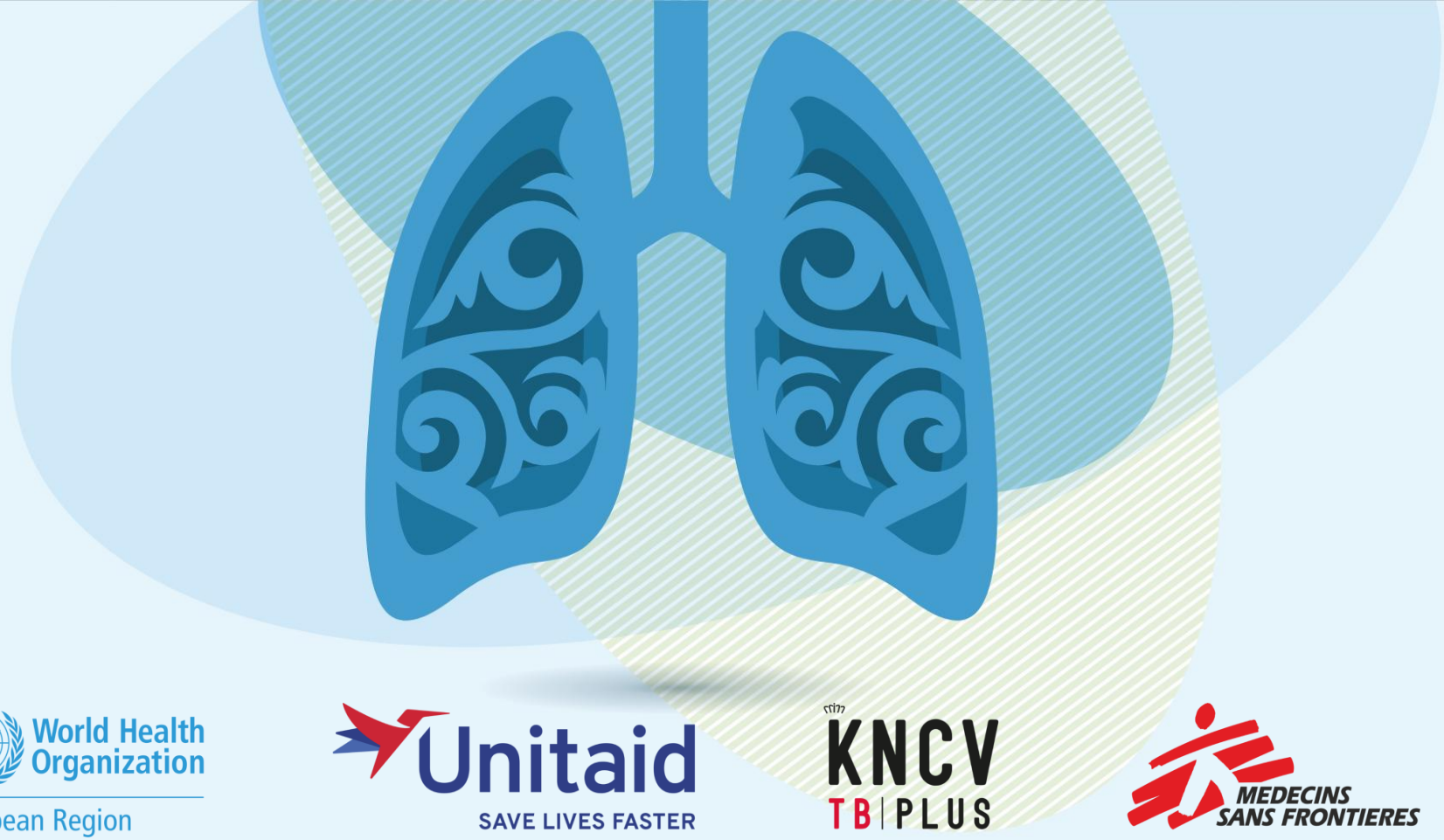

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РЕГИОНАЛЬНЫЙ СЕМИНАР ПО ВОПРОСУ УСКОРЕННОГО ВНЕДРЕНИЯ

РУКОВОДСТВА ВОЗ ПО ПРОФИЛАКТИКЕ И ДИАГНОСТИКЕ ТУБЕРКУЛЕЗА И ЛЕЧЕНИЮ ТУБЕРКУЛЕЗА С ЛЕКАРСТВЕННОЙ УСТОЙЧИВОСТЬЮ (ЛУ-ТБ)

REGIONAL WORKSHOP ON ACCELERATED IMPLEMENTATION OF WHO GUIDELINES

ON TB PREVENTION, DIAGNOSIS, AND DRUG-RESISTANT TB (DR-TB) TREATMENT

WHO Policy Updates: TB Infection Testing with TBSTs and IGRAs

EURO workshop to plan the accelerated implementation of new WHO policies

Almaty 28-30 April, 2025

Alexei Korobitsyn
Patricia Hall-Eidson

Diagnostic Team
Global TB Programme

World Health Organization

Testing for TB Infection

- Tuberculosis infection (TBI) is defined as a state of persistent immune response to stimulation by *M. tuberculosis* antigens with no evidence of clinically manifest TB disease
- ~ ¼ of the world's population is estimated to have been infected with *M. tuberculosis*
- An average 5–10% of people who are infected will develop TB disease over the course of their lives, usually within the first 5 years after initial infection
- TB Preventive Treatment (TPT) is a critical component of the WHO End TB Strategy and of other work to eliminate TB
- WHO guidelines on TPT are premised on the probability that TBI will progress to TB disease in specific risk groups, on the underlying epidemiology and burden of TB and on the feasibility and the public health benefit of the intervention
- Mass, population-wide testing and treatment of TBI are not feasible at present because the tests are imperfect, there is a risk of serious, potentially fatal adverse drug reactions, and the cost would be high, thus providing unclear benefit for populations at lower risk.
- Testing for TBI increases the certainty that individuals targeted for TPT will benefit better from it; however, testing is not required to initiate TPT

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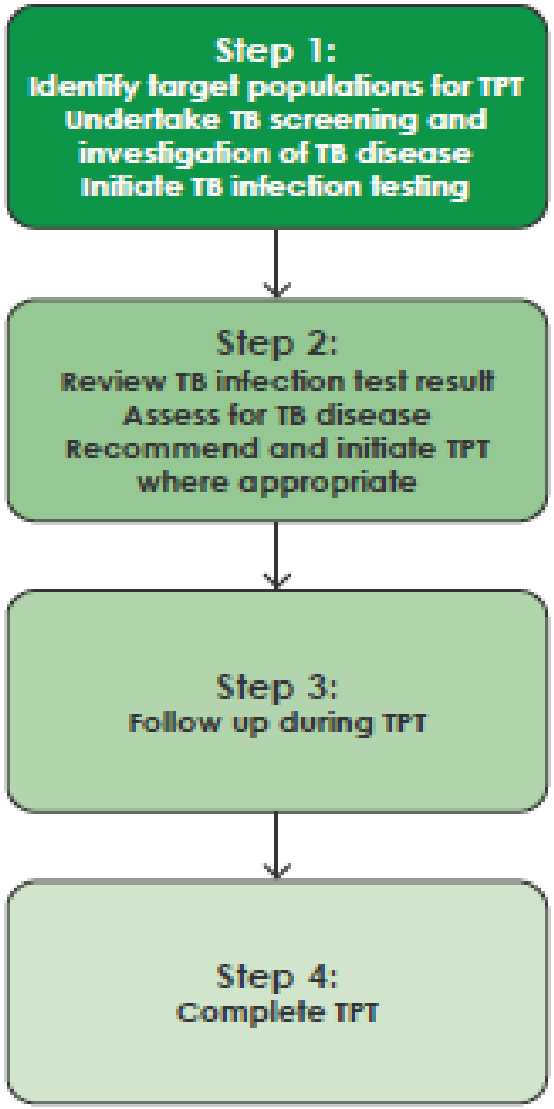
Four-step Person-Centered TB Infection Cascade of Care



All health care personnel, in all programmes and all settings, identify target populations for TPT and screen for TB, assessing TB symptoms and preferably using more accurate tools (e.g. CXR) to detect TB disease; those with a positive TB screen are promptly investigated for TB disease. At the same visit, qualified personnel administer skin tests (TST or TBST) or draw samples for IGRA to detect TB infection.

Trained health care personnel read and interpret the TB infection skin test result or obtain the IGRA result. If the test result is positive, they reconfirm that the earlier assessment satisfactorily excluded the likelihood of TB disease, then determine TPT eligibility through clinical evaluation, counsel the patient and initiate TPT, and complete the baseline recording during the same visit.

Trained health care personnel oversee provision of TPT for early identification, recording and reporting of adverse events and follow the patient through TPT completion
Adopting shorter and safer TPT will improve this step.

TPT completion will be facilitated by factors such as ongoing support during TPT and use of a shorter regimen. The final TPT outcome is recorded and reported.

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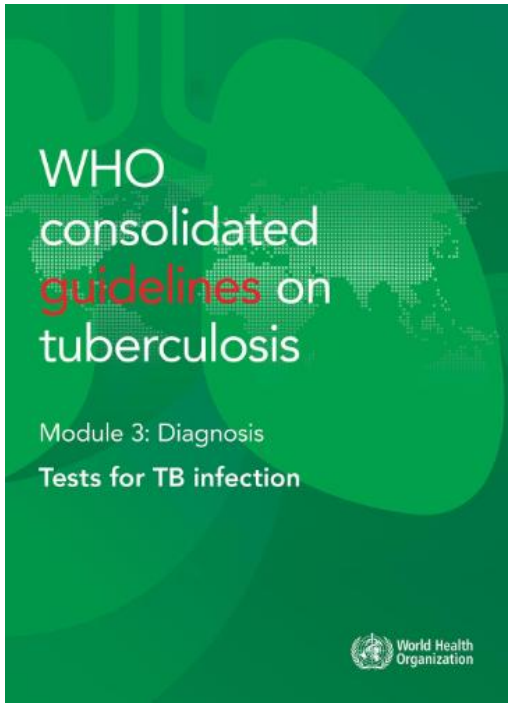
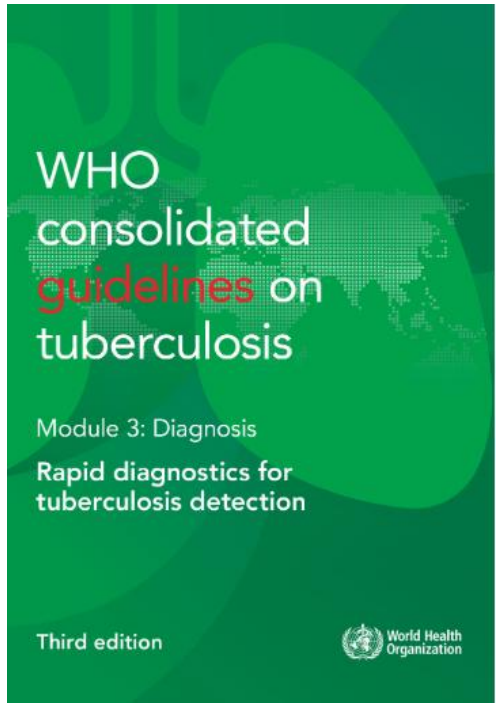
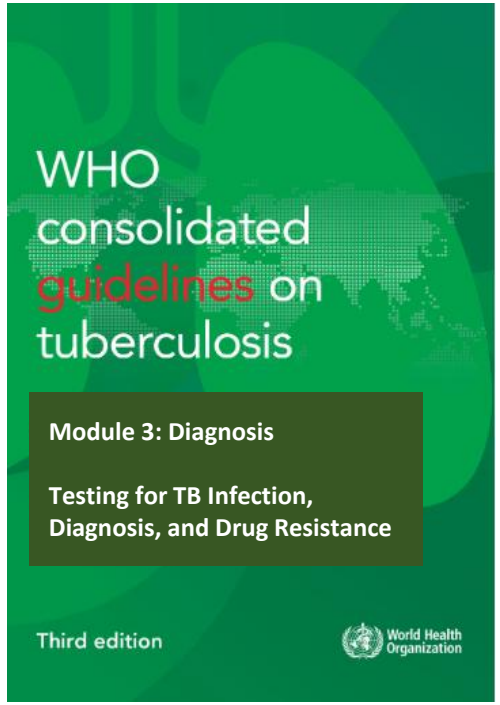
Upcoming 2025 WHO Guidelines & Operational Handbook Combine Testing for TB Infection, Diagnosis of TB and Drug Resistance





Edition 2024



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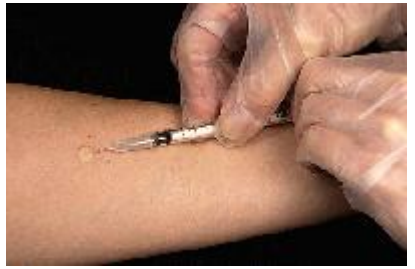
3 WHO Diagnostic Classes of Tests for TB Infection

	Recommendation	Products
TB Skin Tests (TSTs)	Either a tuberculin skin test (TST) or interferon-γ release assay (IGRA) can be used to test for TB infection. *(Strong recommendation, very low certainty of evidence)*	Tuberculin skin tests (PPDS)
Interferon Gamma Release Assays (IGRAs)		QuantiFERON TB Gold Plus ELISA (Qiagen, Hilden, Germany) T-SPOT®.TB (Oxford Immunotec, Oxford, UK) Wantai TB-IGRA ELISA (Wantai BioPharm Enterprise Co, Bejing, China) STANDARD E TB-Feron ELISA (SD BIOSENSOR, Gyeonggi-do, Republic of Korea) LIAISON QFT-Plus CLIA (Diasorin, Saluggia, Italy)
Mtb Antigen-Specific Skin Tests (TBSTs)	Mycobacterium tuberculosis antigen-based skin tests (TBST) may be used to test for TB infection. *(Conditional recommendation, very low certainty of evidence)*	Siiltibcy (Serum Institute of India, Pune, India) Diaskintest (Generium, Moscow, Russia) C-TST (Chongqing Zhifei Biological Products, Chongqing, China)

- There is no “gold standard” test for TBI
- WHO recommendations for three testing classes with multiple products

TB skin test (TST) using tuberculin



- Tests deliver a standardized preparation of Purified Protein Derivative (PPD) from *M. tuberculosis* intradermally
- PPD contains a mix of antigens, including some that are specific to *M. tuberculosis,* but also many that are found in nontuberculous mycobacteria (NTM) and BCG. Hence, false positive reactions can occur in people with NTM disease, with sensitization to NTM antigens, or who received BCG vaccination
- Testing is very safe, including for pregnant and lactating women. Only 2-3% of all people tested experience local reactions with blistering that typically self-resolve

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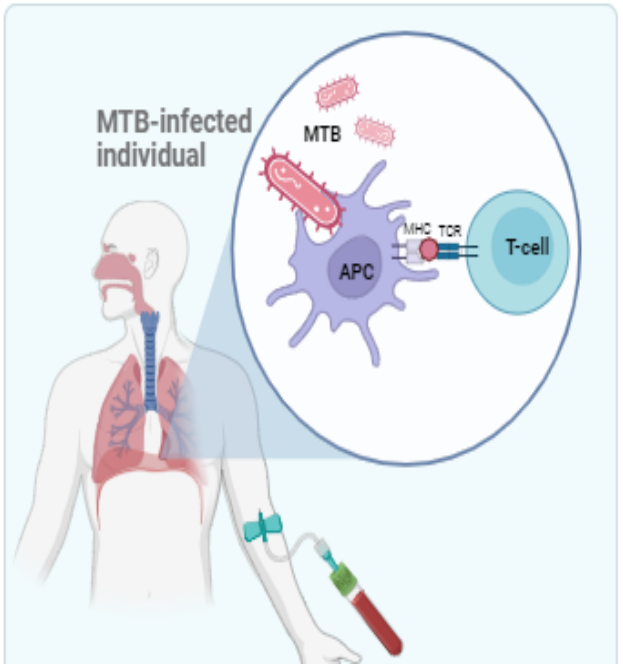
Interferon Gamma Release Assays (IGRAs)

- Blood-based in vitro tests used for detection of TB infection
- They are alternatives to antigen-based skin tests which also measure cell- mediated immune responses
- More specific than Tuberculin Skin Tests (TSTs) as they use TB-specific antigens
  - All include ESAT-6, CFP-10, +/- TB7.7
- Similar specificity to *Mycobacterium tuberculosis* (Mtb) antigen-specific skin tests (TBSTs)
- Requires blood draw (phlebotomy), laboratory infrastructure, technical expertise, equipment for incubation and interpretation

Steps of IGRAs

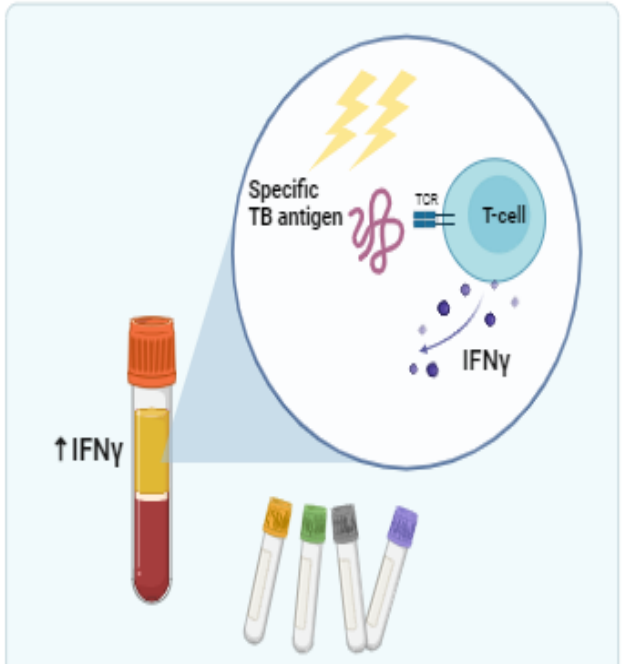
1 Blood Collection

Collect a blood sample from the individual



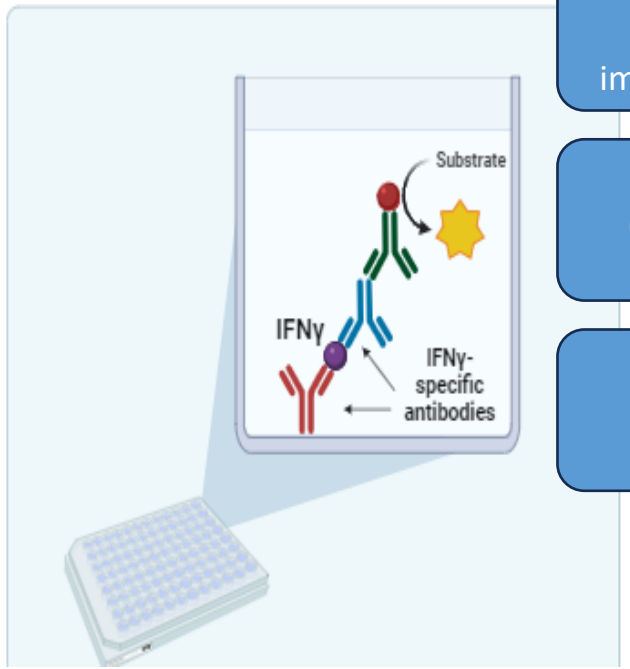
2 T-cell Stimulation

Stimulate T-cells with TB-specific antigens to trigger the release of IFNγ in antigen-coated tubes



3 IFNγ Measurement

Measure IFNγ release



ELISA
(enzyme-linked immunosorbent assay)

CLIA
(chemiluminescent immunoassay)

FIA
(fluorescence immunoassay)

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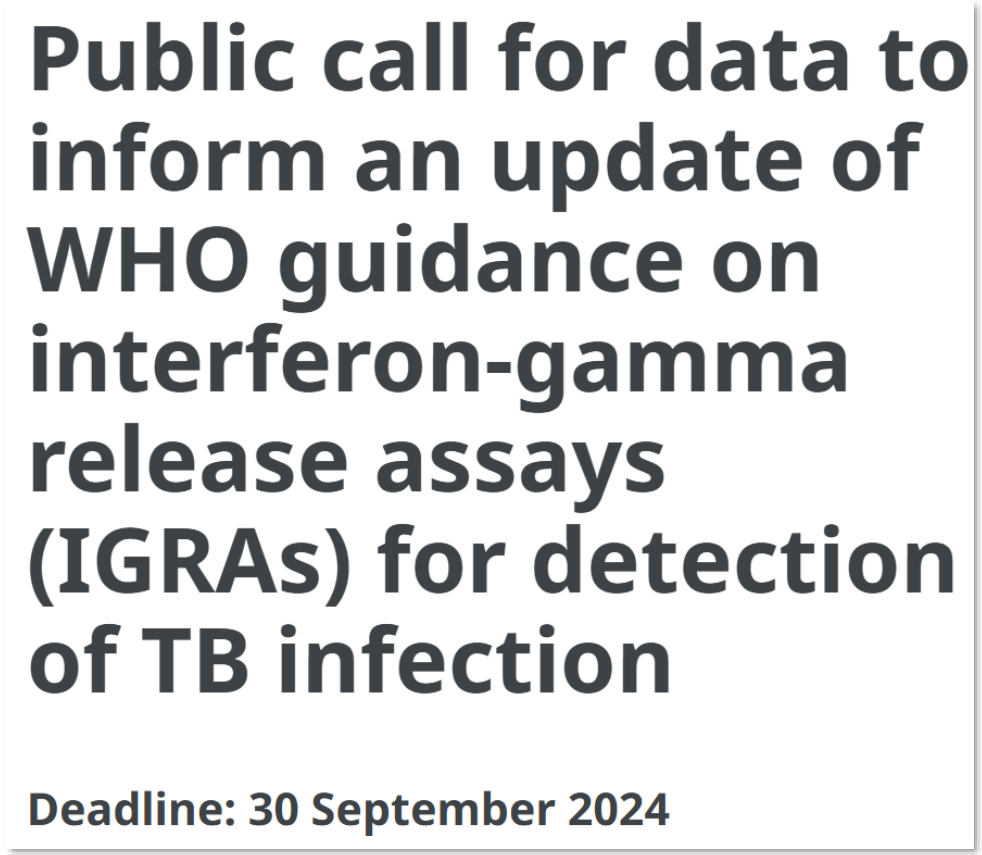
2025 WHO Assessment of New IGRAs



- Expanded availability of new IGRAs for detection of TB infection
- February 2024 WHO has commissioned a systematic review of evidence which considered primary and secondary performance analyses and practical information
- August 2024 WHO Issued public and targeted manufacturer call for data on new IGRAs to inform policy updates
- Data was received for 13 new IGRAs; 6 met assessment eligibility requirements (2 published studies on test performance)
- Technical Advisory Group assessment conducted in January 2025

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New IGRAs identified in 2025

Wan200+

Wan100

Thirteen tests were submitted for evaluation:

- STANDARD E TB-Feron (ELISA), SD Biosensor, Gyeonggi-do, Republic of Korea
- ASACIR.TB (ELISA), Haikou VTI Biological Institute, Hainan Sheng, China
- LIOFeron TB/LTBI IGRA (ELISA), Braunschweig, Germany
- VIDAS TB-IGRA (ELISA), bioMérieux, Marcy-l'Étoile, France
  AIMTB (ELISA, FLF), Leide Biosciences Co, LTD, Guangzhou, China
  AFIAS IGRA-TB (FIA), Boditech Med Inc., Gangwon-do, Republic of Korea
  Ichroma IGRA-TB (FIA), Boditech Med Inc., Gangwon-do, Republic of Korea
  STANDARD E TB-Feron (FIA), SD Biosensor, Gyeonggi-do, Republic of Korea
  Wantai TB-IGRA (FIA), Wantai Biological Pharmacy Enterprise Co, Bejing, China
- AdvanSure i3 TB-IGRA (CLIA) Invitros, Seoul, Republic of Korea
- LIAISON QFT-Plus (CLIA) Diasorin, Saluggia, Italy
- Wantai TB-IGRA (CLIA) Wantai BioPharm, Bejing, China
- T-Cell Select & T Cell Xtend, Oxford Immunotec, Oxford, UK

Of these, six met the inclusion criteria (two or more published studies on test performance) to proceed to the Pathway B TAG evidence assessment.

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New 2025 WHO Policy Statements on IGRAs

SD Biosensor STANDARD E TB-Feron ELISA

Diasorin LIAISON QFT-Plus CLIA

- Performance of the STANDARD E TB-Feron (ELISA) and LIAISON QFT-PLUS (CLIA) **is comparable** to that of the current WHO-recommended IGRAs for the detection of TB infection.
- Current WHO recommendations for the use of IGRAs **are valid** for the STANDARD E TB-Feron (ELISA) and LIAISON QFT-PLUS (CLIA).
- The performance of the ASACIR.TB, ichroma IGRA-TB (FIA), Wantai TB-IGRA (CLIA), and AvanSureI3 TB-IGRA (CLIA) **could not be adequately compared** to that of WHO-recommended IGRAs for the detection of TB infection.

Considering these new policy statements, recommendations on the use of IGRAs for the detection of TB infection now apply to **five within-in class products***:

- QuantiFERON TB Gold Plus ELISA (Qiagen)
- T-SPOT.TB (Oxford Immunotec)
- Wantai TB-IGRA ELISA (Wantai BioPharm Enterprise Co)
- STANDARD E TB-Feron ELISA (SD BIOSENSOR)
- LIAISON QFT-Plus CLIA (Diasorin)

**QuantiFERON Gold and QuantiFERON Gold In-Tube were previously recommended by WHO but have been discontinued by the manufacturer.*

M. tuberculosis antigen-based skin tests (TBSTs)

Serum Institute of India Siiltibcy

Generium Diaskintest

Chongqing Zhifei Biological Products C-TST

- New skin tests that use the same antigens as many IGRAs and without safety concerns
- Like TSTs, use intradermal injection of antigen and have induration read after 48–72 hours
- Based on available evidence, a 2022 WHO Guideline Development Group concluded that the **diagnostic accuracy of TBSTs is comparable to that of IGRAs and greater than that of the TST**

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TBST Population, Cost, Equity & Feasibility Considerations

- **Recommendation extrapolated** to the following populations with limited data:
  - PLHIV, children and adolescents ≤ 18 years, people who have been vaccinated with BCG
- **Cost-Effectiveness** (limited data): Modelling found that in Brazil and South Africa use of TBSTs would be cost saving compared with both TSTs and IGRAs, while in the UK, it would be cost saving compared with the TST but only cost-effective compared with IGRAs.
- **Equity**:
  - Likely to improve health equity through provision of a more accurate, low-cost test for resource-limited settings where TSTs are already in use
  - Perceived to have greater accuracy than TSTs
  - Considered desirable without the negative consequences of false positive TST results
- **Feasibility**: Qualitative evidence was supportive in settings where the TST is already in use, because the required resourcing and training are already in place.

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Next Steps: Regulatory Approvals & Assessments

- The TBST, Siiltibcy (Cy-TB), is the first test to receive stringent regulatory approval (SRA)
- Available for Stop TB Partnership Global Drug Facility Medicines Catalogue (unit cost 1.5USD)
- WHO Prequalification process for TBSTs with SRA is now available and specific to each product
- WHO Prequalification process for IGRAs is under development; New and updated tests may be reviewed through the interim GTB Pathway B (Technical Advisory Group) pathway

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Conclusions

- TB infection is an important driving force for the global TB epidemic
- Testing for TB infection increases certainty that those that receive TPT will benefit
- There are three classes of technologies recommended by WHO for detection of TB infection:
  - TB skin tests (TSTs)
  - Interferon gamma release assays (IGRAs)
  - *M. tuberculosis* antigen-based skin tests (TBSTs)
- January 2025 WHO Technical Advisory Group evidence assessment resulted in the addition of two new IGRAs to the class
- WHO Prequalification process for TBST is available, and the process for IGRA is under development

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THANK YOU!
СПАСИБО!

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