# DRAFT TARGET PRODUCT PROFILE:

# TEST FOR PROGRESSION OF TUBERCULOSIS INFECTION

*The TPP was drafted by Prathiba Seshadri and Claudia Denkinger, FIND, with the input from experts and stakeholders in the field. This a working draft that is intended to provide a conduit for communication.*

# Target Product Profile: Test for Progression of Tuberculosis Infection



Definitions:

**TB infection**: Any person with a positive test for TB infection (TST≥5mm, positive IGRA according to manufacturer's instructions) without microbiological, radiological, or clinical evidence of active TB.

**Subclinical TB disease** (for research purposes): Asymptomatic patients with evidence of TB on radiographic and/or microbiological examination or with development of TB within 2 months of initial evaluation. Two forms of subclinical TB are conceivable: (i) disease is early and still contained (mostly immunocompetent patients) or (ii) disease is early but not contained however the patient is unable to mount an inflammatory response that would result in symptoms (mainly immunocompromised patients). A subset of patients with subclinical disease (primarily immunocompetent patients) will not progress to active disease.

**TB disease**: Symptomatic patients with compatible clinical and/or radiology and/or histology for TB and a positive microbiological test and started TB treatment (confirmed TB), or with compatible clinical and/or radiology and/or histology for TB and started TB treatment (clinical TB).

Background:

About one third of the world's population is infected with *M. tuberculosis* (MTB) [1, 2]. Infected individuals are at risk of endogenous reactivation of the same strain and progression to active tuberculosis (TB) with the highest risk in the first two years after infection [3-5].

While TST/IGRAs show that an individual has been infected with MTB, they poorly predict whether an individual will progress to active TB in the future [6-8]. They also lack the capacity to differentiate between recent and remote infection, which is important as most cases of reactivation occur in the first 2 years after infection [9]. If the prior TST/IGRA status of a patient is known, sequential testing can be done to identify new conversions, which are associated with higher risk of progression to TB disease (compared to non-converters). However, even among converters, the overall risk of progression to active TB disease is low [10]. In addition, sequential testing for IGRAs is associated with large number of false positives given the limited reproducibility of the tests [11]. TST/IGRAs also have limited use in monitoring response to preventive therapy for infection given the same issues around reprobducibility [9]. Biomarkers other than IFN-gamma have been evaluated for detection of infection. Only one study of IP-10 looked at the predictive value employing incident TB as the gold standard; likely reflecting the excessive cost of studies with long-term follow up [12].

An ideal test of progression would likely differentiate patients in the various stages from infection to active TB [13]. However these stages are currently poorly defined and understood. The test could possibly rely on identification of a mycobacterial product or host response marker that is identified in individuals farther in the spectrum towards active TB [14]. This may be particularly challenging as active TB is itself an eclectic disease largely dependent on host response i.e. primary pulmonary vs. disseminated/miliary TB.

In addition, for a test to have impact in high-burden settings, it needs to be repeated frequently to detect patients shortly after they have acquired an infection in order to prevent progression to disease. Therefore, the test should use an easily accessible sample and be suited for use in a primary or secondary healthcare facility by health care personnel with minimal training. The test should have high positive predictive value (>95%) for progression of infection to active TB and high negative predictive value for active TB, which may be mutually exclusive. Alternatively, a two-step process involving a highly sensitive screening test for infection followed if positive by a biomarker test to assess progression risk may be employed. A test with a lower positive predictive value may be acceptable in the setting of a less-complex and less toxic regimens for the treatment of infection, but will still be sub-optimal owing to the risk of subjecting a low risk individual to potential drug toxicity.

It may be challenging to develop an affordable test with all the above-mentioned characteristics. However, increasing use in developed nations and saving costs on treatment of infection/monitoring may help reduce test costs and costs to the health care system overall in the future.

TPP outline:

| CHARACTERISTIC | OPTIMAL | MINIMAL | EXPLANATIONS/ LIMITATIONS |
|---|---|---|---|
| **Intended Use** | | | |
| Goal of test/ Intended use | Biomarker-based test that can be used to predict risk of progression to active TB from TB infection (TBI) within the next 2 years, with the ability to rule out active TB. Ideally the test result should decrease or revert to negative with treatment and thus allow an assessment of treatment success or cure and consequentially also reinfection. | Biomarker-based test that can be used to predict risk of progression to active TB from TB infection within the next 2 years. As this test may also be positive in patients with active TB, identification of these individuals needs to be done by a highly sensitive test | TST and IGRAs form the mainstay for the diagnosis of TB infection. However, these tests do not predict which individuals are likely to progress to active TB. Progression of TBI may involve varying immuno-pathogenic processes depending on stage (subclinical or clinical), type and site of disease (e.g. pulmonary vs. military TB).<br><br>TWO TEST concept of test: one test that is good in identifying infection that does not progress paired with a test that identifies infection (i.e. IGRA) |

| | | | |
|---|---|---|---|
| Type of test | Single or multiple biomarker based graded or qualitative test (positive/ negative result) | Single or multiple biomarker based qualitative test | Although this test should have the ability to rule out active TB, it may not be possible to achieve this if we consider that sub-clinical disease is part of the spectrum of active TB. Therefore a graded test with different cutoffs for sub-clinical and active TB may be useful.<br>Alternatively, a two-step process comprising a highly sensitive test as a first step to define the at risk population, followed by a test that can identify individuals at high risk for TBI progression can be considered. |
| Type of specimen | Capillary whole blood (finger stick sample) / saliva/ sputum/ urine /stool | Whole blood by phlebotomy (or subpopulation of cells if simple processing included) | |
| Target population | Individuals who have increased likelihood of exposure to a person with active TB (close contacts, health care workers, immigrants) and individuals with conditions that predispose to progression of TBI to active disease (HIV infection, diabetes, chronic renal failure, chronic medical illness, recent TST converters, children < 5 years of age, and persons receiving anti-TNF). These individuals should be asymptomatic, ideally with negative physical examination and chest X-rays for active TB | Individuals who have increased likelihood of exposure to a person with active TB (close contacts, health care workers, immigrants) and individuals with conditions that predispose to progression of TBI to active disease (HIV infection, chronic medical illness, recent TST converters, children < 5 years of age). | |
| Target user of the test | Health care workers with no or minimal laboratory training e.g. nurses | Health care workers with laboratory training e.g. skilled laboratory technicians | |
| Setting (lowest level of implementation in | Health post | Referral facilities with some laboratory facilities | |

| | | | |
|---|---|---|---|
| health care system) | | | |
| **Performance characteristics** | | | |
| Diagnostic sensitivity for progression to active TB | ≥90% sensitivity | ≥75% sensitivity | These targets and explanations provided here are suggested as basis for discussion. The basic rationale for the proposed targets is the following: accuracy needs to be high enough such that a 'test-and-treat' strategy is acceptable from the perspectives of patients, clinicians and public health policy makers. We judged acceptability by these groups by assessing the PPV and NNT across the range of all possible combinations of Sens/Spec for a given 2-year cumulative incidence active TB (risk of progression). A more detailed description of rationale is provided in the note below the table. |
| Diagnostic specificity for risk of progression to active TB | ≥90% specificity | ≥75% specificity | |
| Diagnostic specificity for TBI (able to differentiate from active TB) | >97% | NA (expected to be positive in active TB) | An ideal test of progression from TBI to active TB would likely differentiate patients in the various stages of the spectrum from infection to active TB [13]. However these stages are currently poorly defined and understood. |
| Reproducibility | Reproducibility: Inter-assay CV =< 10.0% at high and low extremes of the assay | | If quantitative outcomes of a test are measurable (e.g. limit of detection, CT-values) |
| **Operational characteristics** | | | |
| No. of steps to be performed by operator | < 2, no timed steps | < 10, 1-2 timed steps | |
| Volume measurements | None | Measuring device provided with kit | |
| Sample preparation | None or fully integrated | Allows for centrifugation/ incubation | A test even if comparable in term of cost and complexity to the current IGRAs would add substantial value if it would allow to treat only those who will progress to active disease |
| Data analysis | Integrated | Integrated | |
| Time to results | < 24 hours | 2-5 days | |

| | | | |
|---|---|---|---|
| Biosafety | Universal precautions | Universal precautions, Biosafety Level II | |
| Operating Temperature | Between 5 and 50° C, 90% humidity | Between 5 and 30° C, 70% humidity | |
| Reagents | Self-contained within test kit | Up to 2 external reagent, reconstitution not required | |
| Stability of test kit / reagent | 24 months at 40° C, 90% humidity, should be able to tolerate stress during transport (3 days at 50° C) | 12 months at 30° C, 70% humidity, cold chain required for transport | |
| Instrumentation | No instrument | Preferably instrument free.<br>If instrument: Small, portable or hand-held instrument (<1kg) that can operate on battery or solar in places with interrupted power supply | |
| Waste disposal | Standard infected waste disposal at health center | | |
| Internal Quality control | Included positive control | | |
| External Quality control | Included positive and negative controls | Included positive and negative controls | |
| Maintenance/ calibration | No calibration/maintenance required | Annual calibration by company staff; maintenance every 1,000 tests or 12 months | |
| Power requirements | Ideally instrument free test; all equipment with rechargeable battery lasting up to 8 hours | 110-220 V AC current; UPS for power failures | |
| Result capturing, documentation, data display | Ideally instrument free test, but should allow for attaching, or scanning result to the reader to have the ability to save and print the results | Ability to save the results either via instrument or via a separate reader (or alternative)<br><br>When instrument is used the test menu should be simple with integrated LCD screen; simple key | |

| | | | |
|---|---|---|---|
| | | pad or touch screen | |
| Data export (connectivity and interoperability) | Preferably instrument free but test should allow data export via reader<br><br>Full data export (on usage of device, error/invalid rates, and personalized, protected results data) over USB port and network. Network connectivity through GSM/UMTS mobile broadband modem. Results should be encoded using a documented standard (such as HL7) and be formatted as JSON text. JSON data should be transmitted through HTTP(S) to a local or remote server as results are generated. Results should be locally stored and queued during network interruptions and sent as a batch when connectivity is restored | Full data export (on usage of device, error/invalid rates, and personalized, protected results data) over USB port and network. Network connectivity through Ethernet, Wi-Fi, and/or GSM/UMTS mobile broadband modem. Results should be encoded using a documented standard (such as HL7) and be formatted as JSON text. JSON data should be transmitted through HTTP(S) to a local or remote server as results are generated. Results should be locally stored and queued during network interruptions and sent as a batch when connectivity is restored | |
| Electronics and software | None | Integrated | |
| Training | <1 day dedicated training for non-laboratory trained health personnel | 3-7 days dedicated training for a laboratory trained health personnel | Optimally, this test should be simpler than a TST requiring minimal training (5-7 days). |
| **Pricing** | | | |
| Cost of equipment | < 500 USD/ test | < 5000 USD/ test | |
| Cost of consumables (reagents/ test strips) | < 5 USD/ test | < 150 USD/ test | As an initial step, it is acceptable to have an assay costing as much as the currently available QuantiFERON - TB Gold. Making the test affordable will be an important next step. |

Note on choice of performance targets: As a benchmark for acceptable performance characteristics, we looked at PPV/NNT achieved with currently available tests (TST/IGRA) when applied to populations for whom a a 'test-and-treat' strategy is currently recommended based on the WHO guideline. Sens/Spec for risk of progression have been estimated (based on recent SR by Kik et al) to be ~54/56 for TST and ~78/58 for IGRAs. Based on these estimates e.g. for HIV-negative adult contacts (assuming a 2-year cumulative incidence of active TB of 2%) TST/IGRA achieve a PPV of 2.4%/3.7% and a NNT of 252/69.

The minimum performance targets suggested here would achieve roughly a doubling of PPV (to 5.8%) and halving of NNT (to 39) compared to IGRA, and substantially greater improvement compared to TST. This would represent a substantial improvement over currently recommended tests while hopefully being achievable by novel tests in the near future. These relative improvements would stay in a similar range in other target populations (with higher/lower risk of progression).

We note that very similar/identical improvements in terms of PPV and NNT can be achieved with a variety of combinations of Sens/Spec, other than the proposed combination of 75/75 or 90/90. We therefore suggest to indicate in the TPP that some deviation from these targets may be acceptable, as long as they lead to similar values of PPV and NNT. This is in order to avoid the situation where potentially promising tests (able to lead to acceptable values of PPV and NNT by virtue of either very high Sens or very high Spec but deficiency in the other parameter) are not further developed. For example: similar PPV/NNT to the minimum targets (Sens/Spec of 75/75) are also achieved with a 'high-sensitivity test' (Sens/Spec of 95/65) and a 'high-specificity test' (Sens/Spec of 50/85). However, while varying combinations of Sens/Spec can lead to similar PPV/NNT, trading sensitivity against specificity has other consequences that would need to be considered, such as a larger absolute number of patients "overtreated" with IPT (for the 'high-sensitivity test') or a larger absolute number of patients "missed" (for the 'high-specificity test').

**References:**


1. Vynnycky E, Fine PE. The natural history of tuberculosis: the implications of age-dependent risks of disease and the role of reinfection. Epidemiol Infect **1997**; 119(2): 183-201.
2. World Health Organization. Global Tuberculosis Control: WHO report 2014. Geneva: World Health Organization, **2014**.
3. Sutherland I, Svandova E, Radhakrishna S. The development of clinical tuberculosis following infection with tubercle bacilli. 1. A theoretical model for the development of clinical tuberculosis following infection, linking from data on the risk of tuberculous infection and the incidence of clinical tuberculosis in the Netherlands. Tubercle **1982**; 63(4): 255-68.
4. Andrews JR, Noubary F, Walensky RP, Cerda R, Losina E, Horsburgh CR. Risk of progression to active tuberculosis following reinfection with Mycobacterium tuberculosis. Clin Infect Dis **2012**; 54(6): 784-91.
5. van Leth F, van der Werf MJ, Borgdorff MW. Prevalence of tuberculous infection and incidence of tuberculosis: a re-assessment of the Styblo rule. Bull World Health Organ **2008**; 86(1): 20-6.
6. Diel R, Loddenkemper R, Nienhaus A. Predictive value of interferon-gamma release assays and tuberculin skin testing for progression from latent TB infection to disease state: a meta-analysis. Chest **2012**; 142(1): 63-75.
7. Rangaka MX, Wilkinson KA, Glynn JR, et al. Predictive value of interferon-gamma release assays for incident active tuberculosis: a systematic review and meta-analysis. Lancet Infect Dis **2012**; 12(1): 45-55.
8. Mandalakas AM, Detjen AK, Hesseling AC, Benedetti A, Menzies D. Interferon-gamma release assays and childhood tuberculosis: systematic review and meta-analysis. Int J Tuberc Lung Dis **2011**; 15(8): 1018-32.

9. Getahun H, Chaisson RE, Raviglione M. Latent Mycobacterium tuberculosis Infection. N Engl J Med **2015**; 373(12): 1179-80.
10. Machingaidze S, Verver S, Mulenga H, et al. Predictive Value of Recent QuantiFERON Conversion for Tuberculosis Disease in Adolescents. Am J Respir Crit Care Med **2012**; 186(10): 1051-6.
11. Tagmouti S, Slater M, Benedetti A, et al. Reproducibility of interferon gamma (IFN-gamma) release Assays. A systematic review. Annals of the American Thoracic Society **2014**; 11(8): 1267-76.
12. Tuuminen T, Salo E, Kotilainen H, Ruhwald M. Evaluation of the filter paper IP-10 tests in school children after exposure to tuberculosis: a prospective cohort study with a 4-year follow-up. BMJ open **2012**; 2(6).
13. Barry CE, 3rd, Boshoff HI, Dartois V, et al. The spectrum of latent tuberculosis: rethinking the biology and intervention strategies. Nat Rev Microbiol **2009**; 7(12): 845-55.
14. Esmail H, Barry CE, 3rd, Young DB, Wilkinson RJ. The ongoing challenge of latent tuberculosis. Philosophical transactions of the Royal Society of London Series B, Biological sciences **2014**; 369(1645): 20130437.