TUBERCULOSIS (TB) SCREENING BEFORE INITIATING ANTI-TNF THERAPY

A resource guide for healthcare professionals

This booklet contains important safety information about anti-TNF therapies including Humira® (adalimumab) and advice on risk minimisation.

This booklet was developed by AbbVie.

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ABOUT THIS RESOURCE GUIDE

ABBVIE HAS CREATED THIS GUIDE FOR THE PURPOSE OF INCREASING AWARENESS OF SPECIFIC SCREENING RECOMMENDATIONS FOR TB BEFORE INITIATING ANTI-TNF THERAPY. THE GUIDANCE CONTAINED IS BASED ON INFORMATION AND RECOMMENDATIONS PROVIDED BY THE CENTERS FOR DISEASE CONTROL AND PREVENTION, THE AMERICAN THORACIC SOCIETY, AND THE NICE CLINICAL GUIDELINE (NG33).

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TABLE OF CONTENTS

WHY, WHO, AND HOW

Q. Why are there recommendations for TB screening for certain high-risk populations?

A. Globally, TB is a common and often deadly infectious disease.[1] The majority of individuals infected with *Mycobacterium tuberculosis* (M. tuberculosis) have latent TB infection (LTBI) rather than active TB disease. As such, identification and treatment of persons with LTBI has been essential in controlling the progression to active TB.[1,2] [Please see the screening checklists in Appendices A and B, pages 14 and 15]

Q. Who is at risk?

A. NICE define individuals who are considered to be at increased risk of developing either active or latent TB infection as:[3]

- Adults, young people, and children from any ethnic background, regardless of migration status who:
  - Are under-served*
  - Are identified as contacts with someone with active pulmonary or laryngeal TB
  - Are new entrants from high-incidence countries.
  - Are immunocompromised because of:
    - Prolonged steroid use
    - TNF-α antagonists
    - Anti-rejection drugs such as cyclosporin, various cytotoxic treatments and some treatments for inflammatory bowel disease, such as azathioprine
    - The use of immunosuppressive drugs
    - Comorbid states affecting the immune system, for example HIV, chronic renal disease, many haematological and solid cancers, and diabetes.

Q. Is TB screening recommended with use of all TNF antagonists?

A. Yes. Evidence indicates that development of active TB can be a risk with the use of any agent that blocks TNF-α.[4] As such; all patients should be screened for LTBI prior to initiating a TNF antagonist. [Please see the screening checklists in Appendices A and B, pages 14 and 15]

Q. How do I go about the screening and treatment process? Are there guidelines?

A. Yes, NICE provides guidance on the screening, and the treatment, of LTBI in patients receiving, or about to receive, anti-TNF therapy.

* "Under-served" is defined by NICE in this context as applying to groups of adults, young people and children from any ethnic background, regardless of migration status if:

- Their social circumstances, language, culture or lifestyle (or those of their parents or carers) make it difficult to:
  - Recognise the clinical onset of TB
  - Access diagnostic and treatment services
  - Self-administer treatment (or, in the case of children and young people, have treatment administered by a parent or carer)
  - Attend regular appointments for clinical follow-up.

LATENT VERSUS ACTIVE TUBERCULOSIS

Q. What is LTBI?

A. Latent TB infection occurs when an individual is infected with *M. tuberculosis*, but the mycobacteria is contained by an effective immune response.[19] The mycobacteria remain alive but dormant. The infection is asymptomatic and not communicable. It is possible for patients to develop active TB if they don't receive treatment. The risk of evolving to active TB depends on the ability of the immune system to control the mycobacteria replication and may occur at any time (from weeks to years) after the infection.

Q. How does LTBI differ from active TB?

A. Latent TB is defined by infection with mycobacteria of the *M. tuberculosis* complex, where the bacteria are alive but not currently causing active disease. LTBI and active TB differ primarily in the presentation of symptoms. A patient with LTBI usually has no symptoms, does not feel sick and cannot spread TB to others. Diagnosis of LTBI is demonstrated by a positive Mantoux test or TB blood test. Patients may have a normal chest x-ray or they could exhibit radiographic signs of LTBI, such as calcifications or pleural thickening.[19] Conversely, patients with active TB present with symptoms dependent on the region of the body where TB mycobacteria are growing; this may either be respiratory (including the lungs, pleural cavity, mediastinal lymph nodes etc.) or non-respiratory (including in bone, joints, central nervous system, skin etc.).[6, 19]

TB mycobacteria usually replicate in the lungs, and therefore may cause symptoms such as severe and persistent cough, pain in the chest, and coughing up of blood or sputum. Other symptoms include weakness or fatigue, weight loss, loss of appetite, chills, fever, and night sweats.

Diagnosis of active respiratory TB can be gained through abnormal chest x-ray, acid-fast bacilli in sputum, and/or positive sputum culture. Extra-pulmonary signs and symptoms may be present and will depend on the organ system affected, such as lymph nodes, pleura, upper airways, genitourinary tract, bones and joints, central nervous system, gastrointestinal tract, pericardium, etc.[6, 19]

Q. Will both LTBI and active TB show up on a Mantoux test or TB blood test (e.g., interferon-gamma test [IGT]*)?

A. Evaluation of LTBI consists of a variety of assessments, including medical history and ruling out active TB, as well as diagnostic tests, such as Mantoux tests and/or TB blood tests (e.g., IGT) and/or chest x-rays.[6, 19] Latent TB infection usually produces a positive Mantoux test or TB blood test, and treatment should be considered to prevent progression to active disease. Although Mantoux tests and TB blood tests may also be positive in patients with active TB, neither test can distinguish LTBI from active TB.[17] Additionally, these tests are not used to definitively diagnose active TB. Therefore, it is both prudent and practical to further investigate and determine whether the patient has active TB and treat accordingly.

Interferon-gamma tests were developed to be more specific as they detect antigens which are not present in BCG vaccination. They, therefore, reduce the number of false positive results and are better at indicating latent TB infection.[6, 19] [Please see the details of TB testing in Appendix C, pages 16 to 18]

*Abbvie does not provide, carry out, recommend or finance either Mantoux or Interferon-Gamma tests

SYMPTOMS OF TUBERCULOSIS

Q. What should I tell my patients who are receiving TNF antagonist therapy about TB?

A. Physicians who prescribe any TNF antagonist therapy should educate their patients about the symptoms of TB.[20] Patients should be counseled to report any symptoms of active TB, including*:

Pulmonary symptoms of TB[20]

- A cough that lasts 3 weeks or longer
- Pain in the chest
- Coughing up blood or sputum (phlegm from deep inside the lungs)

Other symptoms of TB[20]

- Weakness or fatigue
- Weight loss
- No appetite
- Chills
- Fever
- Sweating at night

Extra-pulmonary symptoms of TB[20]

- Depends on the organ system affected

*This list is not meant to be comprehensive.

Q. Who should be treated for TB?

A. Although the treatment regimens differ for active TB and LTBI, both individuals with active disease, as well as those with LTBI who are at high risk of developing TB, should be treated according to appropriate TB guidelines and/or standards of care.[3]

Q. If LTBI is dormant, why is it necessary to treat it?

A. While many individuals infected with *M. tuberculosis* will have LTBI and never develop active TB disease, those with a compromised immune system may not be able to contain the mycobacteria and are at risk of progression to active TB. Therefore, appropriate treatment is recommended for individuals who have LTBI and fall into a high-risk group.[3]

Q. Which high-risk groups should be treated for LTBI?

A. After a positive Mantoux test (induration of 5mm or larger, regardless of BCG history) +/- positive IGT, and once active TB has been excluded radiographically and, where appropriate, by relevant microbial culture/nucleic acid amplification of specimens, treatment of LTBI should be considered for people who:[3]

- Are younger than 65, with or without HIV infection, that have been in close contact with people who have suspected or confirmed active TB.
- Are HIV positive.
- Are healthcare workers and will be in contact with patients or clinical materials if:
    - They are not new entrants from a high incidence country, and not had a BCG vaccination (or show no sign of BCG vaccination), and if they also have a positive IGT result.
    - They are new entrants from a high incidence country, and have either a positive Mantoux test result or a positive IGT result.
- Are younger than 5 years old.
- Have excessive alcohol intake.
- Are injecting drug users.
- Have had solid organ transplants.
- Have a haematological malignancy.
- Are having chemotherapy.
- Have had a jejunoileal bypass.
- Have diabetes.
- Have chronic kidney disease or receive haemodialysis.
- Have had a gastrectomy.
- Are having treatment with anti-tumour necrosis factor-alpha or other biologic agents.
- Have silicosis.

If the person has a comorbidity or coexisting condition (such as liver disease), work with a specialist multidisciplinary team with experience of managing TB and the comorbidity or co-existing condition.

People with social risk factors like alcohol and drug misuse, should be linked to social support services. Especially services relating to adherence and treatment completion.

Q. How is LTBI treated?

A. After consultation with the appropriate, local TB specialists, for people, including those with HIV, aged younger than 65, the typical treatment regimen for LTBI is either 3 months isoniazid (with pyridoxine) and rifampicin, or 6 months of isoniazid (with pyridoxine).

If hepatotoxicity is a concern after assessment of liver function and related risk factors, offer people under 35 years old 3 months isoniazid (with pyridoxine) and rifampicin. Where interactions with rifampicin are a concern, for example in people with HIV or who have had a transplant, offer 6 months of isoniazid (with pyridoxine).[3]

PUTTING TUMOUR NECROSIS FACTOR ANTAGONISTS IN PERSPECTIVE

Q. What is the normal biologic role of TNF-α?

A. TNF-α is a naturally occurring pro-inflammatory cytokine involved in normal cell-mediated immune response against disease, including mycobacterial infection, such as TB.[8]

Q. How do TNF antagonists work in treating chronic inflammatory diseases?

A. Elevated levels of TNF-α play a key role in stimulating the pathologic inflammation underlying chronic inflammatory diseases such as rheumatoid arthritis (RA), juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, and psoriasis.[9,10]

Q. What is the role of TNF-α in the immune response to TB?

A. Tumour necrosis factor plays an important role in protection against murine *M. tuberculosis* infection[11]. *In vitro* and *in vivo* studies demonstrate that TNF-α provides protective mechanisms in macrophages against *M. tuberculosis*. The studies further show that the absence of TNF-α has a detrimental effect on the ability of granulomas to contain and restrict the replication of tubercle bacilli.

Q. Why is screening for TB necessary with TNF antagonist therapy?

A. Any immunosuppressive agent, including TNF antagonists, can potentially result in reactivation of LTBI or progression of recently acquired mycobacterial infection to active TB.[2,12,13,14] for this reason, NICE and other experts, including Public Health England, recommend screening for LTBI. They also recommend following through with appropriate management if infection is detected before initiating therapy with any TNF antagonist. [Please see the screening checklists in Appendices A and B, pages 14 and 15]

Q. Is screening important in managing the risk of TB?

A. Yes. Tuberculosis screening prior to initiation of TNF antagonist therapy has resulted in a decreased rate of progression of latent TB to active TB.[13,14] for example, in European clinical trials, implementation of TB screening prior to initiation of TNF antagonist therapy for the treatment of RA resulted in a reduction in the incidence rates of TB in the clinical trials.[12,13] patients receiving TNF antagonist therapies should be monitored for signs and symptoms of active TB before, during, and after treatment.[4]

Patients who have negative Mantoux tests results should be monitored, as active TB has developed in these patients.[4] [Please see the screening checklists in Appendices A and B, pages 14 and 15]

GETTING DOWN TO BASICS – TUBERCULIN SKIN TESTING

Q. What is the standard TB skin test?

A. The Mantoux test (Appendix C), also known as the Tuberculin Skin Test (TST) or Purified Protein Derivative (PPD) test is a method used globally. It contains a tuberculin protein antigen.[15,16] The test is used to aid diagnosis of TB infection in persons at increased risk of developing active disease. However, the Mantoux test has limitations, particularly in the detection of LTBI.

Current NICE guidelines recommend that clinicians offer Mantoux testing to diagnose latent TB in adults aged 18 to 65 who are close contacts of a person with pulmonary or laryngeal TB, or in a high risk group. If the Mantoux test is inconclusive, refer the person to a TB specialist. If the Mantoux test is positive (an induration of 5 mm or larger, regardless of BCG history), consider an interferon-gamma release assay. If either is positive, assess for active TB, if this assessment is negative, offer patients treatment for latent TB. In specific groups, such as people who are immunocompromised, IGT alone or a dual strategy with IGT plus Mantoux test is recommended by NICE, but not a Mantoux test alone.

Only consider using interferon-gamma release assays alone in children and young people if Mantoux testing is not available or is impractical.[3]

Q. I am not trained to perform the Mantoux Test. Where can I send my patients for testing?

A. Mantoux tests and results should only be administered, read and interpreted by a trained healthcare professional. Infectious disease physicians, respiratory physicians and specialised nurses have been trained and routinely do Mantoux Tests (dependent on local infrastructure).

Q. Should I encourage my patients to do anything?

A. Any TB screening test (Mantoux test or IGT) that a patient receives should be recorded on their Patient Alert Card. Patients should be advised to carry their up to date Patient Alert Cards at all times, and show it to any doctor or healthcare professional they see.

GETTING DOWN TO BASICS – INTERFERON-GAMMA TESTS

Q. What are IGTs?

A. Interferon-gamma tests are whole-blood tests that can aid in diagnosing both LTBI and active TB.[19] You will find general instructions on administering the test and interpreting the results at the back of this brochure for your reference. [Please see the TB test instructions in Appendix C, pages 16 to 18]

Q. How do IGTs work?

A. Interferon-gamma tests measure a person's immune reactivity to *M. tuberculosis*.[19] They detect two tuberculosis antigens, 'early secretion antigen target 6' (ESAT-6) and 'culture filtrate protein 10' (CFP-10). These antigens are not present in BCG and are found in only a few species of environmental mycobacteria which explains the increased specificity, reduced likelihood of false positive results and better correlation with detection of latent infection of dormant organisms.[17]

Again, please advise your patients that any TB screening test (Mantoux test or IGT) that they receive should be recorded on their Patient Alert Card. Patients should also be advised to carry their up to date Patient Alert Cards at all times, and show it to any doctor or healthcare professional they see

Q. What are the advantages of IGTs?

A.

> Only requires one patient visit in comparison to Mantoux which requires two visits[18]
> Improved specificity in comparison to Mantoux, i.e. fewer false positive results which means it is less likely people will be unnecessarily treated for presumed LTBI[19]
> Depending on your local infrastructure, results can be available within 24 hours[18]
> Does not boost responses measured by
> subsequent tests[18]

Q. What are the disadvantages and limitations of IGTs?

A.

> Blood samples must be processed within 8 hours after collection while white blood cells are still viable[18]
> Factors that decrease the accuracy of the test include errors in:[18]
    - Collecting blood samples
    - Transporting blood samples
    - Running and interpreting the test

Q. When should IGTs be used?

A. Interferon-gamma tests can be used in place of or in addition to the Mantoux test in all situations recommended by NICE. Interferon-gamma tests can be used in addition to the Mantoux test in people suspected of having latent TB, e.g. adults aged 18 to 65 who are close contacts of a person with pulmonary or laryngeal TB. IGTs should be considered for people whose Mantoux test shows positive (an induration of 5 mm or larger, regardless of BCG history) and who shown no sign of active TB. [3]

As IGTs are recommended by NICE for their specificity in detecting latent TB infection they are primarily recommended in patients being screened for LTBI. Specific recommendations and considerations for the use of IGT and Mantoux test in this setting are listed below:[3]

IGT and Mantoux test (dual strategy) is recommended for:[3]

> Severely immunocompromised patients (e.g. HIV and CD4 cell count less than 200 cells/mm^3, or after solid organ or allogenic stem cell transplant)
> Other adults who are immune compromised consider an IGT alone (single IGT only) or dual strategy.
> Employees of any age who are new to the NHS and are from a country with a high incidence of TB or have been in close contact with patients in a setting with high TB prevalence

If either test is positive a clinical assessment to exclude active TB and for the consideration of treatment of latent TB is suggested.

IGT only (single strategy) is recommended for:[3]

> People from under-served groups*

Please see the screening checklists in Appendices A and B, pages 14 and 15, and also the TB Test Instructions in Appendix C, pages 16 to 18.

* Under-served groups refer to children, young people or adults whose social circumstances, language, culture, or lifestyle, or those of their parents or carers that make it difficult to:[3]

> Recognise the clinical onset of TB
> Access diagnostic and treatment services
> Self-administer treatment (or, in the case of children and young people, have treatment administered by a parent or carer)
> Attend regular appointments for clinical follow up

Patients in underserved groups should also be advised that any TB screening test (Mantoux test or IGT) that they receive should be recorded on their Patient Alert Card. Patients should be advised to carry their up to date Patient Alert Cards at all times, and show it to any doctor or healthcare professional they see.

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APPENDICES

The contents of the Appendix have been adapted from and developed in-line with information from the following sources:

1. Centers for Disease Control and Prevention
2. NICE Clinical Guidance NG33
3. Public Health England.

APPENDIX A: TUBERCULOSIS SCREENING CHECKLIST: ADULTS

This is a clinical practice tool, developed by AbbVie, adapted from Centre for Disease Control materials and updated in-line with recommendations from NICE clinical Guidance NG33, to assist healthcare professionals with evaluating patients for the risk of developing active TB before, during and after therapy with a TNF antagonist. Consult your local TB guidelines for comprehensive information regarding TB screening and treatment recommendations in your area. *Please mark or fill out correspondingly*

/ /

Name of Patient Date of Birth

A

Does the patient currently have any symptoms consistent with active TB such as:

	Yes	No	Comments
Cough ≥3 weeks	☐	☐	
Haemoptysis or sputum production	☐	☐	
Chest pain	☐	☐	
Fever	☐	☐	
Night sweats or temperature	☐	☐	
Weakness or fatigue	☐	☐	
Anorexia	☐	☐	
Weight loss ≥10% ideal body weight	☐	☐	

If one or more of the above is answered with "YES", active TB needs to be completely ruled out before initiation of therapy

B

Immunosuppressive therapy (e.g., steroids, methotrexate, and biologics) may increase the risk of active TB in patients with latent disease. Does the patient have this or other risk factors* for activation of latent TB including:

	Yes	No	Comments
Born or lived in TB endemic area	☐	☐	
Contact with people with sputum smear positive TB	☐	☐	
Resident or employee of a high risk residential settingresidential facility e.g. prison, remand centre	☐	☐	
Mycobacteriology laboratory staff	☐	☐	
Child or adolescent exposed to adult in high risk category	☐	☐	
Immunosuppression due to treatment or other condition	☐	☐	
Homeless or problem drug use	☐	☐	
Diabetes	☐	☐	
Silicosis	☐	☐	
Organ transplant	☐	☐	
Chronic renal failure	☐	☐	
Gastrectomy or jejunoileal bypass	☐	☐	
Head or neck cancer, leukemia, lymphoma	☐	☐	

**Medical consultation with expert recommended in patients with a negative test but having risk factors for TB infection.*

C

BCG Vaccination:	Yes	No	Comments
BCG Vaccination	☐	☐	
Date of Chest X-ray	_____/_____/_____		

Perform an IGT alone or IGT and Mantoux test concurrently. If either test is positive examine patient for signs of active TB and assess radiographically and via culture.**

D

Results of the IGT assay	
Type of assay performed	
Date of assay performed	___/___ /___
Assay measurement/Interpretation	_____/_____
Date of LTBI treatment initiation	___/___ /___

D

Results of the Mantoux Test:	
Date of Mantoux Test application	___/___ /___
Date of Mantoux Test reading	___/___ /___
Induration at Mantoux Test site (in mm)	

Results of the Second Mantoux Test (if appropriate):	
Date of Mantoux Test application	___/___ /___
Date of Mantoux Test reading	___/___ /___
Induration at Mantoux Test site (in mm)	

**** An IGT should be performed concurrently with a Mantoux test for severely immunocompromised patients (i.e. HIV and CD4 cell count less than 200 cells/mm3), NHS employees of any age who are new to the NHS and are from a country with a high incidence of TB or have been in close contact with patients in a setting with high TB prevalence.**

E

Results of Chest X-ray Screening for TB	Yes	No	Comments
Normal	☐	☐	
Abnormal	☐	☐	
Latent TB	☐	☐	
Others (please specify test and normal/abnormal)	☐	☐	
Date of Chest X-ray			___/___ /___

Referral to a TB specialist is recommended for any patient with positive results for the Mantoux or IGT tests or with abnormal findings on the chest X-ray.

F

If the patient presents a positive medical history and/or Mantoux Test shows an induration of ≥5 mm (regardless of BCG history) and/or IGT results are positive and/or the chest X-ray shows signs of LTBI, respective LTBI treatment should be initiated.

Mantoux Test or IGT	Chest X-ray	LTBI Treatment
<5 mm or Negative	Normal	Not recommended*
≥5 mm or Positive	Abnormal	Medical consultation with Expert recommended
<5 mm or Negative	LTBI signs	Recommended
≥5 mm or Positive	Normal	Recommended
<5 mm or Positive	Normal	Recommended
Prescribed LTBI treatment regimen (drug/dose):		_____/_____
Date of LTBI treatment initiation		___/___ /___

* Medical consultation with expert recommended in patients with a negative test but having risk factors for TB infection or with inconclusive Mantoux test. Exclude active TB before pursuing LTBI treatment.

G

Does the patient have hepatic disease or any other risk factors for hepatic disease, which may require additional monitoring with LTBI treatment such as:

	Yes	No	Comments
Underlying liver disease (e.g., hepatitis B or C, history of heavy alcohol consumption)	☐	☐	
Pregnant or postpartum (within 3 months of delivery)	☐	☐	
Other risk factors for chronic liver disease	☐	☐	

/ /

Name of Doctor Date of evaluation

Abbreviations: IGT, interferon gamma test; LTBI, latent tuberculosis infection; TB, tuberculosis; TNF, tumour necrosis factor; TST, tuberculin skin test.

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APPENDIX B: TUBERCULOSIS SCREENING CHECKLIST: PAEDIATRICS

This is a clinical practice tool, developed by AbbVie, adapted from Centre for Disease Control materials and updated in-line with recommendations from NICE clinical Guidance NG33, to assist healthcare professionals with evaluating patients for the risk of developing active TB before, during and after therapy with a TNF antagonist. Immunocompromised children who are suspected of having LTBI should be referred to a TB specialist. Consult your local TB guidelines for comprehensive information regarding TB screening and treatment recommendations in your area. *Please mark or fill out correspondingly*

	/ /
Name of Patient	Date of Birth

A **Does the patient currently have any symptoms consistent with active TB such as:**

	Yes	No	Comments
Cough ≥3 weeks	☐	☐	
Haemoptysis or sputum production	☐	☐	
Chest pain	☐	☐	
Fever	☐	☐	
Night sweats or temperature	☐	☐	
Weakness or fatigue	☐	☐	
Anorexia	☐	☐	
Weight loss ≥10% ideal body weight	☐	☐	

If one or more of the above is answered with "YES", active TB needs to be completely ruled out before initiation of therapy

B **Immunosuppressive therapy (e.g., steroids, methotrexate, and biologics) may increase the risk of active TB in patients with latent disease. Does the patient have this or other risk factors* for activation of latent TB including:**

	Yes	No	Comments
Born or lived in TB endemic area	☐	☐	
Contact with people with sputum smear positive TB	☐	☐	
Resident or employee of a high risk residential settingresidential facility e.g. prison, remand centre	☐	☐	
Mycobacteriology laboratory staff	☐	☐	
Child or adolescent exposed to adult in high risk category	☐	☐	
Immunosuppression due to treatment or other condition	☐	☐	
Homeless or problem drug use	☐	☐	
Diabetes	☐	☐	
Silicosis	☐	☐	
Organ transplant	☐	☐	
Chronic renal failure	☐	☐	
Gastrectomy or jejunoileal bypass	☐	☐	
Head or neck cancer, leukemia, lymphoma	☐	☐	

**Medical consultation with expert recommended in patients with a negative test but having risk factors for TB infection.*

C

BCG Vaccination:	Yes	No	Comments
BCG Vaccination	☐	☐	
Date of Chest X-ray	_____/_____/_____		

Perform an IGT alone or IGT and Mantoux test concurrently. If either test is positive examine patient for signs of active TB and assess radiographically and via culture.**

D

Results of the IGT assay	
Type of assay performed	
Date of assay performed	___/___ /___
Assay measurement/Interpretation	_____/_____
Date of LTBI treatment initiation	___/___ /___

D

Results of the Mantoux Test:	
Date of Mantoux Test application	___/___ /___
Date of Mantoux Test reading	___/___ /___
Induration at Mantoux Test site (in mm)	
Results of the Second Mantoux Test (if appropriate):	
Date of Mantoux Test application	___/___ /___
Date of Mantoux Test reading	___/___ /___
Induration at Mantoux Test site (in mm)	

**** Only consider using interferon-gamma release assays alone in children and young people if Mantoux testing is not available or is impractical. If a child or young person aged between 2 and 17 years has been in close contact with people with pulmonary or laryngeal TB and if the Mantoux test is inconclusive, refer the patient to a TB specialist.**
If the Mantoux test is positive (5 mm or larger, regardless of BCG history), assess for active TB; if this assessment is negative, offer them treatment for latent TB infection. If the initial Mantoux test is negative, offer an IGT after 6 weeks and repeat the Mantoux test.
If latent TB is suspected in children and young people who are anticipated to be or are currently immunocompromised (for example, if they are from a high incidence country or have been in close contact with people with suspected infectious or confirmed pulmonary or laryngeal TB), refer to a TB specialist.

E

Results of Chest X-ray Screening for TB	Yes	No	Comments
Normal	☐	☐	
Abnormal	☐	☐	
Latent TB	☐	☐	
Others (please specify test and normal/abnormal)	☐	☐	
Date of Chest X-ray			___/___ /___

Referral to a TB specialist is recommended for any patient with positive results for the Mantoux or IGT tests or with abnormal findings on the chest X-ray.

F **If the patient presents a positive medical history and/or Mantoux Test shows an induration of ≥5 mm (regardless of BCG history) and/or IGT results are positive and/or the chest X-ray shows signs of LTBI, respective LTBI treatment should be initiated.**

Mantoux Test or IGT	Chest X-ray	LTBI Treatment
<5 mm or Negative	Normal	Not recommended*
≥5 mm or Positive	Abnormal	Medical consultation with Expert recommended
<5 mm or Negative	LTBI signs	Recommended
≥5 mm or Positive	Normal	Recommended
<5 mm or Positive	Normal	Recommended
Prescribed LTBI treatment regimen (drug/dose):		_____/_____
Date of LTBI treatment initiation		___/___ /___

* Medical consultation with expert recommended in patients with a negative test but having risk factors for TB infection or with inconclusive Mantoux test. Exclude active TB before pursuing LTBI treatment.

G **Does the patient have hepatic disease or any other risk factors for hepatic disease, which may require additional monitoring with LTBI treatment such as:**

	Yes	No	Comments
Underlying liver disease (e.g., hepatitis B or C, history of heavy alcohol consumption)	☐	☐	
Pregnant or postpartum (within 3 months of delivery)	☐	☐	
Other risk factors for chronic liver disease	☐	☐	

	/ /
Name of Doctor	Date of evaluation

Abbreviations: IGT, interferon gamma test; LTBI, latent tuberculosis infection; TB, tuberculosis; TNF, tumour necrosis factor; TST, tuberculin skin test.

APPENDIX C: TUBERCULOSIS TEST INSTRUCTIONS

Mantoux Tuberculin Skin Test

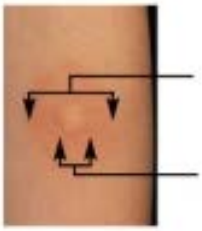
1. Administration

For each patient, conduct a risk assessment that takes into consideration

> Record all the information required for documentation by your institution (e.g., date and time of test administration, injection-site location, lot number of tuberculin)

2. Reading

The skin test should be read between 48 and 72 hours after administration. A patient who does not return within 72 hours will probably need to be rescheduled for another skin test.



1. Inspect site

> Visually inspect site under good light
Erythema (reddening of the skin)—do not measure

Induration (hard, dense, raised formation)

2. Palpate induration

> Use fingertips to find margins of induration

3. Mark induration

> Use fingertip as a guide for marking widest edges of induration across forearm

4. Measure induration (not erythema)

> Place “0” ruler line inside left dot edge
> Read ruler line inside right dot edge (use lower measurement if between two gradations on mm scale)

5. Record information

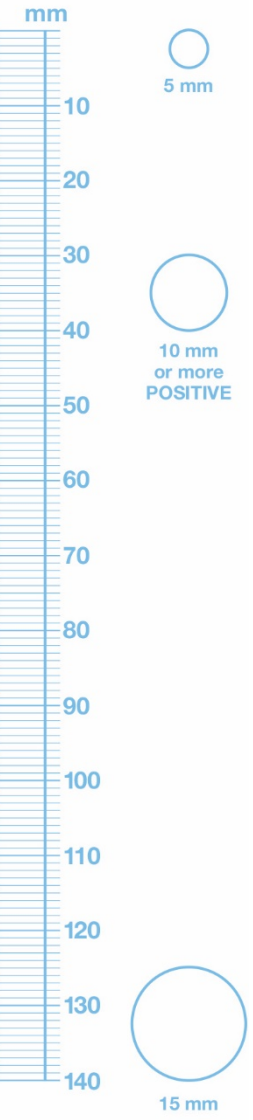
> If no induration, record as 0 mm
> Do not record as “positive” or “negative”
> Only record measurement in millimeters (mm)

Adapted from the CDC NCHSTP Office of Communications’ Mantoux Tuberculin Skin Test Wall Chart 2004.

TUBERCULOSIS TEST INSTRUCTIONS

Mantoux Tuberculin Skin Test

3. Interpretation



Skin test interpretation depends on 2 factors:

> Measurement in millimeters (mm) of the induration

> Person's risk of being infected with TB and progression to disease if infected

The diagram to the left should be used to determine whether the skin test reaction is positive. A person with a positive reaction should be referred for a medical evaluation for latent TB infection and appropriate follow-up and treatment if necessary. A measurement of 0 mm or a measurement below the defined cut point is considered ***negative***.

INDURATION OF ≥5 MM IS CONSIDERED POSITIVE IN, FOR EXAMPLE, THE FOLLOWING GROUPS:[3,19]

> Human immunodeficiency virus (HIV)–infected persons

> Recent contacts of TB case patients

> Persons with fibrotic changes on chest radiograph consistent with prior TB

> Persons with organ transplants and other immunosuppressed patients (e.g., receiving the equivalent of ≥15 mg/d of prednisone for 1 month or more), patients receiving TNF blockers

> Recent immigrants (i.e., within the last 5 years) from countries with a high prevalence of TB

> Injection drug users

> Residents and employees* of the following high-risk congregate settings:

– Prisons and remand centres
– Nursing homes and other long-term facilities for the elderly
– Hospitals and other healthcare facilities
– Residential facilities for patients with acquired immunodeficiency syndrome (AIDS)
– Homeless shelters

> Mycobacteriology laboratory personnel

> Persons with the following clinical conditions that place them at high risk:

– Silicosis
– Diabetes mellitus
– Chronic renal failure
– Some hematologic disorders (e.g., leukemias and lymphomas)
– Other specific malignancies (e.g., carcinoma of the head, neck, or lung)
– Weight loss of ≥10% of ideal body weight
– Gastrectomy
– Jejunoileal bypass

> Children less than 5 years of age

> Infants, children, and adolescents exposed to adults at high risk for developing active TB

> Persons with no known risk factors for TB

*For employees who are otherwise at low risk for TB and who are tested as part of an infection control screening program at the start of employment, a reaction of ≥5 mm is considered positive. Some healthcare workers participating in an infection control screening program may have had an induration >0 mm that was considered negative at baseline. If these healthcare workers have an increase in induration size upon subsequent testing, they should be referred for further evaluation.

Note: Reliable administration and reading of the Mantoux test involves standardization of procedures, training, supervision, and practice. Always follow your institution's policies and procedures regarding infection control, evaluation, and referral. Also remember to provide culturally appropriate patient education before and after administration, reading, and interpretation of the skin test.

This list is not intended to be comprehensive

For more information on tuberculosis, visit **www.nice.org.uk**.

Adapted from the CDC NCHSTP Office of Communications' Mantoux Tuberculin Skin Test Wall Chart 2004 and NICE Guidelines (NG33).

TUBERCULOSIS TEST INSTRUCTIONS

Interferon-Gamma Release Assays

1. Administration

Confirm arrangements for testing in a qualified laboratory, and arrange for delivery of the blood sample to the laboratory in the time the laboratory specifies to ensure testing of samples with viable blood cells.

- Draw a blood sample from the patient according to the test manufacturer's instructions
- Schedule a follow-up appointment for the patient to receive test results, and to arrange for further medical evaluation and possible treatment for latent tuberculosis infection (LTBI) or active TB if needed.
- If you cannot locate a local laboratory to prove IGTs then contact your local Public Health England centre: https://www.gov.uk/guidance/contacts-phe-regions-and-local-centres

2. Interpretation

Interpretation based on the amount of interferon-gamma (INF-γ) that is released or on the number of cells that release INF-γ

- Both the standard qualitative test interpretation (positive, negative, or indeterminate) and the quantitative assay measurements (Nil, TB, and Mitogen concentrations or spot counts) should be reported
- As with the tuberculin skin tests, interferon gamma release assays should be used as an aid in diagnosing infection with *M. tuberculosis*
    - Positive test result: *M. tuberculosis* infection is likely
    - Negative test result: *M. tuberculosis* infection is unlikely
    - Indeterminate test result: uncertain likelihood of *M. tuberculosis* infection
    - Borderline test result (T-Spot only): uncertain likelihood of *M. tuberculosis* infection
- Diagnosis of LTBI requires that TB diagnosis be excluded by medical evaluation, including:
    - Checking for signs and symptoms suggestive of TB disease
    - Chest radiograph
    - Examination of sputum or other clinical samples for the presence of *M. tuberculosis*, when indicated
    - Considerations of epidemiological and historical information

For more information on tuberculosis, visit **https://www.gov.uk/government/collections/tuberculosis-and-other-mycobacterial-diseases-diagnosis-screening-management-and-data**

Reference: Centers for Disease Control and Prevention. Interferon-gamma release assays (IGRAs) –blood tests for TB infection [fact sheet]. Available at: http://www.cdc.gov/tb/publications/factsheets/testing/IGRA.htm. Accessed October 2016.

CONTACT INFORMATION

The current recommendations for targeted testing for TB and treatment regimens for LTBI have been endorsed by NICE. The HPA and the British Thoracic Society provide further information in the screening and management of TB. Contact information for these 3 important national organisations is as follows:

TB information – UK organisations:

National Institute for Clinical Excellence

> +44 (0)300 323 0140

> http://www.nice.org.uk/

Health Protection Agency

> +44 (0) 20 7811 7000

> http://www.hpa.org.uk/

British Thoracic Society

> +44 (0) 20 7831 8778

> https://www.brit-thoracic.org.uk/

TB Information – National Contact

Chest Clinic, Mater Dei Hospital, Msida

General no: +356 2545 0000

abbvie