Guidelines on IGRAs: Concordant or Discordant?

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Disclosure of conflicts

• No financial conflicts

• I consult for Foundation for Innovative New Diagnostics, a non-profit agency
  ▫ FIND partners with several industries, including Cellestis, to develop new diagnostics for neglected diseases

• I co-chair the Stop TB Partnership’s New Diagnostics Working Group (NDWG)
Context and methods

- In the past 5 years, several guidelines and position statements have been published on the role and use of IGRAs.
- In this presentation, we will review, compare and synthesize these guidelines and point out areas of agreement and disagreement.
- By searching the literature and contacting > 50 experts in over 25 countries, we identified guidelines or statements on IGRAs from 17 countries.
- Some countries had more than one guideline or statement that included IGRAs.
- Not all guidelines were “official” country guidelines; so, they may or may not be actually implemented.
- 13/17 guidelines were in languages other than English, translations were obtained from local experts and guideline authors.
Results

• There are several countries that do not yet have an official guideline or statement on IGRAs; these include, for example:
  - China, India, Russia, Ukraine, Brazil, Belgium S Africa, Mexico, New Zealand, Finland, Ireland, Bulgaria, Croatia, Slovenia, Austria, Turkey, Viet Nam, Singapore, Portugal, Sweden, and Saudi Arabia.

• This does not mean IGRAs are not being used:
  - Some are using the tests (E.g. Singapore, Finland)
  - Some are developing guidelines (E.g. Finland, Saudi Arabia, Portugal)

• No high-burden, low-income country has published guidelines on IGRAs
  - But IGRAs are available in some high-burden countries (e.g. India, S Africa), and being used mostly in the private sector and in research settings
  - No NTP in a high burden, low-income country is using these assays
Results

• 17 countries that have at least one guidelines include:
  ▫ USA, Canada, UK, Japan, France, Spain, Italy, Germany, Switzerland, Australia, Netherlands, Denmark, Czech Republic, Slovak Republic, Korea, Poland and Norway.

• Of the countries that have guidelines, 3 main approaches are discernable:
  ▫ TST should be replaced by IGRA (i.e. only IGRA)
  ▫ Either TST or IGRA may be used
  ▫ Two-step approach of TST first, followed by IGRA

• Although the broad approach may fall into one of these, some guidelines recommend more than one approach, depending on the risk group tested
## Results*

<table>
<thead>
<tr>
<th>General testing approach</th>
<th>Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST should be replaced by IGRA (i.e. only IGRA is used)</td>
<td>Germany (anti-TNF-a), Swiss (anti-TNF-a), Poland (anti-TNF-a), Denmark (anti-TNF-a, BCG-vaccinated contacts/adults)</td>
</tr>
<tr>
<td>Either TST or IGRA may be used</td>
<td>USA, France, Australia(refugees), Japan (QFT preferred in all groups except in children &lt;5 y), Denmark(child contacts)</td>
</tr>
<tr>
<td>Two-step approach: TST first, followed by IGRA (either to improve specificity or sensitivity)</td>
<td>Canada, UK, Italy, Spain, Australia, Slovakia Germany (contacts), Swiss (contacts), Netherlands (contacts, immigrants), Norway, Korea(contacts)</td>
</tr>
</tbody>
</table>

* some guidelines recommend more than one approach, depending on the risk group tested (e.g. contacts, immunocompromised, children, etc)
Country-specific guidelines
USA: CDC Guidelines 2003: QFT

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

Summary

Until 2001, the only test used to diagnose latent tuberculosis infection (LTBI) was the tuberculin skin test (TST). However, in 2001, a new test (QuantiFERON®-TB or QFT; manufactured by Cellexis Limited, Carnegie, Victoria, Australia) that measures the release of interferon-γamma in whole blood in response to stimulation by purified protein derivative was approved by the Food and Drug Administration. This statement provides interim recommendations for using and interpreting QFT. As with TST, interpretation and indicated applications of QFT differ for persons according to their risk for LTBI and for developing tuberculosis (TB). This report provides guidance for public health officials, health-care providers, and laboratorians with responsibility for TB control activities in the United States in their efforts to incorporate QFT testing for detecting and treating LTBI. Regardless of the test used to identify LTBI, testing should be primarily targeted at diagnosing infected patients who will benefit from treatment.

### TABLE 1. Interim recommendations for applying and interpreting QuantiFERON®-TB (QFT) (Cellexis Limited, Carnegie, Victoria, Australia)

<table>
<thead>
<tr>
<th>Reason for testing</th>
<th>Population</th>
<th>Initial screening</th>
<th>Positive results</th>
<th>Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculosis (TB) suspect</td>
<td>Persons with symptoms of active TB</td>
<td>Tubercoline skin testing (TST) might be useful; QFT not recommended</td>
<td>Induration ≥5 mm</td>
<td>Chest radiograph, smears, and cultures, regardless of test results</td>
</tr>
<tr>
<td>Increased risk for progression active TB, if infected</td>
<td>Persons with recent contact with TB; changes on chest radiograph consistent with prior TB, organ transplants, or human immunodeficiency virus infection, and those receiving immunosuppressing drugs equivalent of ≥15 mg/day of prednisone for ≥1 month*</td>
<td>TST; QFT not recommended</td>
<td>Induration ≥5 mm</td>
<td>Chest radiograph if TST is positive; treat for latent TB infection (LTBI) after active TB disease is ruled out</td>
</tr>
<tr>
<td></td>
<td>Persons with diabetes, silicosis, chronic renal failure, leukaemia, lymphoma, carcinoma of the heart, eye, or lung, and persons with weight loss of ≥10% of total body weight, gastrointestinal, or peptic ulcer bypass*</td>
<td>TST; QFT not recommended</td>
<td>Induration ≥10 mm</td>
<td></td>
</tr>
<tr>
<td>Increased risk for LTBI</td>
<td>Recent immigrants, injection-drug users, and residents and employees of high-risk congregate settings (e.g., prisons, jails, homeless shelters, and certain healthcare facilities)*</td>
<td>TST or QFT</td>
<td>Induration ≥10 mm; percentage tuberculin response ≥15%</td>
<td>Chest radiograph if either test is positive: confirmatory TST is optional if QFT is positive; treat for LTBI after active TB disease is ruled out; LTBI treatment when any QFT is positive should be based on clinical judgment and estimated risk</td>
</tr>
<tr>
<td>Other reasons for testing among persons at low risk for LTBI</td>
<td>Military personnel, hospital staff, and health-care workers whose risk of prior exposure to TB patients is low, and U.S. citizens at certain colleges and universities†</td>
<td>TST or QFT</td>
<td>Induration ≥15 mm; percentage tuberculin response ≥30%</td>
<td>Chest radiograph if either test is positive; confirmatory TST if QFT is positive; treatment for LTBI if QFT and TST are positive and after active TB disease is ruled out on the basis of assessment of risk for drug toxicity, TB transmission, and patient preference</td>
</tr>
</tbody>
</table>

First published guidance on IGRAs
CDC recommends that QFT-G may be used in all circumstances in which the TST is currently used, including contact investigations, evaluation of recent immigrants, and sequential-testing surveillance programs for infection control (e.g., those for healthcare workers).
Given the high risk for progression to active disease in HIV-infected persons, any HIV-infected person with reactivity on any of the current LTBI diagnostic tests should be considered infected with *M. tuberculosis*.
At this time, neither an IGRA nor the TST can be considered a "gold standard" for diagnosis of LTBI. Current recommendations for use of IGRA in children are as follows:

- For immune-competent children 5 years of age and older, IGRA can be used in place of a TST to confirm cases of *M. tuberculosis* or cases of LTBI and likely will yield fewer false-positive test results.

- Children with a positive result from an IGRA should be considered infected with *M. tuberculosis* complex. A negative IGRA result cannot universally be interpreted as absence of infection.

- Because of their higher specificity and lack of cross-reaction with BCG, IGRA may be useful in children who have received BCG vaccine. IGRA may be useful to determine whether a BCG-immunized child with a reactive TST more likely has LTBI or has a false-positive TST reaction caused by the BCG.

- IGRA cannot be recommended routinely for use in children younger than 5 years of age or for immune-compromised children of any age because of a lack of published data about their utility with these groups.

- Indeterminate IGRA results do not exclude *tuberculosis* infection and should not be used to make clinical decisions.
USA: CDC Guidelines
2009: QFT-GIT/TSPOT.TB

To be released soon
USA: ATS/CDC/IDSA
Revised Diagnostic Standards for TB
2009: QFT-GIT/TSPOT.TB

American Thoracic Society

Diagnostic Standards and Classification of
Tuberculosis in Adults and Children

This official statement of the American Thoracic Society and the Centers for Disease Control and Prevention was adopted by the ATS Board of Directors, July 1999. This statement was endorsed by the Council of the Infectious Disease Society of America, September 1999


To be released

Will be broadly consistent with the new CDC
2009 recommendations

Will cover all TB diagnostics, not just LTBI
UK: NICE Guidelines 2006

To diagnose latent TB:

- Mantoux testing should be performed in line with the ‘Green Book’\(^\text{21}\)
- those with positive results (or in whom Mantoux testing may be less reliable) should then be considered for interferon-gamma immunological testing, if available
- if testing is inconclusive, the person should be referred to a TB specialist (see chapter 10 for management of latent TB).
UK: HPA Guidelines 2008

**HPA recommendation for IGRA testing in the diagnosis of active TB**

IGRA tests should currently not be used as a routine diagnostic tool for active TB.

**HPA recommendation on testing for LTBI**

TST (Mantoux) should generally be used as the first line test for LTBI in contacts of infectious cases and others considered to be at increased risk of LTBI. Those with positive TST results (based on the criteria in the ‘Green Book’[^12] should then be considered for IGRA testing, if available. Those with inconclusive results on an IGRA test should be reviewed by a specialist.

In certain circumstances IGRA testing, if available, can be considered as the sole test for LTBI:

(a) In individuals in whom the result of TST may be falsely negative due to immunocompromise.

(b) When screening large numbers of individuals as part of a public health investigation where logistic issues make repeated visits for sequential testing impractical.
• Two-step approach in contacts, immunocompromised

• Not recommended in children

• Not recommended for active TB and serial testing
Canada: Updated CTC Guidelines, 2008

1. Not recommended for active TB in adults
2. Can be used as a supplementary aid in children with suspected TB
3. IGRA may be used as a confirmatory test for a positive TST in contacts (adult or child)
4. IGRA may be performed in TST-positive, immunocompetent adults and children who are at relatively low risk of being infected and of progressing to active disease
5. In an immunocompromised person (adult or child), the TST should be the initial test; however, a clinician still concerned about the possibility of LTBI may perform an IGRA
6. Not recommended for serial testing of HCWs; IGRA may be used as a confirmatory test if a false-positive TST is suspected in a low-risk HCW or prison staff /employee or inmate.
currently TST remains the preferred method of screening for LTBI pending further evaluation of IGRAs;

- TST and IGRAs have almost no place in the diagnosis of active TB disease;

- state-based TB services should be encouraged to participate in the evaluation of the role of IGRAs for the investigation of LTBI; and

- IGRAs may be used as a supplementary test in individualised clinical assessment for LTBI where increased specificity is valuable in reducing the confounding effect from prior BCG vaccination or prior exposure to non-tuberculous mycobacteria.
Australia: ASID Guidelines 2009

With the exception of those with documented past tuberculosis (TB) disease, all newly arrived refugees, including children, should be assessed for latent TB infection (LTBI), with the following plan:

- Testing is performed with the intention to treat.
- Either a Mantoux test or a blood-based interferon-γ release assay (IGRA) may be used for screening.
- Refer those with a positive Mantoux test result or a positive interferon-γ release assay (IGRA) test to the local TB services, for exclusion of active TB infection and consideration of treatment of latent TB infection (LTBI). (Level 1)
- A Mantoux of ≥ 10mm in adults and children ≥ 5 years of age and a Mantoux of ≥ 5mm in those younger than 5 years or those who are HIV-infected are considered positive.
- Refugees known to be HIV-infected should have a 2-step Mantoux test. In the event that the second test remains <5mm, specialist advice should be sought from TB/HIV services.
- TB (active disease or latent infection) should be managed by clinicians experienced in doing so as part of a centralised, coordinated TB service.
Swiss: Guidelines 2007

IGRAs are used for:

1. Contact investigations, to confirm a positive TST (two-step testing).
2. Regular surveillance of HCWs
3. Initial screen in immuno-compromized patients or before anti-TNFα therapy
4. As an adjunct in extrapulmonary TB, in children or in HIV patients
Screening for tuberculosis infection before initiation of anti-TNF-α therapy

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\end{itemize}

The screening should be based on history, chest x-ray and an IGRA test.

a. History: a detailed history of exposure to or prior treatment for tuberculosis, considering the risk associated with birthplace or country of origin or residence in special environments involving increased risk of TB contact (prisons, shelters).

b. Chest x-ray: a single PA chest x-ray for detection of past or present tuberculosis.

c. IGRA test.

Use of TST is no longer recommended for screening in view of the limitations mentioned. Even a history of positive TST should be confirmed by an IGRA test.
Based on published data and the experts recommendations, four indications are validated for use of IGRA tests:

1. investigation of contacts of a person with TB
2. surveillance of health professionals at the moment of taking their job, and continuously for professionals of high risk wards
3. diagnostic help in case of extra-pulmonary TB
4. to exclude LTBI before starting anti-TNFα treatment

For these indications, an IGRA test may replace the TST.
Germany: DZK Guidelines 2007: Contacts

- Two-step strategy:
  - TST with a low cut-off (> 5 mm) (high sensitivity), followed by a highly specific IGRA
    - synergy effect
    - cost reduction by avoiding unnecessary chest X-rays

- In case of unclear prevalence IGRA serves as confirmation test for positive TST

- Use of the IGRA solely
  - if acceptance of TST is poor
  - in case of a high probability of a false-positive or false-negative TST
  - in patients with history of BCG vaccination or positive TST pre-test

- INH-chemoprevention only when IGRA is positive (if available)
Empfehlungen für das Tuberkulosescreening vor Gabe von TNF-α-Inhibitoren bei rheumatischen Erkrankungen

Recommendations for Tuberculosis Screening Before Initiation of TNF-α-Inhibitor Treatment in Rheumatic Diseases

Zusammenfassung

Abstract
Due to the increased risk of tuberculosis (TB) under treatment with TNF-α-inhibitors for rheumatoid arthritis and other autoimmune diseases, precautionary measures are required before initiating TNF-α-inhibitor therapy. Patients should have active TB ruled out and screening for latent TB infection should be performed. The screening should include chest X-ray, complete medical history, and the administration of a highly specific Interferon-γ-Release Assay (IGRA). As tuberculosis skin test (TST) results can be expected to be either false-positive or false-negative in these patients, the TST, as commonly performed in the past, is recommended only for exceptional situations. For chemopreventive treatment of latent TB infection (LTBI), isoniazid is usually given for 9 months.

Pneumologie, 2009
1. TST is the standard test for LTBI diagnosis; there is not enough evidence to recommend complete replacement of TST with IGRAs
2. IGRAs are recommended to confirm LTBI diagnosis in TST+ BCG vaccinated individuals
3. IGRAs are recommended to diagnose LTBI in TST- HIV+ or other immunosuppressed individuals

Girardi E et al. Italian National Guidelines for TB Control 2009 [Draft]
Spain: SEPAR Guidelines 2008

RECOMMENDATIONS OF THE SPANISH SOCIETY OF PULMONOLOGY AND THORACIC SURGERY (SEPAR)

Diagnosis and Treatment of Tuberculosis

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Arch Bronconeumol. 2008;44(10):551-66

Not recommended in:
- Active TB
- Serial testing
• Contact investigations: TST is the initial test, if 5 mm or more followed by IGRA

• Immigrant screening of children 4 weeks to 12 years old: initially TST, if 5 mm or more, then IGRA

• Follow-up screening of risk groups (e.g. contacts): either TST or IGRA as initial test

• For detecting LTBI before start of iatrogenic immune suppression (e.g. anti-TNF therapy): TST and clinical information only
Denmark: Draft Guidelines 2009

- TB screening before anti TNFα:
  - IGRA is preferred; TST when IGRA is not available.

- Exposure/contact screening:
  - IGRA if BCG vaccinated/adult
  - Either TST or IGRA in children and unvaccinated young people

- HIV: no specific guidelines

P Ravn (personal communication)
• TST as a first test and then IGRA as a supplementary test for all TST positives >6mm

• Among IGRAs, QFT is recommended as the primary test. If the mitogen control fails or the patient is severely immunosuppressed T-SPOT-TB is recommended as a secondary test

• Referral to an infectious disease specialist or lung physician is recommended for all IGRA positives and also for TST >15mm/IGRA neg. Result of chest X-ray, symptoms, previous history of TB, immune status is also assessed and part of the decision of referral and prescription of preventive treatment.
Japan: JST Guidelines 2006: QFT-2G

- **Children < 5 y:**
  - QFT not recommended [TST preferred] for LTBI
  - QFT can be used as adjunct for active TB
- **Contacts:**
  - Less than 5 years old: TST is preferred over QFT.
  - From 5 to 12 years old: Use QFT with considering use of TST together. The QFT results should be interpreted carefully.
  - From 12 to 18 years: QFT is preferred over TST where QFT test is available. Use TST if necessary.
  - From 18 to 49 years old: QFT is preferred over TST.
  - Over 50 years old: Limited use of QFT or TST
- **HCWs:** QFT preferred over TST
- **Active TB:** adjunct (supporting) evidence
- **High risk groups (diabetes, steroids, TNF-a blockers):** QFT is preferred and can be used for deciding on LTBI treatment
- **Even when QFT is preferred, TST may be done first, followed by QFT in TST+, in order to be cost effective (especially in case of mass screening)**

QFT-G In Tube approved in 2009

Committee of Prevention, Japanese Society of Tuberculosis
(Kekkaku, 81(5): 393-397, 2006)

Japan: Guidelines for contact investigation 2007: Japan Anti-Tuberculosis association
1. IGRA is required to confirm TB infection in contacts over 6 year old with positive TST (5mm in BCG unvaccinated and 10mm in BCG vaccinated).

2. In contacts with negative TST results, IGRA can be performed based on the attending doctor's clinical decision.

Not for active TB or serial testing
Czech: Guidelines 2006

Recommendation of Czech Thoracic Society for QuantiFERON-TB Gold test
Prague, December 2005

QuantiFERON-TB Gold test should be used in following situations:

1. differential diagnosis of active TB
2. detection of TB infection in close contacts
3. screening for LTBI in high risk groups
4. before and during biological (anti TNF-alpha) treatment
Two-step model (TST positive followed by IGRA) indicated in:

- before starting anti-TNFα therapy;
- regularly, once a year, for patients subjected to long-term anti-TNFα therapy;
- healthcare workers exposed to open forms of TB
- contacts
- military personnel after serving in TB endemic countries;
- as a part of medical examination of risk groups in the population – refugees, minorities;
- as a part of differential diagnosis of pulmonary and extrapulmonary TB

Ivan Solovic, National Institute for TB, Lung Diseases and Thoracic Surgery, Slovakia
For TB screening before biologic therapy, the guideline recommends the use of QFT instead of TST.
Results: major trends

- Two-step approach seems to be the most favored strategy for IGRA use
- Two-step approach is particularly favored in contacts, especially BCG-vaccinated contacts
- Trend towards using IGRAs alone prior to anti-TNF-α therapy
- Some guidelines are still cautious about IGRA use in young children
- Few guidelines recommend IGRAs for active TB, but some recommend as an adjunct, especially in kids
- Most guidelines do not mention use for serial testing of HCWs
Results: major trends

• While some guidelines have been updated to keep up with the evidence base (e.g. USA, Canada, Germany), others are yet to be updated (e.g. UK, Australia, France, Czech).

• Few of the guidelines explicitly used evidence summaries (e.g. GRADE) and systematic reviews.
  ▫ Most based on narrative literature reviews and expert opinion
  ▫ Guidelines that used GRADE or such: ATS/CDC/IDSA, NICE
  ▫ Guideline groups that explicitly used systematic reviews: NICE, ATS/CDC/IDSA, and Canadian ACS

• Most guidelines did not include a clear description of potential conflicts of interests and industry involvement in guideline development
RATING QUALITY OF EVIDENCE AND STRENGTH OF RECOMMENDATIONS

GRADE: grading quality of evidence and strength of recommendations for diagnostic tests and strategies

The GRADE system can be used to grade the quality of evidence and strength of recommendations for diagnostic tests or strategies. This article explains how patient-important outcomes are taken into account in this process.

SUMMARY POINTS

As for other interventions, the GRADE approach to grading the quality of evidence and strength of recommendations for diagnostic tests or strategies provides a comprehensive and transparent approach for developing recommendations.

Cross sectional or cohort studies can provide high quality evidence of test accuracy.

However, test accuracy is a surrogate for patient-important outcomes, so such studies often provide low quality evidence for recommendations about diagnostic tests, even when the studies do not have serious limitations.

Inferring from data on accuracy that a diagnostic test or strategy improves patient-important outcomes will require the availability of effective treatment, reduction of test related adverse effects or anxiety, or improvement of patients’ wellbeing from prognostic information.

Judgments are thus needed to assess the directness of test results in relation to consequences of diagnostic recommendations that are important to patients.
Need to move beyond outcomes such as sensitivity/specificity, concordance

- To better inform policy, we need to study outcomes such as:
  - accuracy of diagnostic algorithms (rather than single tests) and their relative contributions to the health care system;
  - incremental or added value of IGRAs;
  - role of these tests in serial testing situations and their role, if any, as biomarkers for treatment monitoring;
  - impact of IGRAs on clinical decision-making and therapeutic choices;
  - cost-effectiveness in routine programmatic settings;
  - impact on patient-centered outcomes (e.g. progression to disease)
Need to promote the use of evidence and transparency in policies and guidelines

- Expert opinion alone is not adequate; the substantial literature base on IGRAs that must be taken into account
- Promote transparency in guideline and policy development
  - E.g. GRADE is now used for all ATS policy statements and all WHO guidelines
- Include methodologists in guideline panels
  - E.g. Methodologists are often co-chairs of guideline committees at WHO
- All guidelines must have disclosures re industry involvement and potential conflicts for all panel members and reviewers
Conclusions

- There is growing interest in the use of IGRAs, although most countries continue to recommend and use TST.
- More than 17 guidelines and statements have been published on IGRAs; many need to be updated.
  - considerable diversity in the approaches
- Guidelines are predominantly from high-income countries with established LTBI screening programs.
- Future guidelines and statements must aim to be explicitly evidence-based and be more transparent in disclosures.
- Future guidelines will need to consider impact of IGRAs on patient outcomes and cost-effectiveness in various settings.
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(all errors are, however, mine)

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