Identification of a Six-Cytokine Biosignature Discriminating Active Tuberculosis from Latent Infection
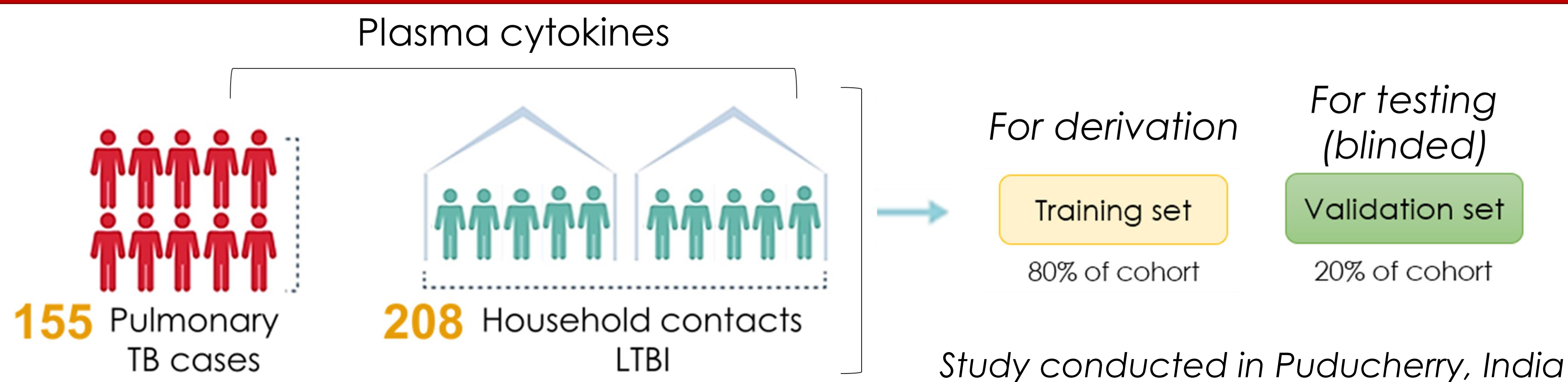
RUTGERS

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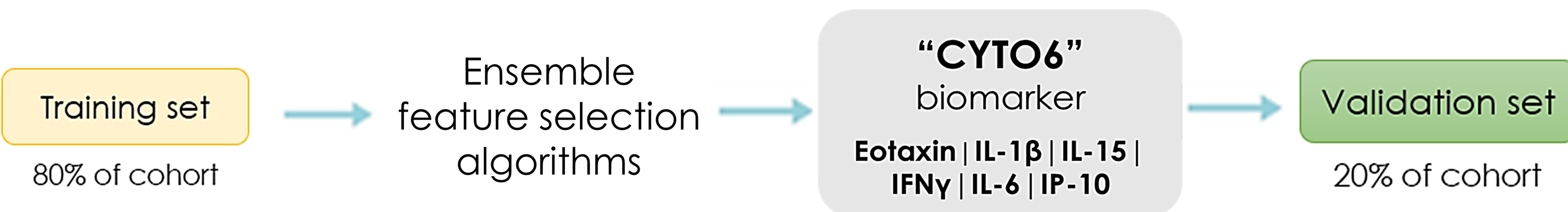
INTRODUCTION

The high cost and logistical difficulty of current sputum-based diagnostic tests impedes **Tuberculosis (TB)** diagnosis in high-burden, resource-poor settings. To improve the efficiency of **TB detection** and treatment, our goal was **to develop a blood-based biomarker that segregates TB from latent infection (LTBI)** to be subsequently deployed **as a community-based triage test**.
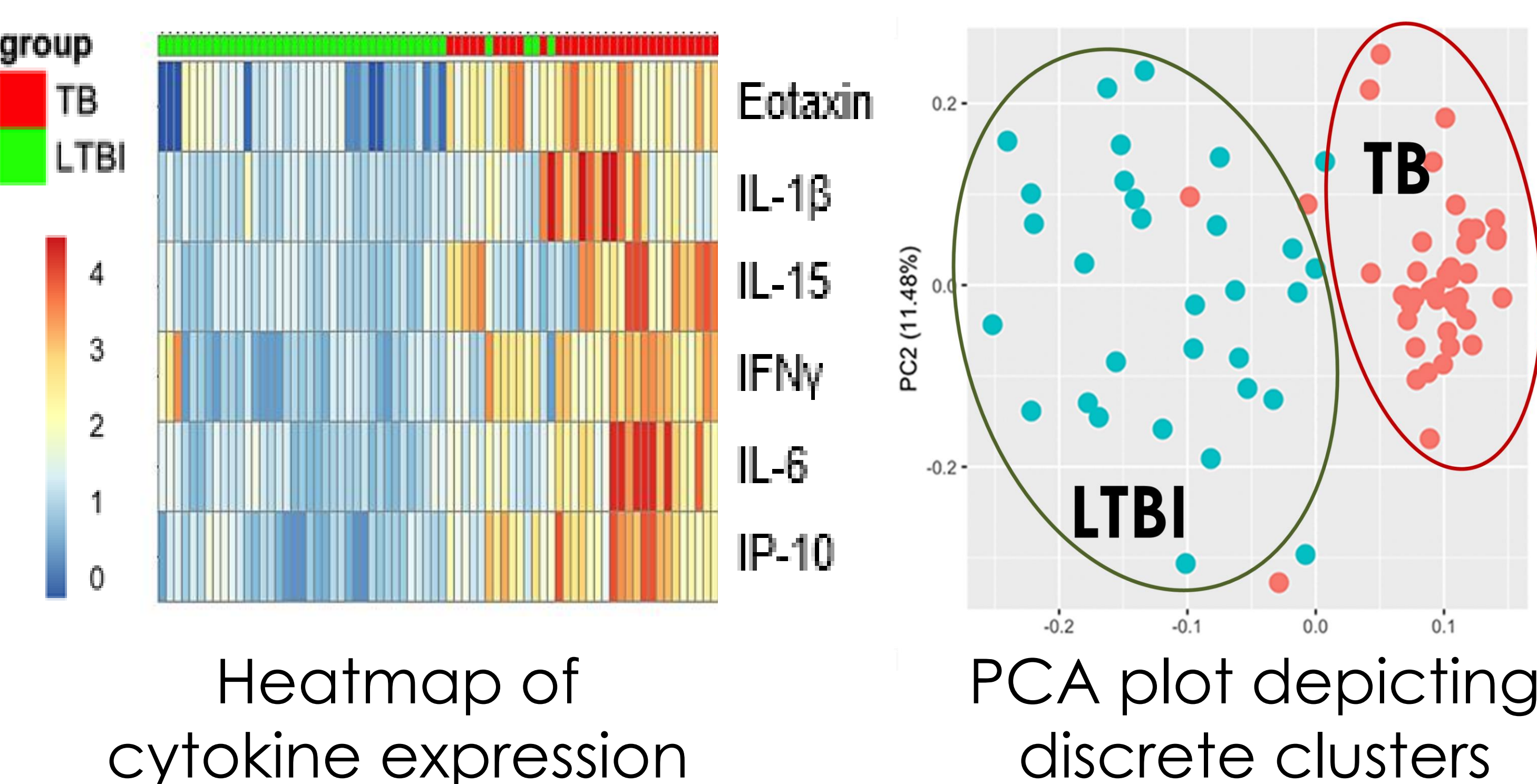
STUDY DESIGN

155 Pulmonary TB cases

208 Household contacts LTBI

Plasma cytokines

For derivation — Training set — 80% of cohort

For testing (blinded) — Validation set — 20% of cohort

Study conducted in Puducherry, India

RESULTS

A. Derivation of cytokine biomarker 'CYTO6' to distinguish TB from LTBI:

Training set — 80% of cohort → Ensemble feature selection algorithms → **"CYTO6" biomarker** Eotaxin | IL-1β | IL-15 | IFNγ | IL-6 | IP-10 → Validation set — 20% of cohort

B. Performance of CYTO6 in the blinded validation set:

group: TB (red), LTBI (green)
Eotaxin, IL-1β, IL-15, IFNγ, IL-6, IP-10

Heatmap of cytokine expression

PCA plot depicting discrete clusters

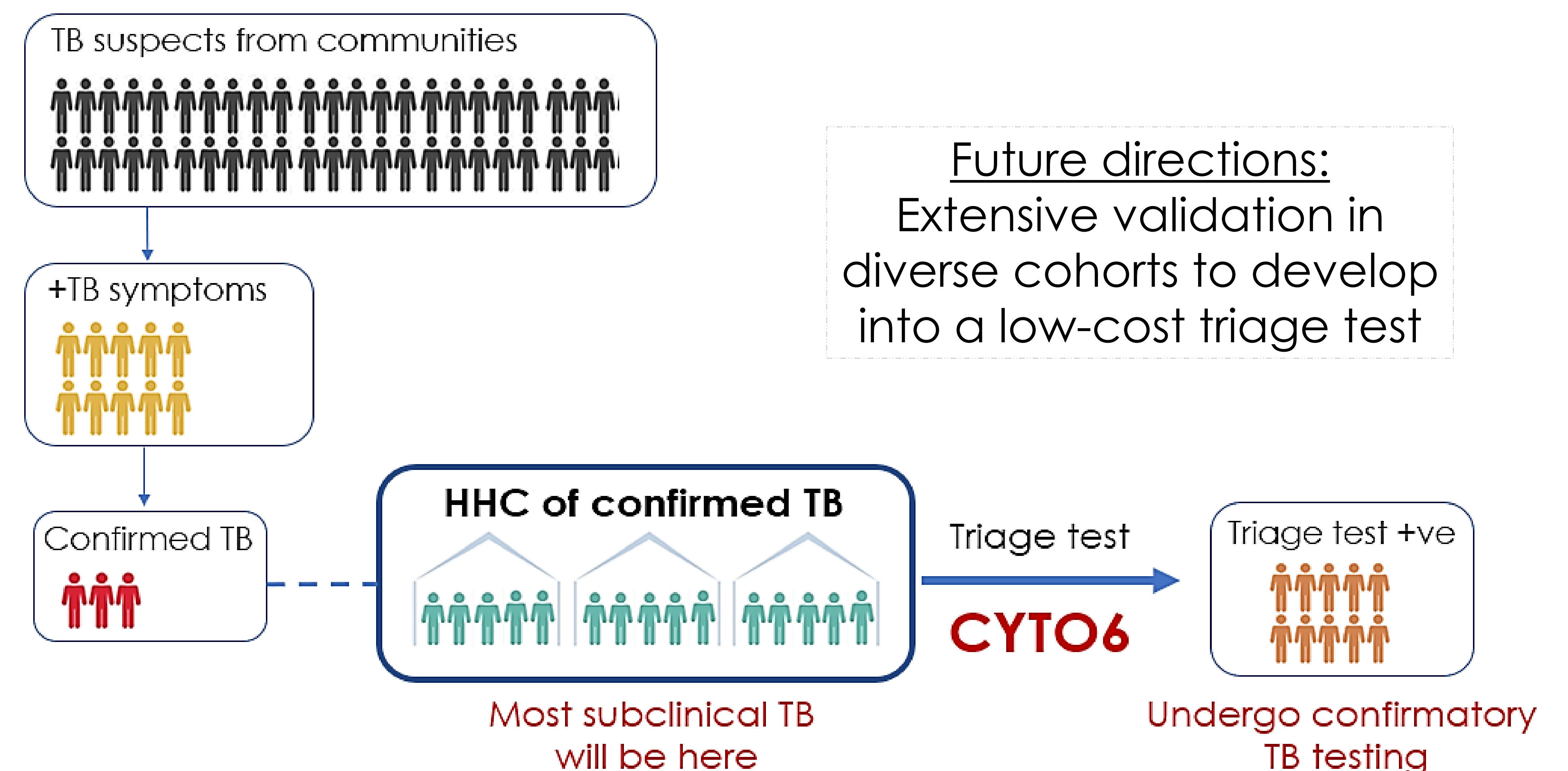| AUC	0.9921
Sensitivity	**100%**
Specificity	**92.68%**
PPV	60.29%
NPV	100%

Quantitative
AUC: area under the curve;
PPV: positive predictive value;
NPV: negative predictive value

CONCLUSIONS

We derived a blood based, six-cytokine biomarker that demonstrates robust performance (**100% sensitivity** and **92.68% specificity**) in distinguishing TB from LTBI in a blinded dataset, meeting the WHO criteria for a non-sputum based triage test.

APPLICATION: Detection of Subclinical TB

36.1-79.7% of prevalent TB cases that remain undetected are asymptomatic and sputum smear negative (subclinical TB). Since unselected community screening is not cost-effective, by **targeting 'high risk' household contacts of TB cases** and administering a triage test such as CYTO6, TB case detection can be dramatically improved, facilitating a reduction in the global TB burden.

TB suspects from communities
+TB symptoms
Confirmed TB
HHC of confirmed TB
Most subclinical TB will be here
Triage test **CYTO6**
Triage test +ve
Undergo confirmatory TB testing

Future directions:
Extensive validation in diverse cohorts to develop into a low-cost triage test

REFERENCES

Frascella et al, Subclinical Tuberculosis Disease—A Review and Analysis of Prevalence Surveys to Inform Definitions, Burden, Associations, and Screening Methodology, Clinical Infectious Diseases, 2020;, ciaa1402, https://doi.org/10.1093/cid/ciaa1402

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