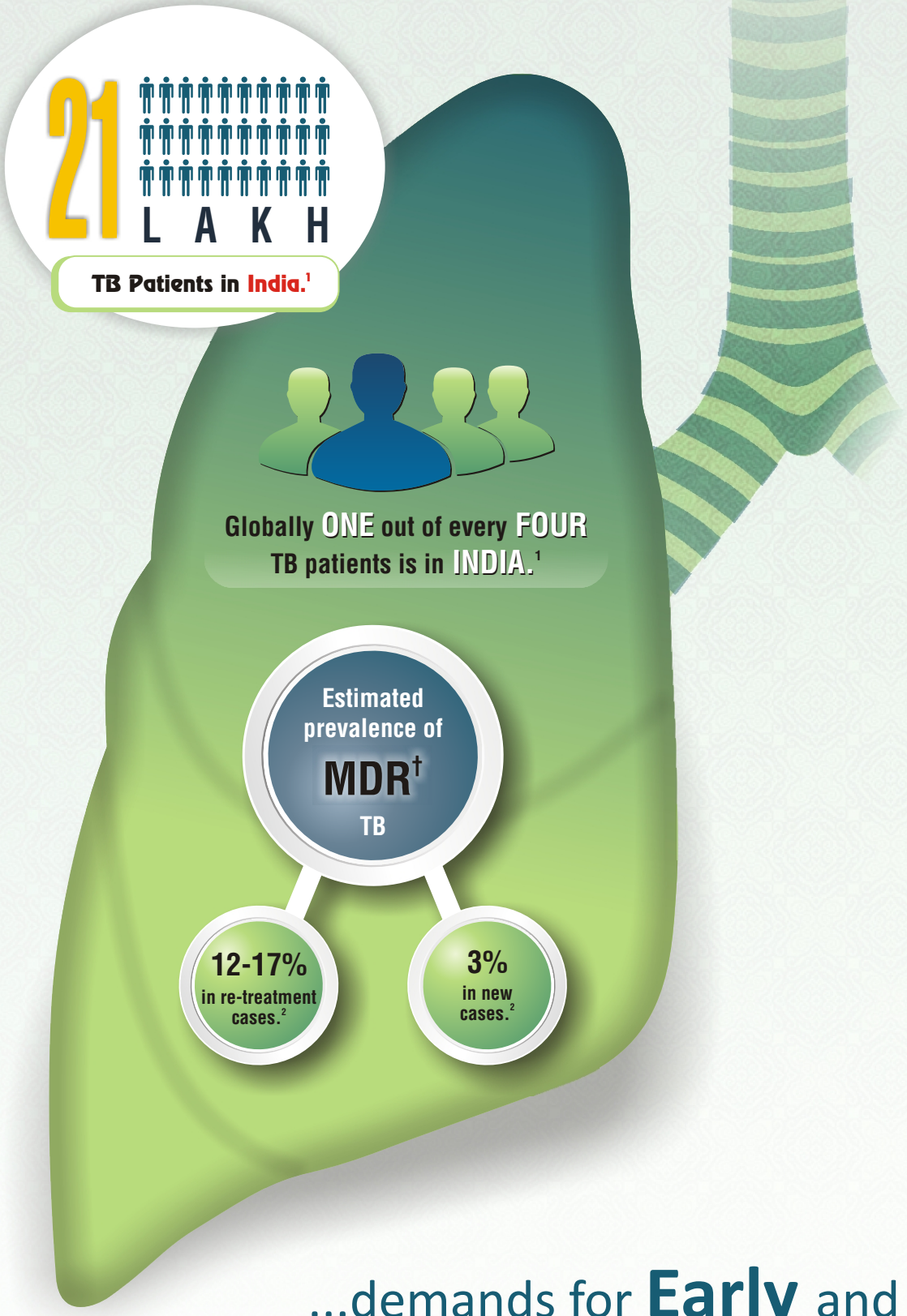
IPAQT
Initiative for Promoting Affordable & Quality TB Tests

TB* | An emerging problem...



...demands for **Early** and **Accurate** Diagnosis.

* Tuberculosis
† Multi Drug Resistance

1. TB INDIA 2015. Revised National TB Control Programme. Annual Status Report.
2. Revised National Tuberculosis Control Programme- Guidelines on Programmatic Management of Drug Resistant TB (PMDT) in India May 2012.

IPAQT
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Exposure to Tuberculosis Bacteria May Cause

Active Disease

- Bacteria overcomes the immune system of the host [1]
- Multiplies resulting in progressive disease.[1]
- Visible signs & symptoms such as weight loss, fever, night sweats, cough for more than 2 weeks.[1,2]
- Risk of transmission as well as transformation into drug resistant cases is high. [1]
- Diagnosed through micro-biological confirmation of appropriate specimens.[3]

Latent Infection

- Host is able to control the infection.[1]
- Bacteria not completely eradicated from the body.[1]
- No clinical signs and symptoms.[1]
- Risk of reactivation[1] but not transmission or infection.
- Diagnosed through immuno-logical tests such as Tuberculin Skin Test (TST) or Interferon Gamma Release Assays (IGRAs)[5]

India accounts for **~23%** of the Global TB cases[4] with a high background of latent TB infections as well.[5]

IGRAs and TST being used off-label for diagnosis of Active TB is of growing concern as it results in:

- Tremendous over treatment of people without TB[5]
- Substantial incremental cost with little gain in health[5]

1. www.jimmunol.org/cgi/doi/10.4049/jimmunol.0903856.
2. http://www.cdc.gov/tb/publications/factsheets/general/ltbiandactivetb.htm
3. STCI – Standards for TB care in India
4. TB India 2015. Revised National TB control programme. Annual Status Report.
5. Little KM, Pai M, Dowdy DW. Costs and Consequences of Using Interferon-γ Release Assays for the Diagnosis of Active Tuberculosis in India. *PLoS ONE*. 2015;10(4):e0124525.

Why IGRAs should not be used for diagnosis of active TB?

There is growing concern that the use of IGRAs has increased since the ban on antibody-based serological TB tests in 2012.[1]

- **Active TB can neither be ruled-in or ruled-out with IGRAs.**[2]
- **IGRAs have sub-optimal sensitivity for active TB.**[3]
- **As per WHO, IGRAs and TST cannot accurately predict the risk of infected individuals developing active TB disease.**[3]
- **Higher cost implications-** For every individual tested by IGRA rather than sputum smear microscopy the incremental cost of TB diagnosis and treatment was ₹2964. *(i.e USD 49.4 million for every million individuals tested- Fig 1)*[1]

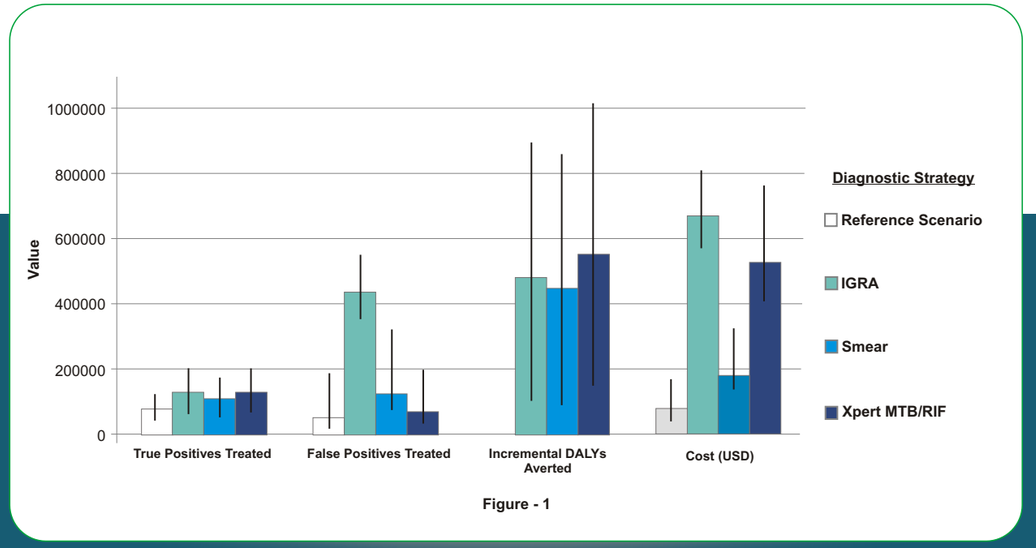


Figure - 1

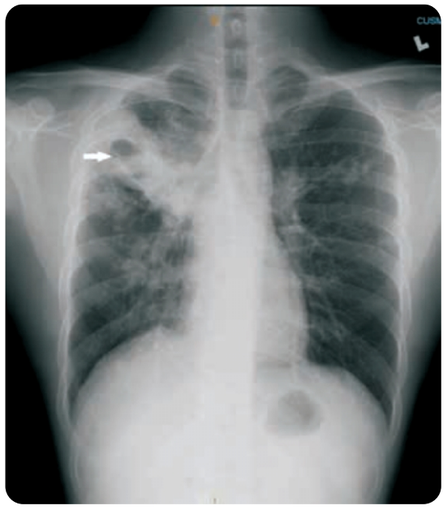
Figure-1: Economic and epidemiological outcomes among 1 million adults with TB symptoms in India. Model outcomes, including true positive TB cases treated, false positive cases treated, incremental DALYs averted and costs (USD). [1]

1. Little KM, Pai M, Dowdy DW. Costs and Consequences of Using Interferon-γ Release Assays for the Diagnosis of Active Tuberculosis in India. *PLoS ONE*. 2015;10(4):e0124525.
2. Pai M, Denkinger CM, Kik SV, *et al*. Gamma interferon release assays for detection of Mycobacterium tuberculosis infection. *Clin Microbiol Rev*. 2014 Jan;27(1):3-20.
3. http://www.who.int/tb/features_archive/igra_policy24oct/en/

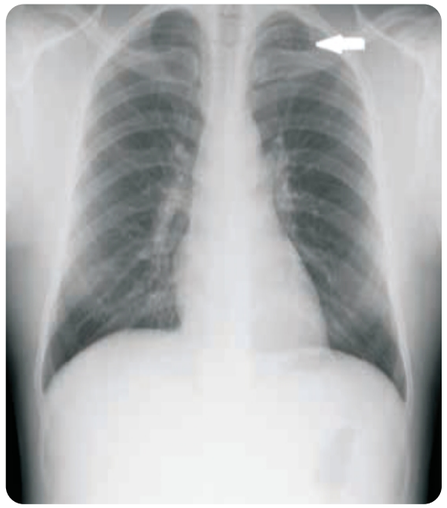
Chest Radiography

It is a screening but not confirmatory tool

Classical picture of active pulmonary TB[1]



Potential TB suspect*[1]



* Minimal TB with minor densities in the left upper lobe. Induced sputum grew TB on culture

- Chest X-rays: Provides supportive evidence for pulmonary TB.[2,3]
- Chest X-rays: Neither specific nor sensitive.[2,3]
- Other diseases may mimic TB on chest X-rays.[2,3]
- Supplement to microscopy, NAAT+ and culture.[2,3]

Treatment of TB purely on the basis of X-rays can result in significant unnecessary treatment with adverse consequences for non-TB patients.[1]

+ NAAT - Nucleic Acid Amplification Test

1. Interpretation of chest X-rays in Tuberculosis. *GP Clinics. Let's Talk TB* (supplement). First edition, 2014.
2. Pai M. Diagnosis of pulmonary tuberculosis: what every GP should know. *GP Clinics* 2013;3:22–28.
3. Hopewell PC, Pai M, Maher D, *et al.* International standards for tuberculosis care. *Lancet Infect Dis* 2006;6:710–725.

WHO recommends

All patients suspected of having pulmonary TB should have a WHO endorsed molecular test or culture which may be supplemented by two sputum specimens submitted for microscopic examination.[1]

Light Emitting Diode Fluorescence Microscopy (LED FM)

- LED FM is 10% more sensitive as compared to conventional light microscopy.[2]
- LED FM requires less than 25% of the time taken to read slides using conventional light microscopy.[2]
- Report obtained on the same day

XPERT MTB/RIF

- Overall pooled sensitivity* of 88% and pooled specificity* of 99%.[3]
- For RIF resistance, pooled sensitivity** of 95% and pooled specificity** of 98%.[3]
- Report obtained in 2 hours

*as compared to culture

** as compared to culture based drug susceptibility testing

Line Probe Assay (Genotype MTBDR plus)

- For RIF resistance, pooled sensitivity of 98.1% and specificity of 98.7%.[4]
- For INH resistance, pooled sensitivity of 84.3% and specificity of 99.5%.[4]
- Report obtained in 1 to 2 days
- Provides MTB or 29 MOTT† differentiation from culture by latest Genotype CM and AS Kits

Liquid Culture (MGIT / BacT Alert)

- Regarded as international gold standard for drug susceptibility testing.[5]
- Report obtained in 2 weeks

† MOTT - Mycobacterium other than Tuberculosis

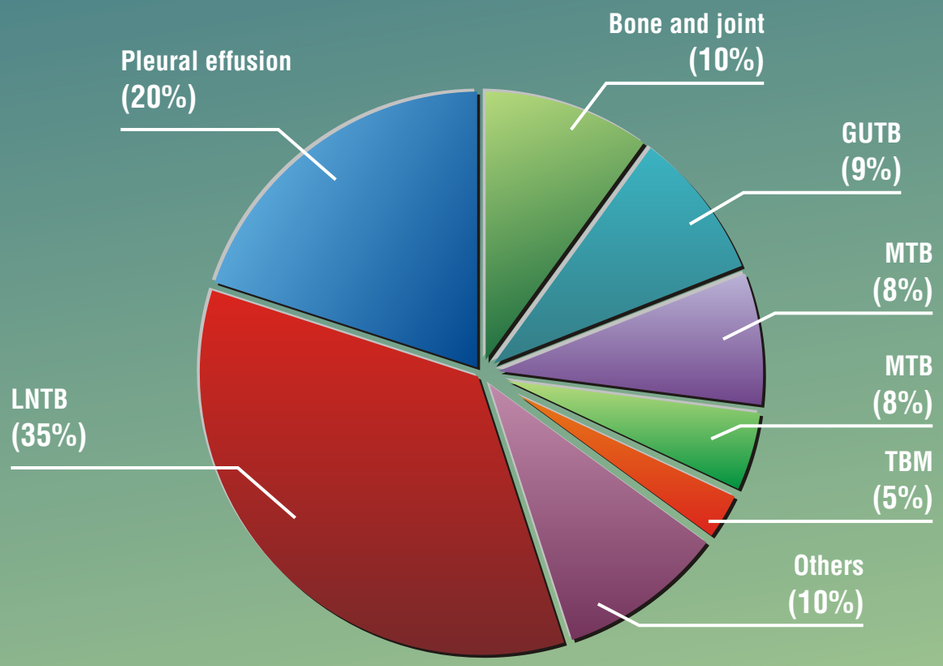
RIF - Rifampicin, INH - Isoniazid, WHO - World Health Organization

1. Hopewell PC, Pai M, Maher D, *et al*. International standards for tuberculosis care. *Lancet Infect Dis* 2006;6:710–725.
2. Alfred N, *et al. BMJ Open* 2014;4:e004093. Doi:10.1136/bmjopen-2013-004093
3. WHO policy Update : Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children
4. Ling DI, *et al* . *Eur Respir J* 2008; 32: 1165–1174.
5. http://www.who.int/tb/laboratory/whopolicyframework_rev_june2011.pdf

Extrapulmonary TB (EPTB)

- EPTB can occur in almost any site, the most common sites being lymph nodes, bones, pleural, abdominal and meningeal.[1]

- Clinical presentations of EPTB are diverse and protean leading to missed cases and delayed diagnosis.[2]



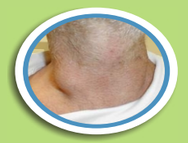
GUTB: Genitourinary tuberculosis
MTB: Miliary tuberculosis
TBM: Tuberculosis meningitis
LNTB: Lymph node tuberculosis

Appropriate specimen from the concerned site is imperative for accurate diagnosis.

The International Standards for TB Care (ISTC) recommends that all patients, including children, who are suspected of having EPTB, should have appropriate specimens obtained from the suspected sites of involvement for microbiological, microscopy and histological exam.[3]

1. Diagnosis of Tuberculosis: Importance of Appropriate Specimen Collection. *GP Clinics* Vol 3, No 12, March 2013.
2. Pai M, Nathavitharana R. Extrapulmonary tuberculosis: new diagnostics and new policies. *Indian J Chest Dis Allied Sci.* 2014 Apr-Jun;56(2):71–73.
3. Extrapulmonary Tuberculosis: New Diagnostics and New Policies. *GP Clinics. Let's Talk TB* (supplement) First edition, 2014.

Active, extrapulmonary TB

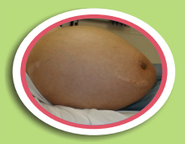


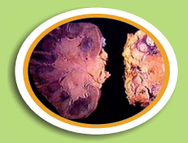
TB lymphadenitis[1]

Lymph node aspirate or biopsy

Ascitis (Abdominal TB)[1]

Ascites fluid and peritoneal biopsy



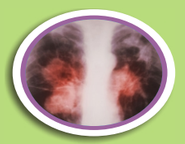


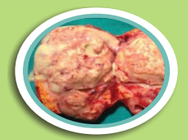
Urinary tract and kidneys Tb[1]

Urine and tissue via biopsy

Pleural effusion (TB pleuritis)[1]

Pleural fluid and pleural biopsy



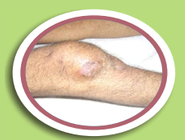


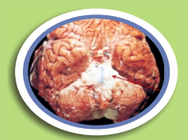
Genito-urinary tract Tb[1]

Tissue via biopsy
(Endometrial tissue in women)

Bone and joint Tb[1]

Bone/synovial tissue via biopsy





TB meningitis[1]

Cerebrospinal fluid (CSF)

Body fluids should be aesthetically collected in a sterile container by the physician using aspiration techniques or surgical procedures.*

* Standard operating procedure for EPTB as per RNTCP.

1. Diagnosis of Tuberculosis : Importance of appropriate specimen collection. *GP clinics, Let's talk TB* (supplement) First edition 2014.

The most common diagnostic tests on EPTB samples are:[1]

- Smear for acid fast bacilli (AFB)
- Liquid cultures on fluids or tissue samples
- Molecular(PCR) tests eg: Xpert MTB RIF
- Histopathological examination of biopsy tissue
- Adenosine deaminase or free interferon gamma levels in sterile fluids such as pleural, peritoneal and pericardial fluids

XPERT MTB/RIF should now be considered as a central test in the work up of EPTB and should be used along with existing tools such as microscopy, liquid cultures and histopathology to arrive at final diagnosis.[2]

Once diagnosed, EPTB must be treated with standardized treatment regimens, as recommended by STCI and ISTC.[2]

1. Diagnosis of Tuberculosis : Importance of appropriate specimen collection. *GP clinics, Let's talk TB* (supplement) First edition 2014.
2. Extrapulmonary Tuberculosis: New Diagnostics and New Policies. *GP Clinics. Let's Talk TB* (supplement) First edition, 2014.

Standard 8: Monitoring Treatment Response (Standards for TB Care in India)

8.1 Follow up sputum microscopy[1]

- Response to therapy in patients with pulmonary tuberculosis, new as well as retreatment cases, should be monitored by follow-up sputum microscopy (one specimen) at the time of completion of the intensive phase of treatment and at the end of treatment.

8.2 Extension of intensive phase[1]

- The extension of the intensive phase is not recommended.

8.3 Offer DST in follow up sputum positive cases[1]

- If the sputum smear is positive in follow-up at any time during treatment, a rapid molecular DST (as the first choice) or culture-DST (at least for R and if possible for Isoniazid (H); Ofloxacin (O) and Kanamycin (K), if R-resistant/MDR) should be performed as laboratory facilities become available.

8.4 Response to treatment in extra-pulmonary TB[1]

- In patients with extra-pulmonary tuberculosis, the treatment response is best assessed clinically.
- The help of radiological and other relevant investigations may also be taken.

8.5 Response to treatment in children[1]

- In children, who are unable to produce sputum the response to treatment may be assessed clinically.
- The help of radiological and other relevant investigations may also be taken.

8.6 Long-term follow up[1]

- After completion of treatment the patients should be followed up with clinical and/or sputum examination at the end of six months and 12 months.

- Recent evidence from India show that collecting more than one sample added little to the detection of failure of treatment and therefore only one sample at two months is recommended for initial treatment monitoring.[2,3]
- Follow up of extra- pulmonary and smear negative TB is challenging and best done by clinical review.
- Chest X- ray has shown limited accuracy in follow-up of treatment response.[3]

1. http://www.searo.who.int/india/mediacentre/events/2014/stci_book.pdf
2. Kundu D, MV Kumar A, Satyanarayana S, Dewan PK, Achuthan Nair S, et al. (2012) Can Follow-Up Examination of Tuberculosis Patients Be Simplified? A Study in Chhattisgarh, India. PLoS ONE 7(12): e51038.
3. Toshniwal M, MV Kumar A, Satyanarayana S, Dewan PK, Achuthan Nair S, et al. (2012) – IUATLD – Abstract Book – UNION World Conference for Lung Health, November 2012 – Kuala Lumpur, Malaysia

Notes

Notes

IN INDIA 2 PERSONS DIE EVERY 3 MINUTES DUE TO TUBERCULOSIS

NEARLY 1000 EVERYDAY

Indian J Tuberc 2011; 58:51–53.

THE NEED

TB affects around 21 lakh people annually in India and each undiagnosed and wrongly diagnosed case may spread the disease in their family and community.

Approximately 3% new TB patients may have Multi-Drug Resistant (MDR) strains of TB; amongst patients who had been treated for TB before, about 12-17% may have MDR-TB.

Earlier antibody tests were popular in the private sector, but these tests have proved to be inaccurate and hence banned by the Government of India. Blood-based tests like IGRAs* could be helpful in detecting latent TB infection, but are not useful for diagnosing active TB.

There has always been a need to rely on affordable and accurate tests *i.e.* those endorsed by the WHO and the RNTCP† and Standards for TB Care in India (STCI).

*IGRA - Interferon Gamma Release Assays
†RNTCP - Revised National TB Control Program

WHAT IT MEANS FOR YOUR PRACTICE?

For the first time in India, via IPAQT, these WHO endorsed tests are being offered at substantially reduced prices. You can now get your patients tested for TB and MDR-TB and get results quickly through molecular tests which offer high accuracy and are available through a network of quality-assured laboratories.

ABOUT IPAQT

IPAQT is an initiative of non-profit stakeholders and over 100 private sector labs/hospitals (approximately 3,150 collection centers) with a pan-India presence that have come together to provide WHO approved tests for TB at or below the following prices to patients.

- XPERT MTB/RIF TEST ₹2000
- Genotype MTBDRplus Test ₹1600
- BACTEC MGIT liquid culture ₹900 for TB detection
- BacT/ALERT 3D liquid culture ₹900 for TB detection

TO FIND A LAB NEAR YOU THAT IS A PART OF IPAQT AND FOR MORE INFORMATION ON THE TESTS PLEASE VISIT **WWW.IPAQT.ORG**

IPAQT

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