (031)**
   Sub-group analysis, different reference standards?

   ________________________________

   ________________________________

   ________________________________

   ________________________________

---
25. **Patient characteristics (032)**
   (Check if yes)
   Check all that apply.
   - HIV co-infection (1)
   - BCG vaccination (2)
   - Latent TB infection (3)
   - Extrapulmonary TB infection (4)
   - Smear status (5)
   - History of prior TB (6)
   - Other immuno-compromised condition (7)
   - Chemo prophylaxis (8)
   - None (9)
   - Other: __________________________

26. **Negative Population (033)**
   Status of individuals used for comparison (reference test negative patients). Was the enrolment
   based on TB suspects (thus negatives have other respiratory diseases >> ORD) or individuals with
   other diseases/symptoms or did the study use healthy controls (endemic vs. non-endemic)? Select
   multiple if combinations were used to calculate the diagnostic performance (as reported below).
   Check all that apply.
   - (OD) Other disease (1)
   - (ORD) Other respiratory disease (2)
   - Healthy endemics (3)
   - Healthy non-endemics (4)
   - Disease contacts (5)
   - LTBI (6)
   - Other: __________________________

**DIAGNOSTIC ACCURACY: PERFORMANCE DATA**

27. **TP (True Positives) (035)**

28. **FN (False Negatives) (036)**
   Sick-TP

29. **TN (True Negatives) (037)**

30. **FP (False Positives) (038)**
   Healthy-TN
31. **Sensitivity (not percentage) (039)**
   sensitivity, example 0.956, use NR for not reported

32. **Confidence interval of sensitivity (040)**
   i.e. [x,x], example [0.942,0.956]

33. **Specificity (not percentage) (041)**
   specificity, e.g. 0.843, use NR for not reported

34. **Confidence interval of specificity (042)**
   i.e. [x,x]

35. **Statistical significance (p-value) (043)**
   full p-value statement, e.g. p<0.01; p=0.05, use NR for not reported

36. **Area Under ROC Curve (044)**
   example 0.867, use NR for not reported

37. **Was the chosen point on the ROC curve pre-defined? (071)**
   *Mark only one oval.*
   - [ ] Yes (1)
   - [ ] No (2)

38. **Explanatory notes re: justification of curve point (064)**

39. **Sick (#Positive reference standard) (045)**
   Total number of sick patients based on reference standard (=Positive Reference Standard Results), Value only needed if study did not report on TP, FP, TN, FP
40. **Healthy (#Negative reference standard) (050)**
   Total number of patients without TB based on reference standard (=Negative Reference Standards Results), Value only needed if study did not report on TP, FP, TN, FP

41. **PPV (051)**
   \[ \text{PPV} = \frac{TP}{TP + FP} \]
   use NR for not reported, Value only needed if study did not report on TP, FP, TN, FP

42. **NPV (052)**
   \[ \text{NPV} = \frac{TN}{TN + FN} \]
   use NR for not reported, Value only needed if study did not report on TP, FP, TN, FP

43. **Expression of biomarkers**
   = either upregulated or downregulated in TB cases or controls

---

Powered by

Google Forms