PROVISIONAL Guidelines for Use of Interferon Gamma Release Assays (IGRAs) to Detect *Mycobacterium tuberculosis* Infection in the United States

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Overview

- FDA approved IGRAs
- Prior guidelines for IGRA use
- Approach to updating guidelines
- Provisional recommendations

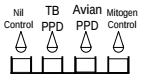
FDA Approved IGRAs

- QuantiFERON®-TB (QFT)
  - FDA approved Nov 2001 but no longer available
- QuantiFERON®-TB Gold (QFT-G)
  - FDA approved May 2005
- QuantiFERON®-TB Gold In-Tube (QFT-GIT)
  - FDA approved Oct 2007
- T-Spot®.*TB* (T-Spot)
  - FDA approved July 2008

QuantiFERON®-TB (QFT)

Stage 1: Whole Blood Culture in Tissue Culture Plate

Draw blood
+ heparin

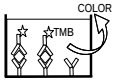


Aliquot blood &
add antigen

Incubate → INF-γ from
sensitized T-cells

Stage 2: Measure [IFN- γ] & Interpret

Harvest plasma from
above settled cells



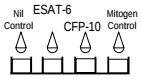
Measure [IFN-g] in
'Sandwich' ELISA

Computerized
interpretation

QuantiFERON®-TB Gold (QFT-G)

Stage 1 Whole Blood Culture in Tissue Culture Plate

Draw blood
with heparin

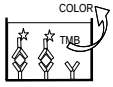


Make 1 ml aliquots
& add antigen

Incubate overnight. INF-
γ from sensitized lymphs

Stage 2: Measure [IFN- γ] & Interpret

Harvest plasma from
above settled cells

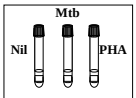


Measure [IFN-g] in
'Sandwich' ELISA

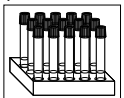
Computerized
interpretation

QuantiFERON®-TB Gold In-Tube **(QFT-GIT)**

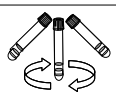
Stage 1 Whole Blood Culture in special blood collection tubes



Collect 1mL of
blood in 3 tubes

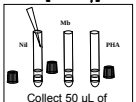


Incubate at 37ºC
for 16-24 hours

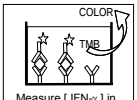


Centrifuge 5 minutes to
separate plasma above gel

Stage 2: Measure [IFN-γ] & Interpret



Collect 50 µL of
plasma for ELISA

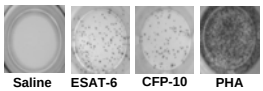


Measure [IFN-γ] in
'Sandwich' ELISA

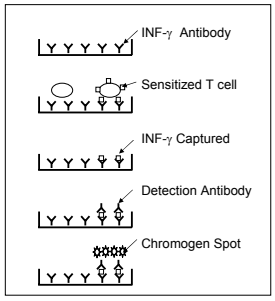
Software calculates
results and prints report

T-Spot.TB

- Collect blood in CPT tube
- Recover, wash, & count PBMCs
- Aliquot 250,000 PBMCs to 4 wells with anti-IFN-γ
- Add saline, PHA, ESAT-6 or CFP-10 & incubate
- Wash away cells
- Develop & count spots where cells produced IFN-γ

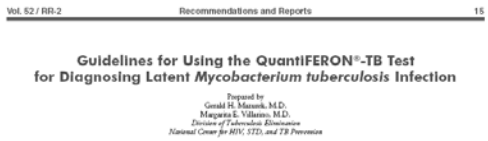


Saline ESAT-6 CFP-10 PHA



U.S. Guidelines for FDA-Approved IGRAs

2003



Vol. 52 / RR-2 Recommendations and Reports 15

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

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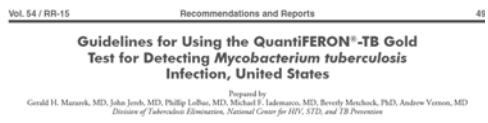
2005



Vol. 54 / RR-15 Recommendations and Reports 49

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

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Guidelines Development Process

- Expert consultants from around the world convened in August 2008
- Coordination with professional societies (ATS, IDSA, AAP) to harmonize guidance
- Drafts by CDC Staff reviewed and revised by peer experts; pending institutional clearance

Focus #1: Persons at High Risk for Infection due to *M. tuberculosis*

- Close contacts of persons with TB disease
- Persons from areas with high incidence of TB
- Persons who visit areas with a high prevalence of TB, especially if visits are frequent or prolonged
- Residents and employees of high-risk congregate settings
- Health care workers who serve high-risk clients
- Populations defined locally as having an increased incidence of infection or disease due to TB
- Infants, children, and adolescents exposed to adults in high-risk categories

Focus #2: Persons at High Risk for Disease Progression if Infected with *M. tuberculosis*

- **Persons with HIV infection***
- Persons recently infected with *M. tuberculosis* (within 2 yrs)
- **Infants and children aged <5 years***
- Persons with history of untreated/inadequately treated TB
- **Persons receiving immunosuppressive therapy***
- Persons with silicosis, diabetes mellitus, chronic renal failure, leukemia, lymphoma, or cancer of the head, neck, or lung
- Persons with gastrectomy or jejunoileal bypass
- Persons who weight less than 90% of ideal body weight
- Populations defined locally as having an increased incidence of infection or disease due to *M. tuberculosis*.

* Indicates groups at increased risk of a poor outcome due to tuberculosis

Provisional Recommendations (1)

- TST or IGRAs (QFT-G; QFT-GIT; T-Spot) used as aids to diagnose infection with *M. tuberculosis*
  - IGRAs should be performed and interpreted according to established protocols using FDA approved test formats, in compliance with Clinical Laboratory Improvement Amendment (CLIA) standards
  - Both standard qualitative interpretation and quantitative assay measurements should be reported
  - Arrangement for IGRA testing should be made prior to blood collection to assure that blood is collected in proper tubes and testing performed within the required timeframe on viable blood cells
- As with the TST, IGRAs should not be used for testing persons with low risk of infection and low risk of disease due to *M. tuberculosis* (noted exception for those likely to be at increased risk in the future)

Provisional Recommendations (2)

- Selection of the most suitable test or combination of tests for detection of *M. tuberculosis* infection based on rationale and context for testing, test availability, and overall cost effectiveness of testing
- IGRAs may be used in place of (not in addition to) TST in all situations in which CDC recommends tuberculin skin testing as an aid to diagnose *M. tuberculosis* infection – with noted preferences and special considerations
  - Despite the indication of a preference, use of the alternative test (IGRA or TST) is acceptable and still considered good medical and public health practice.

CDC

Provisional Recommendations (3)

- IGRA is preferred for testing persons from groups that historically have poor rates of return for TST reading
- IGRA is preferred for testing persons who have received BCG (as a vaccine or for cancer therapy)
- TST is preferred for testing children younger than 5 years of age

CDC

Provisional Recommendations (4)

- IGRAs may be used in place of TST (without preference) to test recent contacts of persons with infectious tuberculosis with special considerations for follow-up testing
  - Negative results prior to 8 wks typically should be confirmed by repeating the test 8–10 weeks after the end of exposure
  - Repeating same test minimizes misclassification due to test discordance
- IGRAs may be used in place of TST (without preference) for periodic screening to address occupational exposure to TB with special considerations regarding conversions and reversions

CDC

Provisional Recommendations (5)

- Both TST & IGRA may be useful if the initial test is negative and:
  - risk of infection, risk of progression, and risk of poor outcomes are high (e.g., persons with HIV infection, children < 5 years exposed to persons with infectious TB)
  - clinical suspicion for active tuberculosis (persons with symptoms, signs, and/or radiographic evidence suggestive of active tuberculosis) and confirmation of *M. tuberculosis* infection is desired

Provisional Recommendations (6)

- Both TST & IGRA may be useful if the initial test is positive and:
  - additional evidence of infection is required to encourage compliance (such as in foreign-born healthcare workers who believe their positive TST is due to BCG)
  - healthy persons who have a low risk of both infection and progression
- Repeating an IGRA or performing a TST may be useful when the initial IGRA result is indeterminate, borderline, or invalid, and reason for testing persists
- Each institution and TB control program should evaluate availability, overall cost effectiveness, and benefits of IGRAs in their setting

Provisional Recommendations (7)

- Diagnosis of *M. tuberculosis* infection, and decisions about medical or public health management should include epidemiological, historical, and other clinical information when using IGRA or TST results
- Persons with a positive TST or IGRA result should be evaluated for likelihood of *M. tuberculosis* infection, for risks of disease progression if infected, and for symptoms and signs of tuberculosis disease
  - With these risks, symptoms, or signs, additional evaluation is indicated and should include a chest radiograph and possibly testing of sputum or other clinical samples for the presence of *M. tuberculosis*
- Diagnosis of LTBI requires that tuberculosis disease be excluded by medical evaluation

Provisional Recommendations (8)

- Persons with symptoms, signs, or radiographic evidence of TB disease, and in those at high risk of disease progression if infected, a positive result with either an IGRA or TST may be taken as evidence of *M. tuberculosis* infection
  - However, negative IGRA or TST results are not sufficient to exclude infection in these persons
- Healthy persons with low likelihood both of *M. tuberculosis* infection and of progression to TB disease if infected, a single positive IGRA or TST result should not be taken as reliable evidence of *M. tuberculosis* infection
  - Reevaluation to confirm lack of risk and consider repeat testing on a case-by-case basis; or
  - alternatively, assume, without additional testing, that the initial result is falsely positive


CDC

Provisional Recommendations (9)

- Persons with discordant test results (one positive and the other negative) – decisions about medical or public health management requires individualized judgment to assess
  - quality of each test & magnitude of each result,
  - probability of infection,
  - risk of disease if infected, and
  - risk of a poor outcome if disease occurs


CDC

Provisional Recommendations (10)

- Further studies should focus on determining the value and limitations of IGRAs in situations critical to TB control
  - Are IGRAs better at predicting subsequent tuberculosis disease than TST?
  - Do IGRAs perform differently in children as compared to adults?
  - Why do simultaneously performed TST, QFT-GIT, QFT-G, and T-Spot results differ?


CDC

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