

CADTH RAPID RESPONSE REPORT: SUMMARY OF ABSTRACTS

# Latent Tuberculosis Infection Testing in People with Compromised Immunity Prior to Biologic Therapy: Diagnostic Accuracy, Clinical Utility and Guidelines

Service Line: Rapid Response Service  
Version: 1.0  
Publication Date: June 26, 2020  
Report Length: 9 Pages

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**Cite As:** *Latent Tuberculosis Infection Testing in People with Compromised Immunity Prior to Biologic Therapy: Diagnostic Accuracy, Clinical Utility and Guidelines*. Ottawa: CADTH; 2020 Jun. (CADTH rapid response report: summary of abstracts).

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**Funding:** CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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## Research Questions

1. What is the diagnostic accuracy of using the tuberculin skin test for patients with compromised immunity prior to initiating biologic treatment?
2. What is the clinical utility of using the tuberculin skin test for patients with compromised immunity prior to initiating biologic treatment?
3. What are the evidence-based guidelines regarding the testing for latent tuberculosis infection in patients with compromised immunity prior to initiating biologic therapy?

## Key Findings

Two non-randomized studies were identified regarding the diagnostic accuracy of using the tuberculin skin test for patients with compromised immunity prior to initiating biologic treatment. Authors of one of the two non-randomized studies also investigated the clinical utility of using the tuberculin skin test for patients with compromised immunity prior to initiating biologic treatment. In addition, one systematic review of guidelines and seven evidence-based guidelines were identified regarding the testing for latent tuberculosis infection in patients with compromised immunity prior to initiating biologic therapy.

## Methods

A limited literature search was conducted by an information specialist on key resources including PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were tuberculosis testing, immunocompromised patients, and biologic therapy. No filters were applied to limit the retrieval by study type. The search was also limited to English language documents published between January 1, 2015 and June 16, 2020. Internet links are provided where available.

This report is a component of a larger CADTH Condition Level Review on tuberculosis. A condition level review is an assessment that incorporates all aspects of a condition, from prevention, detection, treatment, and management. For more information on CADTH's Condition Level Review of tuberculosis, please visit the project page (<https://www.cadth.ca/tuberculosis>).

## Selection Criteria

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

**Table 1: Selection Criteria**

<b>Population</b>	Patients with compromised immunity prior to starting biologic therapy (e.g., anti-TNF $\alpha$ therapy, HIV treatments or other immune suppressants)
<b>Intervention</b>	Q1,2: TST Q3: TST or IGRA
<b>Comparators</b>	Q1: IGRA Q2: No comparator; IGRA; no screening test for latent tuberculosis infection Q3: Not applicable
<b>Outcomes</b>	Q1: Diagnostic accuracy (e.g., sensitivity, specificity) Q2: Clinical utility (e.g., diagnosis of TB, adverse events) Q3: Recommendations regarding the use of TST or IGRA for patients with compromised immunity prior to initiating biologic therapy (i.e., does this confirm a diagnosis of TB and lead to optimal treatment options)
<b>Study Designs</b>	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies, evidence-based guidelines

IGRA = interferon gamma release assay; TB = tuberculosis; TST = tuberculin skin test

## Results

Two non-randomized studies<sup>2,3</sup> were identified regarding the diagnostic accuracy of using the tuberculin skin test (TST) for patients with compromised immunity prior to initiating biologic treatment. Authors of one of the two non-randomized studies<sup>3</sup> also investigated the clinical utility of using the TST for patients with compromised immunity prior to initiating biologic treatment. In addition, one systematic review<sup>1</sup> of guidelines and seven evidence-based guidelines<sup>4-10</sup> were identified regarding the testing for latent tuberculosis infection in patients with compromised immunity prior to initiating biologic therapy. No relevant health technology assessments or randomized controlled trials were identified.

References of potential interest that did not meet the inclusion criteria are provided in the appendix.

## Overall Summary of Findings

Two non-randomized studies<sup>2,3</sup> were identified regarding the diagnostic accuracy of using the TST for patients with compromised immunity prior to initiating biologic treatment. Authors of the first non-randomized study<sup>2</sup> found that both the TST and interferon gamma release assay (IGRA) had low sensitivity when testing patients with chronic immune-mediated inflammatory disease prior to initiating biologic therapy, while IGRA had higher specificity. Agreement between the two tests was low.<sup>2</sup> However, authors of the other non-randomized study<sup>3</sup> found that there was moderate agreement between TST and IGRA in patients with arthritic diseases when the cut-off value for positive TST was lowered to 5mm.

Authors of one of the two non-randomized studies<sup>3</sup> also investigated the clinical utility of using the TST for patients with compromised immunity prior to initiating biologic treatment. None of the patients in the study developed active tuberculosis during the one-year follow-up period.<sup>3</sup>

One systematic review<sup>1</sup> of guidelines and seven evidence-based guidelines<sup>4-10</sup> were identified regarding the testing for latent tuberculosis infection in patients with compromised immunity prior to initiating biologic therapy. A summary of relevant recommendations is

presented in Table 2. As part of the condition level review, two of the guidelines<sup>6,8</sup> in this report were previously included in a CADTH report<sup>11</sup> on guidelines for tuberculosis in people with compromised immunity. The detailed critical appraisal of these two guidelines can be found in that report.<sup>11</sup>

**Table 2: Summary of Relevant Recommendations**

Systematic Reviews
Hasan, 2018 <sup>1</sup>
<ul style="list-style-type: none"> <li>• Most guidelines recommended screening for LTBI in patients starting immunosuppression or were highly likely to start immunosuppression (page 7).</li> <li>• A combination of TST and/or IGRA testing, chest X-ray, detailed background history, and risk factor assessment was the most frequent recommendation for LTBI screening in individuals with compromised immunity (page 7).</li> <li>• Some guidelines specified the preference for IGRA over TST as the standard screening tool for LTBI, particularly among patients with a history of BCG vaccination (page 7).</li> <li>• Other guidelines recommended that TST be used as a triage test. If negative, IGRA was recommended as the second test to confirm the diagnosis (page 7).</li> <li>• A two-step screening strategy was recommended for patients with a history of BCG vaccination (page 7).</li> </ul>
Evidence-Based Guidelines
Ooi, 2019 <sup>4</sup>
<ul style="list-style-type: none"> <li>• LTBI screening before initiating biologics should be performed according to local practice, using either chest X-ray, chest computed tomography, IGRA and/or TST (page 302). <b>(Classification of recommendation: A, Quality of evidence: 11-2)</b></li> </ul>
British Association of Dermatologists, 2017 <sup>5</sup>
<ul style="list-style-type: none"> <li>• Patients with psoriasis should be screened for LTBI using IGRA prior to starting biologic treatment (page 152).</li> <li>• Patients should also be screened for granulomas and other confounding lung diseases with a plain chest radiograph (page 152).</li> </ul>
National Institute for Health and Care Excellence, 2016 <sup>6</sup>
<ul style="list-style-type: none"> <li>• Adults with current or anticipated compromised immunity should undergo a risk assessment to determine whether LTBI testing is necessary (page 16).</li> <li>• Adult with compromised immunity should be tested for LTBI using IGRA alone or IGRA with concurrent TST (page 17).</li> </ul>
Santin, 2016 <sup>7</sup>
<ul style="list-style-type: none"> <li>• Patients with chronic immunomediated inflammatory diseases should be tested for LTBI using IGRA prior to starting biological therapy.</li> </ul>
Singapore Ministry of Health, 2016 <sup>8</sup>
<ul style="list-style-type: none"> <li>• T-SPOT.TB is recommended over TST and QFT-G for LTBI diagnosis in patients with compromised immunity (page 10). <b>(Grade of recommendation: C, Level of evidence: 2+)</b></li> </ul>
Spanish National Health System, 2016 <sup>9</sup>
<ul style="list-style-type: none"> <li>• Patients anticipated to start immunosuppressive treatment for HIV, hepatitis B, hepatitis C, and TB should be screened for LTBI regardless of risk factors (page 43). <b>(Recommended practice based on consensus)</b></li> <li>• Most patients should be screened for LTBI using TST with a cut-off point of 5mm, except for patients with previous BCG vaccination and/or immunosuppression for whom QFT-G would be more reliable (page 43). <b>(Recommended practice based on consensus)</b></li> <li>• Patients with a negative TST result should be retested one week later to rule out false negatives (page 43). <b>(Grade of recommendation: D)</b></li> </ul>

Singh, 2015<sup>10</sup>

- Patients should be tested for LTBI prior to starting biologics for the treatment of rheumatoid arthritis only if risk factors for TB exposure are present (page 14).
- High risk patients may be tested with either TST or IGRA, with a preference for IGRA if the patient has a history of BCG vaccination (page 14).

BCG = Bacillus Calmette–Guérin; IGRA = interferon gamma release assay; LTBI = latent tuberculosis infection; QFT-G: QuantiFERON-TB Gold; TB = tuberculosis; TST = tuberculin skin test

## References Summarized

### Health Technology Assessments

No literature identified.

### Systematic Reviews and Meta-Analyses

1. Hasan T, et al. Screening and prevention for latent tuberculosis in immunosuppressed patients at risk for tuberculosis: a systematic review of clinical practice guidelines. *BMJ Open*. 2018;8(9):e022445. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6144320/>

### Randomized Controlled Trials

No literature identified.

### Non-Randomized Studies

2. Sellami M, et al. Screening for latent tuberculosis infection prior to biologic therapy in patients with chronic immune-mediated inflammatory diseases (IMID): Interferon-gamma release assay (IGRA) versus tuberculin skin test (TST). *Egypt Rheumatol*. 2019 Jul;41(3):225-230. <https://www.sciencedirect.com/science/article/pii/S1110116418301352>
3. So H, Yuen CS, Yip RM. Comparison of a commercial interferon-gamma release assay and tuberculin skin test for the detection of latent tuberculosis infection in Hong Kong arthritis patients who are candidates for biologic agents. *Hong Kong Med J*. 2017 Jun;23(3):246-250. [PubMed: PM28126971](https://pubmed.ncbi.nlm.nih.gov/28126971/)

### Guidelines and Recommendations

4. Ooi CJ, et al. Best practices on immunomodulators and biologic agents for ulcerative colitis and Crohn's disease in Asia. *Intestinal Res*. 2019;17(3):285-310. <https://www.irjournal.org/journal/view.php?doi=10.5217/ir.2019.00026>  
See: Statement 27, page 302
5. British Association of Dermatologists. Guidelines for biologic therapy for psoriasis; 2017 Apr. <https://www.bad.org.uk/shared/get-file.ashx?id=5835&itemtype=document>  
See: 11.1 Tuberculosis, Recommendations, R43, page 152
6. National Institute for Health and Care Excellence. Tuberculosis. (*NICE guideline NG33*); 2016. <https://www.nice.org.uk/guidance/ng33>  
See: Recommendations 1.2.1.2 and 1.2.1.4

7. Santin M, García-García JM, Domínguez J. Guidelines for the use of interferon- $\gamma$  release assays in the diagnosis of tuberculosis infection. *Enferm Infecc Microbiol Clin*. 2016 May;34(5):303.e301-313.  
[PubMed: PM26917222](#)
8. Singapore Ministry of Health. Prevention, Diagnosis, and Management of Tuberculosis. (HOH *clinical practice guidelines*); 2016.  
<https://www.moh.gov.sg/docs/librariesprovider4/guidelines/moh-tb-cpg-full-version-for-website.pdf>  
See: Testing for Latent Tuberculosis Infection, Recommendation #61, page 10
9. Guideline Development Group of the Clinical Practice Guideline on Systemic Lupus Erythematosus. Clinical practice guideline on systemic lupus erythematosus (*Clinical practice guidelines in the Spanish NHS*). Zaragoza (ES): Ministry of Health, Social Services and Equality and Assessment Services of the Canary Is. Health Service.; 2016. [https://portal.guiasalud.es/wp-content/uploads/2018/12/GPC\\_549\\_Lupus\\_SESCS\\_compl\\_en.pdf](https://portal.guiasalud.es/wp-content/uploads/2018/12/GPC_549_Lupus_SESCS_compl_en.pdf)  
See: Recommendations, Latent infection screening, page 43
10. Singh JA, et al. 2015 American College of Rheumatology Guideline for the treatment of rheumatoid arthritis. *Arthr Care Res*. 2015.  
<https://www.rheumatology.org/Portals/0/Files/ACR%202015%20RA%20Guideline.pdf>  
See: Figure 6, page 14

## Appendix — Further Information

### Previous CADTH Reports

11. Brett K, Dulong C, Severn M. Tuberculosis in People with Compromised Immunity: a review of guidelines. (CADTH rapid response report: summary with critical appraisal). Ottawa (ON): CADTH; 2020 Mar.  
<https://www.cadth.ca/sites/default/files/pdf/htis/2020/RC1238%20TB%20immunocompromised%20Final.pdf>
12. Interferon-Gamma release Assays Testing versus Tuberculosis Skin Testing for Tuberculosis: A Review of the Clinical Effectiveness and Guidelines. (CADTH rapid response report: summary with critical appraisal). Ottawa (ON): CADTH; 2011 May.  
[https://www.cadth.ca/sites/default/files/pdf/htis/may-2011/RC0273\\_Interferon\\_Gamma\\_Final.pdf](https://www.cadth.ca/sites/default/files/pdf/htis/may-2011/RC0273_Interferon_Gamma_Final.pdf)

### Non-Randomized Studies

#### *Alternative Population*

13. Kurti Z, Lovasz BD, Gecse KB, et al. Tuberculin Skin Test and Quantiferon in BCG Vaccinated, Immunosuppressed Patients with Moderate-to-Severe Inflammatory Bowel Disease. *J Gastrointest Liver Dis*. 2015 Dec;24(4):467-472.  
[PubMed: PM26697573](#)

#### *Mixed Intervention*

14. Malaviya AN, Aggarwal VK, Rawat R, et al. Screening for latent tuberculosis infection among patients with rheumatoid arthritis in the era of biologics and targeted synthetic disease-modifying anti-rheumatic drugs in India, a high-burden TB country: The importance of Mantoux and Quantiferon-TB Gold tests. *Int J Rheum Dis*. 2018 Aug;21(8):1563-1571.  
[PubMed: PM29345081](#)

#### *Unclear Outcomes*

15. Baričević D, Popović Grlje S, Morović Vergles J, et al. QuantiFERON-TB Gold In-Tube Test in the Diagnosis of Latent Tuberculosis Infection in Arthritis Patients Treated with Tumor Necrosis Factor Antagonists. *Acta Clin Croat*. 2017 Jun;56(2):203-209.  
[PubMed: PM29485786](#)

### Clinical Practice Guidelines – Unclear Methodology

16. Rodríguez-Jiménez P, Mir-Viladrich I, Chicharro P, et al. Prevention and treatment of tuberculosis infection in candidates for biologic therapy: A multidisciplinary consensus statement adapted to the dermatology patient. *Actas Dermosifiliogr*. 2018 Sep;109(7):584-601.  
[PubMed: PM29871738](#)

### Review Articles

17. Calabrese C, Winthrop KL. Mycobacterial Infections Potentiated by Biologics. *Infect Dis Clin North Am*. 2020 Jun;34(2):413-423.  
[PubMed: PM32444014](#)



18. Hashash JG, Abou Fadel C, Hosni M, Hassoun L, Kanafani Z, Regueiro MD. Approach to Latent Tuberculosis Infection Screening Before Biologic Therapy in IBD Patients: PPD or IGRA? *Inflamm Bowel Dis*. 2020 Jun 2.  
[PubMed: PM32483628](#)
19. Martínez-López A, Rodríguez-Granger J, Ruiz-Villaverde R. Screening for Latent Tuberculosis in the Patient With Moderate to Severe Psoriasis Who Is a Candidate for Systemic and/or Biologic Therapy. *Actas Dermosifiliogr*. 2016 Apr;107(3):207-214.  
[PubMed: PM26651325](#)
20. Goyal A, Goyal K, Merola JF. Screening and vaccinations in patients requiring systemic immunosuppression: an update for dermatologists. *Am J Clin Dermatol*. 2015 Jun;16(3):179-195.  
[PubMed: PM25854805](#)

### Additional References

21. Handa R, Upadhyaya S, Kapoor S, et al. Tuberculosis and biologics in rheumatology: A special situation. *Int J Rheum Dis*. 2017 Oct;20(10):1313-1325.  
[PubMed: PM28730751](#)