

CLINICAL GUIDELINES FOR RISK-BASED TB TESTING AND FOLLOW-UP IN THE US

Ronald Hattis, MD, MPH, July 20, 2025

Active TB disease causes serious illness with a 10% or higher mortality rate, is infectious to others, and since the subsidence of the COVID pandemic is the infectious disease causing the greatest annual mortality globally. Active TB disease requires effective treatment, and isolation until non-infectious. The vast majority of TB infections are initially inactive/latent, but at least 10% of may advance to active TB disease. The greatest risk of activation is during the first two years after infection, but about half of recent US active TB cases have occurred 20 or more years after infection, as immunity declines with aging. Detection and treatment can prevent 60-90% of these cases and is recommended (<https://www.ncbi.nlm.nih.gov/books/NBK599527/>).

1. **WHAT PATIENTS SHOULD BE SCREENED FOR TB?**

Most cases of active TB disease in the US occur among the following groups. **Offer TB screening to all patients (unless exempted in Section 2 below), who have:**

- ! **Birth in a country with TB incidence rate 10 or more times the US rate of 2.6/100,000. This includes anyone from Latin America, Asia and Pacific, Africa, and Eastern Europe.** See country rates at <https://worldpopulationreview.com/country-rankings/tb-rate-by-country>. IGRA test is preferred for persons born in these areas (see Section 3 below). Persons who have lived or had extended visits in these areas (e.g., >1 year, or as little as >1 month if in high-risk conditions) should also be screened. Active TB incidence for foreign-born persons is about 13 times that for US-born, and globally about 1 in 3 people are infected and about 1.5 million deaths occur.
- ! History of incarceration or homelessness at any time in the past
- ! HIV or other condition or medication (such as a TNF antagonist or steroids, current or planned) that weakens the immune system
- ! Possible history of close exposure (e.g., residential, occupational, or recreational) to a person with active TB disease at any time (may take up to 10 weeks for test to turn positive).

2. **WHAT PATIENTS SHOULD BE EXEMPTED/DEFERRED FROM SCREENING?**

- ! Lack the capacity to consent, and there is no available conservator who can consent for them
- ! Have had a previous documented negative TB screening test and no new risk factors or symptoms suggestive of active TB disease since then.
- ! **Test exemptions only:** If previous documented positive TB screening test and received documented adequate treatment for inactive/latent TB: question about symptoms, follow Section 4 below if present. If previous documented positive TB screening test but **no** documented adequate treatment: evaluate same as a new positive test, see Section 4 below.

3. **WHAT ARE THE TB SCREENING TESTS AND HOW TO DO THEM?**

Options are a blood test or a tuberculin skin test .

- ! The **blood test** is referred to as **IGRA** (interferon-gamma release assay). Two brands are currently available: Quanti-FERON-TB Gold Plus (QFT-Plus) and T-Spot TB test. Both are drawn from venous blood in the usual manner. **The IGRA is preferred for persons born in the areas listed in Section 1 above, because of the widespread and often undocumented use of BCG vaccine, which can cause false positive TB skin tests.** The lab will incubate the specimen at 37 degrees C and must process the test within 30 hours, so same-day specimen transport is important. Indeterminate or borderline results (up to 4%) should be repeated after >1 week. If still not diagnostic, a later IGRA or a TB skin test may be performed

(<https://www.sccoe.org/newsandfacts/Tuberculosis%20Testing/IGRA%20Fact%20Sheet.pdf>).

! The **skin test** is known by several names, tuberculin, Mantoux, PPD, or TST. It has been used since the 1930s. Two brands are currently available, Aplisol and Tubersol. Skin testing is still an approved TB screening method, but specificity is lower than with the IGRA, false positives are experienced from BCG vaccine or some atypical Mycobacteria, and both application and reading are technically demanding. A tuberculin (not insulin) 1 ml syringe with a 27 gauge beveled needle is used to inject 0.1 ml (5 units) a PPD-S solution intradermally into the inner forearm, with the bevel facing up. **Excellent directions are found at these sites:**

https://www.mcgill.ca/tb/files/tb/tuberculin_skin_testing_tst_technique_training_feb202018_english.pdf

<https://www2c.cdc.gov/podcasts/media/pdf/Mantouxtranscript.pdf>

! **Interpretation of skin test results:** Induration (not erythema) is measured at 48-72 hours. In California, 10 mm of induration is considered positive for everyone. Five mm is considered positive if suspected exposure within the past 10 weeks, HIV or other immune deficiency, taking corticosteroids, or X-ray finding such as fibrosis consistent with old, inactive TB (see Section 4 below). If TB infection is suspected but induration is absent or insufficient for a positive diagnosis, the skin test immune response may be “boosted” with a “second step” test given 7-25 days after the first and read at 48-72 hours, or an IGRA test may be done.

4. **WHAT FOLLOW-UP IS NEEDED IF A TB SCREENING TEST IS POSITIVE, AND HOW TO DIFFERENTIATE ACTIVE TB DISEASE FROM INACTIVE/LATENT INFECTION?**

The great majority of TB infections detected by screening will be inactive/latent and are not infectious.

! **Chest x-ray should be ordered for everyone with a positive TB screening test result (or untreated past positive test), as well as for patients with symptoms suggestive of TB.**

- o X-ray suggesting active TB despite no symptoms requires prompt sputum tests and isolation pending negative sputum smears and NAAT (see below).
- o X-ray suggesting old, inactive TB, such as fibrosis or calcified nodules, if no documented adequate treatment, is also an indication for sputum tests. If sputum is negative, treat as for inactive/latent TB (see Section 5 below), but wait for sputum culture results before starting treatment (see below).

! **All high risk patients should be asked about symptoms suggestive of active TB disease, regardless of test results, if unexplained by other diagnosis**

(<https://www.cdc.gov/tb/about/active-tuberculosis-disease.html>). If any of the following symptoms are present, especially in a person with a positive TB test history but not documented adequate treatment, or if current TB testing status is unknown, order chest x-ray, and initiate sputum tests (and a new-TB screening test if not already done). Multiple symptoms increase the suspicion of active TB disease.

- o Cough for more than 3 weeks, usually producing sputum
- o Persistent fevers
- o Chills
- o Night sweats
- o Hemoptysis (coughing up blood, usually more than tiny flecks)
- o Weight loss (unintentional)
- o Chest pain (non-cardiac)
- o Fatigue accompanying one or more of the other symptoms

- Extra-pulmonary TB (in organs besides the lungs) may cause other symptoms such as enlarged lymph nodes, hematuria (blood in urine), or meningitis
- ! If the patient is coughing, consider sending the patient with an N-95 mask for an immediate x-ray. and initial sputum tests if possible.
- ! **Physical exam** should be done as indicated, using masks if patient is coughing or has suspected active TB disease, e.g., vital signs, ENT, chest, lymph nodes.
- ! **Sputum tests to order if symptoms, or if x-ray is suspicious for active or inactive TB:**
 - **3 specimens** on separate days are typically ordered, including one or more from early morning. Safest to collect outdoors or while leaning out of an openable window.
 - **NAAT** (nucleic acid amplification test): Xpert MTB/RIF assay detects active tuberculosis as well as rifampin resistance (suggestive of multi-drug resistant TB), **in only 2 hours.** <https://www.cdc.gov/tb/php/laboratory-information/xpert-mtb-rif-assay.html>
 - **AFB (acid-fast bacilli) smear** (same since 1880s; can do rapidly, visualizes bacilli, but does not differentiate TB from atypical Mycobacteria, and many more false negative results).
 - **Culture for TB with sensitivity** (gold standard but may take 1-2 months for full results).
 - **Do not begin treatment for inactive/latent TB until a negative sputum culture result has been received, because that treatment is inadequate for active TB disease.**
- ! **Suspect active TB disease** if the patient has symptoms and a chest x-ray result is consistent with active TB. **Diagnosis is confirmed by positive sputum culture, however if AFB smears and NAA are positive, treatment for active TB disease should be initiated** (see Section 6).
- ! **Report suspected active TB disease immediately to local public health department, and consider instituting isolation precautions** (also in Section 6).
- ! **Clinical judgement is needed**, because if infection is recent (past 10 weeks) or immune function is extremely deficient, active TB disease may be present despite a negative screening test and even a negative appearing chest x-ray. Some patients may need sputum induction to produce specimens for testing. Also, a few patients might develop active TB disease despite past treatment for inactive/latent infection.
- ! **A helpful one-page chart summarizing some of the above is found at this site:** <https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/CA-TB-Prevent-TB-in-4-Steps.pdf>

5. **HOW SHOULD INACTIVE/LATENT TB BE TREATED?**

There are three currently recommended regimens for the provider and patient to choose from. (https://www.cdc.gov/mmwr/volumes/69/rr/rr6901a1.htm?s_cid=rr6901a1_x). The provider may choose to order the treatment or to refer the patient to the local public health department or an Infectious Disease specialist if available:

- ! Rifampin 600 mg (or 10 mg/kg if less) daily for 4 months
- ! INH (isoniazid) 300 mg (or 5 mg/kg if less)*, plus rifampin 600 mg(or 10 mg/kg if less) daily for 3 months
- ! INH 15 mg/kg (max. 900 mg)*, plus rifapentine 750-900 mg weekly for 12 weeks
- ! **Lab and symptom monitoring:** (Source: San Francisco Department of Public Health and General Hospital) https://www.sfcdep.org/wp-content/uploads/2018/01/LTBI-Treatment-Guidelines_20131001.pdf)
 - TB medications can be toxic to the liver. Baseline and monthly liver function tests (AST, Alkaline phosphatase and total bilirubin) are recommended for individuals who: have known liver disease, drink more than 2 glasses or shots of alcohol per day, are

injection drug users, have HIV infection, are taking a multi-drug regimens, or take other medications that are metabolized by the liver (e.g., statin). Risk increases with age. Medications for inactive/latent TB should be held if LFTS are > 3x upper normal limit, with symptoms of possible hepatotoxicity (nausea, fatigue, anorexia, abdominal pain), or >5x upper normal limit if so such symptoms.

- INH may cause peripheral neuropathy. For regimens including INH, supplementation with vitamin B6 (pyridoxine) 50mg-100mg daily is recommended. Risk increases with age and with diabetes, uremia, chronic alcoholism, severe malnutrition, HIV infection, and pregnancy. INH overdoses can cause seizures.
- Baseline complete blood count is recommended for those placed on rifampin or rifabutin. If abnormal, repeat measurements should be obtained monthly

6. **HOW SHOULD ACTIVE TB DISEASE BE MANAGED?**

! Because of the risks of complications, drug resistance, and mortality, a primary care provider who has not had experience treating TB should generally refer treatment to the local public health department or an Infectious Disease specialist. However, if these services are not conveniently and promptly available, treatment may be provided or initiated with consultation.

! **Report confirmed active TB disease immediately to local public health department.**

! **Isolation precautions** should be instituted and **continued until AFB smears from specimens on 3 separate mornings have been negative after at least 2 weeks of treatment.** (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3046814/>).

- If hospitalization is needed, patient will be in an isolation room.
- The patient should attend medical appointments wearing an N-95 mask, and should best be taken directly to an exam room to minimize time in a waiting room.
- If at home, the patient should sleep alone, cancel outside engagements, avoid family members (who will need TB screening), use fan and open windows, and use N-95 mask if going to healthcare facilities, public transportation, or any public locations. The public health department can help advise on specific precautions. Outdoor exercise without a mask is generally safe if over 6 feet from other people, especially in sunlight or a breeze.

(<https://www.healthline.com/health/tuberculosis-isolation-precautions#standard-precautions>),

(https://assets.ctfassets.net/8k0h54kbe6bj/oKgibi9pjmAh3463WRRHj/96269d98159eeea8329f762d1f6d3212/B_klingur_berklar_EN_2023.pdf)

! **Starting treatment regimen** generally includes four drugs for two months (usually **INH, rifampicin, ethambutol, and pyrazinamide**), then two drugs to which the cultures show no resistance (usually INH and rifampicin), for four more months. Pyridoxine supplementation is recommended with INH (see Section 5). Lab monitoring for toxicity and sputum response is needed. Daily or three times weekly dosage options are available

(<https://www.ncbi.nlm.nih.gov/books/NBK138743/>). Directly observed therapy, in which a health care worker observes the swallowing of each dose of medication, is recommended for all patients; observation can be remote by smartphone or other electronic means.

(<https://www.cdc.gov/tb/webcourses/TB101/page16489.html>).