National Tuberculosis Controllers Association

Best Practice Recommendations for the use and interpretation of Interferon-Gamma Release Assays (IGRAs)

Disclosures

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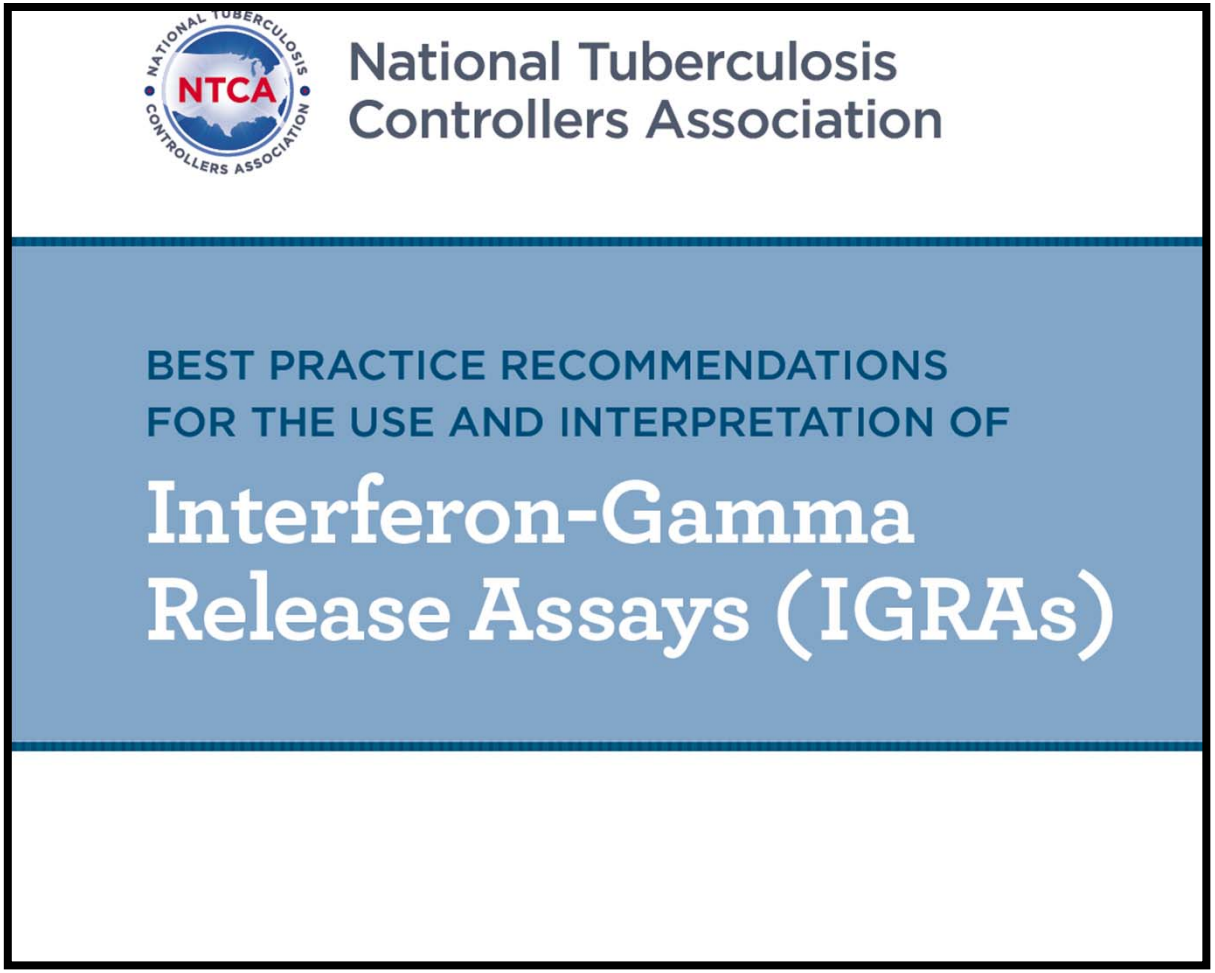
I have nothing to disclose as I am not paid for work associated with the information to be discussed in this presentation.

The information to be shared is summary information of a new NTCA Best Practice Recommendation Document, a workgroup for which I serve as chairperson with no compensation.

Title/Cover Page



Guiding Statement

- The National TB Controllers Association (NTCA) convened a Workgroup to develop tools for use as best practice statements representing the consensus experience (evidence based when available) of United States Tuberculosis (TB) Control Programs for the practical daily use of interferon-gamma release assay (IGRA) technology. These tools are offered as statements of best practice.

Guiding Statement

- These tools are designed to
  - assist TB Controllers and others who are called upon to provide technical assistance and guidance to a wide array of providers and assay users throughout the public and private health sectors
  - provide for best practice options when trouble shooting questions and problems that may arise in the growing use of the IGRA products
  - extend beyond current published Centers for Disease Control and Prevention (CDC) guidelines for interpretation of IGRA to address questions which frequently arise but are not addressed in CDC guidelines

Introduction

- While this document intends to synthesize recommendations and best practices compiled by expert clinicians, laboratorians and public health practitioners, **the user is encouraged to seek further assistance from their respective state or local tuberculosis (TB) program staff, or public health authority, or other tuberculosis expert where uncertainties persist**.

Previous U.S. Guidelines for FDA-Approved IGRAs

Vol. 52 / RR-2 Recommendations and Reports 15

2003

Guidelines for Using the QuantiFERON®-TB Test for Diagnosing Latent *Mycobacterium tuberculosis* Infection

Prepared by
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Vol. 54 / RR-15 Recommendations and Reports 49

2005

Guidelines for Using the QuantiFERON®-TB Gold Test for Detecting *Mycobacterium tuberculosis* Infection, United States

Prepared by
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Division of Tuberculosis Elimination, National Center for HIV, STD, and TB Prevention

Most Recent U.S. Guidelines for FDA-Approved IGRAs

Introduction

- This document expands on the guidelines outlined by CDC for the use of IGRAs and should not be considered a replacement to those guidelines. Instead, these recommendations should be viewed as supplemental to the foundation provided by CDC guidelines.

Introduction

- To be clear, **LTBI is a diagnosis of exclusion** and is based on several factors, including Mantoux skin test or IGRA results, general TB risk, previous TB treatment and current clinical picture. When selecting a test and interpreting results, it is essential the clinician understand why the individual is or was tested.

Format for the Document

- Pre-analytic: test selection, population considerations, environmental/location, logistics, programmatic (cost, availability)
- Testing Dynamics: Cutpoint values, indeterminate results, discordant results, serial testing
- Using the Results: Treatment decisions, interpreting results, retesting

Repeated Emphasis

- As always, any questions or additional information requested, should be directed to the respective state or local tuberculosis (TB) program staff, or public health authority, or other tuberculosis expert where uncertainties persist.

TB Infection vs LTBI

NOTE: *In keeping with current literature, the term Latent Tuberculosis Infection (LTBI) will be used throughout this document, although inclusion of the term "latent" is a point of discussion within the workgroup, with many favoring tuberculosis infection (TBI) over the more traditional LTBI. The workgroup acknowledges that many programs throughout the country have discontinued using the term "latent" to describe non-TB disease infection*.

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PRE-ANALYTIC

Why Test for MTBI?

- Testing for M. tuberculosis infection (MTBI) in the United States is done to aid in the identification of persons who may have tuberculosis and to identify persons who may benefit from treatment to prevent future disease.
- **TB screening should be targeted to**
  - **those persons with increased rates of TB infection**
  - **increased risk of progression to active TB if infected**
  - **persons or groups with increased risk of recent exposure to infectious TB who are likely to have been infected by this exposure**

LTBI is diagnosed in the US by

(1) a positive test for *M. tuberculosis* infection **and**

(2) exclusion of active tuberculosis by further clinical, radiologic, and microbiologic evaluations, when indicated; **or**

(3) when extremely vulnerable persons (e.g. infants or HIV infected persons with low CD4 counts) are exposed to *M. tuberculosis* even when tests for *M. tuberculosis* infection are negative.

What are the costs associated with an IGRA *M. tuberculosis* infection tests?

The cost of individual tests is often cited as a barrier to implementing IGRA testing in a facility. There are many publications that compare the costs of TST with IGRA programs. When considering costs, one should keep in mind both the direct cost of the product selected and the cost associated with misdiagnoses (i.e. false-positives or false negatives). Consideration should include lost work time for the individual being tested, cost of chest x-rays, medication regimens and associated monitoring, and complications from treatment.

Labor and Supply Cost considerations when selecting an IGRA

Staff time costs
To enter results manually (some IGRAs)
Consultation for LTBI positive test result
Chest X-ray review for LTBI evaluation
Annual symptom review for LTBI positive
IGRA costs
Phlebotomy
Patient time and cost to have blood drawn
For QFT-GIT (run in-house):
Cost of test kit
Lab labor cost
For QFT-GIT (send out):
Cost of QFT-GIT send-out test
For T-SPOT.TB (send out):
Cost of T-SPOT.TB

Labor and Supply Cost considerations when selecting an IGRA

Positive test costs (false or true positive)
Cost of the Chest X-ray
Consultation (Infectious Disease or Private MD consultation)
Failure to Follow Up (~10% IGRA)
Cost time to call/email/track lost IGRA and TST patients
Time to place and/or read repeat TST
Negative Test Costs (False Negative Test)
Missed Diagnosis
Treatment
Cost of regimen (e.g. 9H/4R/3HP)
Cost of INH toxicity with/without hospitalization
Cost of monitoring lab tests and phlebotomy
Cost of staff for DOT can compliance calls
Opportunity costs (to institution)
Delays to hire

What are the recommended quality assurance (QA) factors to consider?

- **Pre-analytical**
  - Manufacturing issues (e.g. standardization of reagents/Quality Control among/between lots)
  - Improper storage of tubes (ref guerrera)
  - Time of day of blood draw (Both)
  - Inadequate cleansing of skin (Both)
  - Improper blood volume collection (QFT-GIT)
  - Variability in mixing of antigen/mitogen in tubes (e.g., inverting vs vigorous shaking of tubes; QFT-GIT), or agitation of cells (Both)
  - Specimen temperature and transportation time prior to processing (even within manufacturers' specification ranges)

What are the recommended quality assurance (QA) factors to consider?

- Analytical
  - Between-operator variability in performing procedures
    - Imprecise centrifugation, washing, and counting of cells (T Spot)
    - Imprecise pipetting (Both)
    - Operation of analyzers (Both) or manual reading of EliSpot wells if automated counting methods are not used (T Spot)
    - Variable incubation times and temperatures (even within manufacturers' specifications) (Both)
    - Number and sensitivity (CHECK) of detectors employed on different ELISA analyzers (QFT-GIT)
    - Improper handling (including storage) of plasma following incubation (QFT- GIT)
  - Within assay variability (reproducibility)

RECOMMENDATIONS FOR MANAGING DISCORDANT TESTS RESULTS

IGRA	TST	Risk for Progression*	Recommendation	Comments
Positive or Borderline	**Unknown/ not done**	High	Consider the individual infected with *M. tuberculosis* and treat accordingly.	**Low positive:** Data suggests low risk individuals with QFT results in the 0.35 to 1.0 IU/ml range show a high rate of reversion to negative upon retesting. Low-risk Individuals with test results in this range should be retested. (see section xxx) **Borderline:** Borderline results are clinically meaningful and should be followed up by retesting through collection of another sample.
		Low	**Consider repeating the IGRA as soon as feasible, especially if low positive (QFT) or borderline (T-Spot).** If repeat test negative, treat first IGRA as a false positive. If a first IGRA is NOT low positive or if second IGRA is positive on retesting, consider the individual infected with *M. tuberculosis* and treat accordingly.	
Unknown/ not done	**Positive**	High	Consider the individual infected with *M. tuberculosis* and treat accordingly or, if BCG-vaccinated and BCG is considered as a possible confounder (see above), consider an IGRA for improved specificity.	Interpretation of the TST is risk-based; large (>15mm) reactions are more likely to represent true TB infection than NTM. Consider the risk/ benefits of treatment. In some individuals who have been BCG-vaccinated, testing with an IGRA offers increased specificity over testing with the TST (see "BCG Vaccination, "above) In US-born individuals, there are no data to suggest increased utility of one test over the other.
		Low	Consider testing with an IGRA to increase specificity, especially if the patient is likely BCG-vaccinated and BCG is considered as a possible confounder (see above), or likely infected with an NTM.	

IGRA	TST	Risk for Progression*	Recommendation	Comments
Positive or Borderline	Negative	High	Consider the individual infected with *M. tuberculosis* and treat accordingly.	**Low positive:** Data suggests low risk individuals with QFT results in the 0.35 to 1.0 IU/ml range show a high rate of reversion to negative upon retesting. Low-risk individuals with test results in this range should be retested. **Borderline:** Borderline results are clinically meaningful and should be followed up by retesting through collection of another sample.
		Low	**Consider repeating the IGRA as soon as feasible, especially if low positive (QFT) or borderline (T-Spot).** If repeat test negative, treat first IGRA as a false positive. If a first IGRA is NOT low positive or if second IGRA is positive on retesting, consider the individual infected with *M. tuberculosis* and treat accordingly	
Positive or Borderline	Positive	High	Individuals who test positive by both tests can be considered as infected with *M. tuberculosis* and should be treated accordingly	**Low positive:** Data suggests low risk individuals with QFT results in the 0.35 to 1.0 IU/ml range show a high rate of reversion to negative upon retesting. Low-risk individuals with test results in this range should be retested. **Borderline:** Borderline results are clinically meaningful and should be followed up by retesting through collection of another sample.
		Low	**Consider repeating the IGRA as soon as feasible if low positive (QFT) or borderline (T-Spot).** In a low risk person, a positive test is more likely to be false positive. Consider the risk/benefits of treatment vs evaluation.	
Negative	Negative	High (Not immune suppressed)	The individual can be considered not to be infected with *M. tuberculosis*. Patients with signs, symptoms or radiographic evidence of infection or with strong epidemiologic TB risk may undergo further evaluation despite negative TST/IGRA. Consider the risk/benefits of treatment. Neither test should be the deciding factor for children <5 at risk for progression or immunocompromised individuals as they may be infected with Mtb and test negative on all tests.	Children <5 years of age who are part of a contact investigation who are screening test/exam/ radiographically negative should receive window prophylaxis until the test can be repeated 8-10 weeks after break in contact.
		Low	The individual can be considered not to be infected with *M. tuberculosis*.	

IGRA	TST	Risk for Progression*	Recommendation	Comments
Negative	Positive	High	Consider the individual potentially infected with *M. tuberculosis* and treat accordingly based on clinical assessment weighing the risk/ benefit of treatment vs. non-treatment If BCG-vaccinated and BCG may be considered a possible confounder (see above), may be false positive TST.	In some individuals who are BCG-vaccinated, testing with an IGRA offers increased specificity over testing with the TST.
		Low	Indicate that the TST is likely a false-positive and act on the IGRA result. Recommend that the individual be tested with an IGRA for future testing	

Next Steps

- Current under final review (should complete by end of October)
- Currently with graphic designer simultaneously with final review
- Building to NTCA Website
- Release in November (?)
- Publicize broadly

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COMPLAINTS
COMMENTS
COMPLIMENTS


QUESTIONS
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