Interferon Gamma Release Assay Testing for Latent Tuberculosis Infection: Physician Guidelines

Background

Historically, Latent Tuberculosis Infection (LTBI) diagnosis was based on risk assessment, chest x-ray (CXR) and Tuberculin Skin Test (TST) results. The TST is a well-studied and inexpensive test but has limitations. A TST may be false-positive if there is history of BCG vaccination or exposure to non-tuberculous mycobacteria (NTM), or false negative if the client is immunocompromised.

Interferon Gamma Release Assays (IGRAs) are immunological tests that are not influenced by prior BCG vaccine or exposure to most NTM and are more robust than TST in their performance in immunocompromised patients. IGRAs and TSTs are both imperfect tests which must be interpreted within the context of the risk for TB exposure and results of radiographic imaging (Table 1). There are many advantages and disadvantages of LTBI testing with TST and/or IGRA (Table 1). IGRA testing does not replace the TST for most patients but rather may be used as an adjunct test in specific populations that require additional information to better determine LTBI status (see Tables 2 and 3).

The two IGRA tests available in British Columbia (BC) are:

- QuantiFERON-Gold Plus® [QFT- Plus] (Enzyme-linked Immunosorbent Assay (ELISA) on whole blood)
- T-SPOT® (Enzyme-linked Immunospot Assay on peripheral blood mononuclear cells)

Both require specific collection methods and care of samples after collection, which, if not followed, can result in erroneous or inconclusive test results. The QFT-Plus is the preferred test in most circumstances. Final processing is only performed at the BC Center for Disease Control Public Health Laboratory, but sample collection and pre-processing are available in a number of locations in British Columbia. Please refer directly to the eLab Handbook or the BCCDC website for the most up to date list of BC IGRA Screening Sites.

Purpose

This document aims to provide clear guidance on publicly funded IGRA indications, providers who can order publicly funded IGRAs, and well as the process of arranging IGRA testing in BC.

These guidelines will be formally reviewed every two years.

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TST versus IGRA

There is no gold standard test to diagnose Latent TB Infection. The sensitivity and specificity of testing varies depending upon the population being tested.

Table 1: Comparison of TST, QFT-Gold and T-SPOT[123]

TST	IGRA (QFT-Plus & T-SPOT)
Two visits	Single visit
Less accurate if immunocompromised*	More accurate in specific immunocompromised*
Between reader variability in test interpretation	Low between reader variability in test interpretation
Inexpensive	Costly
Similar sensitivity & specificity to IGRA in healthy, non-BCG vaccinated populations	Similar sensitivity & specificity to TST in healthy, non-BCG vaccinated populations
Recommended for serial testing and routine screening	Serial IGRA test results may vary within one individual so not recommended
Does not confirm active TB disease	Not currently used for confirmation of active TB disease

	Research is underway on possible use of QFT-Plus for active TB disease testing
TST	**IGRA (QFT-Plus & T-SPOT)**
Estimated 5-10% risk of developing active TB disease over lifetime in individuals with a positive TST test result	No definitive data is available regarding the lifelong risk of progression to active TB in individuals with a positive IGRA result, however shorter term studies estimate that positive IGRA results are either comparable or slightly superior to TST in predicting progression
Universally accessible where health workers are trained and with access to tuberculin	Blood drawing techniques and time restrictions for specimen transport and laboratory analysis limit availability of IGRA testing

***** For example, HIV, AIDs, transplant or cancer patient on immunosuppressive treatment, chronic kidney disease requiring hemodialysis

Who can order IGRA:

In BC, publicly funded IGRA testing can be ordered by BCCDC TB Services (TBS) clinicians, hospital based physicians for in-patients (often in communication with local medical microbiology), nephrologists, and respiratory, transplant and infectious disease specialists when following the indications noted in Table 2 (see below). Other physicians may order publicly funded IGRAs upon consultation with their local respiratory or infectious disease specialists, or BCCDC TB Services.

Publicly funded IGRAs can only be performed at designated testing sites. Please refer directly to the eLab Handbook or the BCCDC website for the most up to date list of BC IGRA Screening Sites.

Private pay IGRA is also available at certain LifeLabs locations across the province. Please see the LifeLabs website for further information.

When IGRA may be indicated

Table 2: Indications for IGRA Testing

Indications for IGRA[ʊ]	Explanation	Example(s)	Test
BCG Vaccinated			
TST positive AND BCG vaccinated AND Low risk of TB exposure[^] or reactivation	To avoid unnecessary LTBI therapy or serial CXR in those who had a BCG and are at low risk of developing active TB i.e. to exclude LTBI diagnosis	• Indigenous • Foreign-born • Student or Health Care Worker with BCG • Returned traveller with BCG	QFT-Plus
TST positive AND BCG vaccinated AND High risk of TB exposure[ŧ] or reactivation	To provide additional information (increase specificity) to those who very likely have LTBI (based on history and TST) and are considering LTBI treatment and only willing to accept LTBI therapy if IGRA is positive[ɵ]	• Contact in BCG vaccinated individual who does not believe TST result • TST positive but testing shortly after BCG vaccination	QFT-Plus
Independent of BCG Vaccination			
TST negative AND Immunocompromised[*] AND High risk of TB exposure[ɵ]	To provide additional information (increase sensitivity) to help diagnose LTBI in specific individuals in whom TST is negative but there is strong clinical suspicion of LTBI with increased risk for morbidity/mortality	• Individuals with HIV and significant immunosuppression	QFT-Plus or T-SPOT[µ]

Indications for IGRA[σ]	Explanation	Example(s)	Test
Independent of BCG Vaccination			
Unlikely to return for TST read AND High risk of TB exposure[Θ] or reactivation	In those who are unlikely to return to TST read or the follow-up TST test in high risk populations[§]	• Under-housed • Substance Use • Mental Health • New migrants from high TB burden countries	QFT-Plus
Specific medical condition	High likelihood of progression to active TB disease and poor predictive value of TST in these populations	• New dialysis clients • Before solid organ or bone-marrow transplants (see specific program guidance)	QFT-Plus[μ]
Previous indeterminate IGRA	To confirm an indeterminate IGRA test if a change in clinical management will result. IGRA is repeated once only.	May consider a different testing method (e.g. test with T-SPOT if QFT-Plus was indeterminate and vice versa)	QFT-Plus or T-SPOT
At discretion of TB Physician	Complex medical circumstances that do not fit into general guidelines	• Foreign-born (TB endemic country), BCG, TST negative, and pre-biologic	QFT-Plus or T-SPOT[ϕ]

[σ] A negative IGRA does not rule out active TB disease. If active disease is suspected, a chest x-ray and mycobacterial culture of sputa (and/or other relevant clinical specimens) are indicated
[^] E.g., From low incidence country or never in contact with active pulmonary TB
[†] E.g., High and medium priority contacts of active pulmonary TB case or from high TB incidence country
[Θ] Patients who are TST positive, at high risk of TB exposure and not BCG vaccinated should be treated for LTBI irrespective of IGRA result. In these patients IGRA should NOT be offered
[*] HIV, AIDS, transplant or cancer patients on immunosuppressive treatment, silicosis, chronic kidney disease requiring dialysis, or patient taking prednisone 15mg/day or more for more than 2 weeks

[μ] Some immunocompromised patient populations may benefit for preferential use of T-spot (e.g., AIDS patients), but for the majority, T-spot and QFT-Plus have equivalent performance and use of QFT-Plus is preferred.
[§] If noncompliance is a concern for reading the TST, noncompliance would be a concern for LTBI therapy so, IGRA may not be warranted.
[ϕ] At times, serial testing may be indicated but ordering both tests simultaneously is usually unnecessary

When IGRA testing is not recommended:

Avoid IGRA in clients:

1) with a prior IGRA result documented, regardless of result
2) with suspected or confirmed history of active TB disease and/or treatment;
3) with history of previous positive IGRA or history of LTBI therapy;
4) requiring serial testing for employment;
5) requiring routine contact follow-up
6) when clinical management will not be influenced by the result (e.g., HIV with +ve TST; pre-biologic client with positive TST and no history of BCG).
7) in clients previously "cleared" with no additional exposure risk

Epidemiologic evidence exists for sequential testing based on result (e.g., test first with TST, then offer IGRA based on TST result) but not for routine parallel testing or universal IGRA testing.

IGRA and pre-biologic screening:

Clients taking biologic therapy (e.g., TNF-alpha inhibitors) are at higher risk for reactivation of TB if they have been previously exposed and are infected with latent TB. Candidates for biologic therapy should be screened for TB **prior to first initiating biologic therapy**. Initial screening should include TB assessment, CXR and TST.

Not every client going on biologic therapy requires IGRA. TST based screening in most cases may be sufficient (see below).

Repeated screening at the time of additional medication change is not required, and is actively discouraged in the absence of new TB exposure or symptoms compatible with active TB.

If treatment of latent TB is recommended, attempts should be made to complete it prior to starting biologic therapy. However, if the risk of delaying biologic therapy is high, clients should receive at least 1-2 months of LTBI treatment prior to starting biologic therapy.

Table 3: Pre-biologic clients that do NOT require an IGRA:

Context	Explanation
• Changing to a new biologic product, different dose, or additional agents	In the absence of new TB exposure since initial screening, IGRA is not needed. Referral to TB Services is not needed if previously screened.
Context	**Explanation**
• Prior history of TB disease and/or treatment • Prior history of LTBI treatment	IGRA is likely to be positive. Repeated treatment not recommended. Referral to TB Services is recommended for clearance to start biologics therapy. This should include a symptom check and CXR.
Canadian-born or foreign-born from non-TB high burden country*	
• No risk factors for TB exposure • TST negative • No prior evidence of TB on chest x-ray	If there is no or low epidemiological risk for TB, an IGRA is not needed. There is a higher risk of false positive IGRA in populations with low rates of TB. Clearance is provided on basis of TST and CXR regardless of current medication regimen.
Canadian-born or foreign-born from non-TB high burden country*	
• TST positive (regardless of risk factors for exposure and chest x-ray results)	Consider offering LTBI treatment as risk of reactivation is high.**
Foreign-born from TB high burden country*	
• TST positive (regardless of BCG vaccination status)	Consider offering LTBI treatment as risk of reactivation is high, particularly if CXR is consistent with prior TB.**

* High Burden Country List http://www.stoptb.org/countries/tbdata.asp
** Physician discretion should be used in determining if there is added benefit in performing an IGRA in these situations (e.g., clients who have received a BCG vaccination from a low TB incidence country or instances in which there is concern about the validity of the positive TST).

Procedures for IGRA testing in BC:

A. Referral Process:

Island Health:
Fax Island Health TB Referral Form and chest x-ray to 250-519-1505.

All other Health Authorities:
Fax or Mail* provider consult letter or TB Screening Form to BCCDC TB Services

BCCDC Provincial TB Services
655 West 12th Avenue
Vancouver, BC V5Z 4R4
Fax: 604.707.2690

*Public Health nurses with access to Panorama may email referrals per internal guidelines

Referrals should include a recent CXR (unless contraindicated):

- Within 3 months if immunocompromised
- Within 6 months if immunocompetent
- New CXR if symptomatic or new positive TST

B. Follow Up Processes for BCCDC Referrals (vary depending on where client resides):

Fraser Health or Vancouver Coastal Health (except Coast Garibaldi):
Once the referral is received, it will be reviewed and an appointment will be booked at one of the TB Clinics. Decision to draw IGRA (or not) at the clinic visit is based on Tables 2 and 3. If space is limited, clients may be sent directly to alternative sites in the lower mainland.

Interior Health, Northern Health, First Nations Health Authority, and Coast Garibaldi region of Vancouver Coastal Health:

1. TB Services will recommend IGRA (or not) based on Tables 2 and 3.

2. Recommendations are mailed and/or faxed to the referring provider, in the form of a standard letter or dictation within 2 weeks of receiving CXR report.

3. Referring provider discusses IGRA recommendation from TB Services with client and calls TB Services (604-707-2901) to arrange for requisition to be sent to preferred site for testing. Please refer directly to the BCCDC website for the most up to date list of BC IGRA Screening Sites.

   Note: If you would like to be cc'd on the result, please include your address and/or MSP billing number.

   Health care providers may use the resources below to inform their discussion. Translated resources are available on the BCCDC website.

   IGRA TB Blood Test Fact Sheet
   Latent TB Infection Fact Sheet
   TB Germ – A Cunning World Traveler (video)

   Note: If the client refuses IGRA testing or is unable to travel to a city where the test is offered, they can still choose to take preventative treatment if offered. This decision needs to be communicated to TB Services Nurse Consultants at 604-707-5678 or via email at: TBNurseConsultants@bccdc.ca

4. TB Services faxes site specific instructions and/or IGRA requisition to the referring provider and/or site of collection. Instructions may vary depending on site of collection. Some sites may have drop in or require clients to book appointments ahead of time or bring the requisition with them.

Ensure the client has **NOT** received **any live, mRNA or viral vector** vaccines in the 4 previous weeks. Delay testing until 4 weeks after live vaccine was received.

> There is a theoretical risk that mRNA and viral vector vaccines (COVID) may temporarily affect cell-mediated immunity, resulting in false-negative TST or IGRA test results.

5. All publicly funded IGRA results are sent to BCCDC TB Services and the referring health care provider (if requested). IGRA results from LifeLabs are only copied to TB Services with explicit client consent.

   All received IGRA results are reviewed and interpreted by a TB physician in the context of accompanying TB risk assessment and CXR. Further follow-up recommendations (via standard letter [clearance or LTBI treatment offer] or dictation) will be mailed to referring physician and all physicians listed in external sources. This may take as long as one month and is often related to delays in receiving accompanying information.

   Public health receives an email when narrative or standard letter is available.

Please note that this entire process may take as long as two - three months, depending on when the CXR and IGRA are completed.

REFERENCES:

[1] Pai M, Zwerling A, Menzies D. T-cell Based Assays for the Diagnosis of Latent Tuberculosis Infection: An Update. Ann Intern Med 2008;149:177-84.

[2] Centers for Disease Control and Prevention. Updated Guidelines for Using Interferon Gamma Release Assays to Detect Mycobacterium tuberculosis Infection. MMWR 2010;59(RR05):1-25.

[3] Canadian Tuberculosis Committee. Recommendations on Interferon gamma release assays for diagnosis of latent tuberculosis infection. An Advisory Committee Statement (ACS). CCDR 2010;36(ACS-5):1-22.