

# Guidelines on interferon- $\gamma$ release assays for tuberculosis infection: concordance, discordance or confusion?

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## Abstract

Identification of latent tuberculosis (TB) infection and preventive therapy is important for TB control, especially in high-risk populations. Since the advent of interferon- $\gamma$  release assays (IGRAs), many studies have evaluated their role in the diagnosis of active and latent TB. With the growing evidence base, many guidelines now include IGRAs. We surveyed the literature and contacted experts to identify 33 guidelines and position papers from 25 countries and two supranational organizations. The results show considerable diversity in the recommendations on IGRAs, with four approaches commonly proposed: (i) two-step approach of tuberculin skin test (TST) first, followed by IGRA either when the TST is negative (to increase sensitivity, mainly in immunocompromised individuals), or when the TST is positive (to increase specificity, mainly in bacillus Calmette–Guérin-vaccinated individuals); (ii) Either TST or IGRA, but not both; (iii) IGRA and TST together (to increase sensitivity); and (iv) IGRA only, replacing the TST. Overall, the use of IGRAs is increasingly recommended, but most of the current guidelines do not use objective, transparent methods to grade evidence and recommendations, and do not disclose conflicts of interests. Future IGRA guidelines must aim to be transparent, evidence-based, periodically updated, and free of financial conflicts and industry involvement.

**Keywords:** Diagnosis, guidelines, immunodiagnostics, interferon- $\gamma$  release assays, tuberculosis

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## Introduction

Tuberculosis (TB) is a major global public health problem. More than 9.4 million new TB cases were reported in 2009, and 1.7 million people died from TB in that year. Although in the high-incidence settings TB is mostly the result of recent acquisition of *Mycobacterium tuberculosis* [1], the epidemiology in low-incidence countries is different and a large proportion of TB disease is the result of reactivation of latent TB [2]. Detection and management of latent tuberculosis infection (LTBI) therefore is a key component of TB control in low-incidence countries. In high-incidence countries screening for

LTBI has a role in high-risk groups such as the human immunodeficiency virus (HIV)-infected individuals and child contacts of people with TB.

Diagnosis of LTBI relies on immunodiagnostic methods, which include one of the oldest tests in medicine, the tuberculin skin test (TST) [3]. Interferon- $\gamma$  release assays (IGRAs) have been added to the diagnostic armamentarium. Two commercial IGRAs are available, the QuantiFERON-TB<sup>®</sup> Gold In-Tube (QFT-GIT; Cellestis Limited, Chadstone, Vic., Australia) and the T-SPOT.TB (Oxford Immunotec, Abingdon, UK).

The use of IGRAs has increased substantially since 2005, mostly in low-incidence countries. Many studies, meta-

analyses and systematic reviews have been performed to assess the role of these tests in the diagnosis of latent and active TB. Since 2003, several guidelines and position papers have been published to direct clinical practice. This review is an attempt to compare and synthesize these guidelines and recommendations.

## Methods

We searched the literature and contacted over 50 experts from more than 28 countries and at supranational organizations to identify guidelines or recommendations on the use of IGRAs. The initial survey was conducted in 2009 and published as a conference proceeding [4]. This 2009 survey identified 17 country guidelines. Building on this survey, we updated our search and contacted experts to identify updated guidelines or new statements from 2009 to March 2011. Whereas some countries have guidelines endorsed by their ministries of health, other countries have recommendations from national or professional organizations. Some countries have more than one guideline or position paper from different national organizations or interest groups. Many countries (e.g. USA, Canada, UK, Switzerland) have published updated versions of their original statements and in these cases we included the most recent iteration in our survey. Position papers from supranational organizations, such as World Health Organization (WHO) and the European Centre for Disease Prevention and Control (ECDC) were included as well.

Most guidelines were available at least in the form of a summary statement in English. If an English version was not available, we either translated the guidelines or asked local experts or guideline authors for a translation. After summarizing the guidelines, we contacted the experts again with our summary statement of their respective national guidelines and asked them to comment on its accuracy.

## Results

In total, 33 guidelines from 25 countries and two supranational organizations were identified: USA (Centers for Disease Control and Prevention (CDC) and American Academy of Pediatrics (AAP)—*The Red Book*), [5,6], Canada (Canadian Tuberculosis Committee) [7], UK (National Institute for Health and Clinical Excellence) [8], Brazil (Ministry of Health (MOH)) [9], France (National Authority for Health) [10], Spain (Spanish Society of Pneumology and Thoracic Surgery) [11], Italy (MOH) [12,13], Germany (German Central Committee Against Tuberculosis) [14,15], Austria (personal

communication with national expert) [16], Portugal (MOH) [17], Ireland (National TB Advisory Committee) [18], Switzerland (Swiss Lung Association) [19], the Netherlands (Committee for Practical Tuberculosis Control) [20], Denmark (Danish Lung Medical Society) [21], Norway (Norwegian Public Health Institute) [22], Finland (National Institute for Health and Welfare, personal communication with national expert) [23], Czech Republic (personal communication with national expert) [24], Slovakia (MOH, personal communication with national expert) [25], Poland (national experts) [26], Bulgaria (personal communication with national expert) [27], Croatia (personal communication with national expert) [28], Saudi Arabia (joint statement of professional societies) [29], Australia (National Tuberculosis Advisory Committee, Australasian Society for Infectious Diseases, and Australian Rheumatology Association) [30–32], South Korea (personal communication with national expert) [33], Japan (Japanese Society for Tuberculosis Prevention, personal communication with national expert) [34], WHO [35,36] and ECDC [37]. Many of these guidelines are available online at <http://www.tbevidence.org>.

Brazil, Bulgaria, Korea and Saudi Arabia were the only moderate-burden to high-burden countries to have published guidelines on the use of IGRAs. The WHO has issued guidelines for the use of IGRAs in resource-constrained settings in HIV-infected and non-HIV-infected patients [35,36]. The ECDC statement also makes a differentiated recommendation for high-incidence and low-incidence settings [37]. Although no high-burden, low-income country is using IGRAs in their national TB programmes, these tests are being used in some high-burden countries (e.g. India, South Africa) in the private sector and in research settings.

A number of countries and organizations are in the process of finalizing their first guidelines or position papers (e.g. Austria, Bulgaria, Poland and Denmark). Others are updating them (including Germany and South Korea) and publication of these guidelines and position papers can be expected in the coming months.

Across all the guidelines, four main approaches are used most commonly:

- two-step approach of TST first, followed by IGRA
- IGRA only, replacing the TST
- both TST and IGRA together
- either TST or IGRA, but not both.

In the following sections, these different approaches are examined for specific indications.

### Diagnosis of active tuberculosis

Both the TST and IGRAs are indirect tests that indicate a cellular immune response to recent or remote sensitization

with mycobacterial antigens. Neither test can distinguish between individuals with LTBI, active TB or even past TB. In a recent meta-analysis of studies in low-income and middle-income countries assessing the use of IGRAs in active TB, the pooled sensitivity in HIV-infected patients was 76% for the T-SPOT.TB assay and 60% for the QFT-GIT. This compared with 83% for T-SPOT.TB and 69% for QFT-GIT in non-HIV-infected patients. The specificity estimates of IGRAs were low for both non-HIV-infected individuals (T-SPOT.TB 61%, QFT-GIT 52%) and HIV-infected individuals (T-SPOT.TB 52%, QFT-GIT 50%) [38].

Another recent meta-analysis assessing studies from both high-incidence and low-incidence countries, including children and HIV-infected individuals, confirmed these findings, especially the low specificity in individuals with suspected TB [39]. In summary, both systematic reviews concluded that IGRAs should not be used in the diagnostic investigations of active TB in adults because a positive IGRA result may not indicate active TB and likewise, a negative IGRA result may not rule out active disease.

Most guidelines reflect these limitations of IGRAs in respect to the diagnosis of active TB (Table 1). If IGRAs are recommended for the diagnosis of active TB, they are clearly considered to be only an adjunct test in addition to, but not replacing, the standard microbiological and radiographic tests. The recently published ECDC guideline summarizes as follows: "IGRAs should not replace the standard diagnostic methods [...] for diagnosing active TB. [...] However, based on limited evidence, in certain clinical situations (e.g. patients with extrapulmonary TB, patients who test negative for acid-fast bacilli in sputum and/or negative for *M. tuberculosis* on culture, TB diagnosis in children, or in the differential diagnosis of infection with NTM (nontuberculous mycobacteria)) IGRAs could contribute supplementary information as part of the diagnostic work-up." [37].

Some guidelines (Canada, Switzerland, Saudi Arabia and Croatia) explicitly recommend against the use of IGRAs in the diagnosis of active TB in adults but include them as part of the diagnostic algorithm in children as tests that provide evidence of TB infection. This acknowledges the difficulty of diagnosing TB by conventional methods in children [40]. The WHO recommends against the use of IGRAs for active TB in low-income and middle-income countries because of the poor specificity on account of a high background prevalence of LTBI [35,36,41,42].

#### Contact investigation in adults

The role of IGRAs in contact tracing is summarized in recent systematic reviews [43–46]. The most obvious strength of IGRAs is their high specificity, because they allow the clinician to differentiate between a sensitization caused by bacillus Calmette–Guérin (BCG) vaccination or non-tuberculous mycobacterial exposure and contact with an active TB case. However, recent cohort studies suggested that IGRAs, similar to the TST, have only modest predictive ability. Only 1–3% of IGRA-positive contacts develop active TB over 2 years of follow-up, even in high burden countries [47–51]. This indicates that interferon- $\gamma$  alone is probably insufficient as a biomarker for disease progression, especially if only measured at baseline [52,53]. A combination of TST/IGRA and risk factor information may be more helpful, especially if made available as web-based algorithms (<http://www.tstin3d.com>) [54]. More recently, a *World BCG Atlas* has been published (<http://www.bcgatlas.org>), to help clinicians decide on whether to use a TST or an IGRA, depending on the local BCG policies and practices [55].

The country guidelines on the use of IGRAs in contact tracing for adults mostly favour a two-step testing approach (Table 2). A TST is performed in the first step and if positive, it is followed up with an IGRA. The two-step approach

**TABLE 1. Guidelines on interferon- $\gamma$  release assays (IGRAs): recommendations for active tuberculosis**

Recommendation	Subgroup	Guideline or position statement <sup>a</sup>
For the use of IGRAs but only as an adjunct (some guidelines specify the use only when other diagnostic tests have been unrevealing)	In adults	ECDC, USA-CDC, UK, France (only for extrapulmonary TB), Australia, Slovakia, Japan, the Netherlands, Norway, Bulgaria, Portugal, Denmark, Austria
	In children	ECDC, Canada, USA (CDC and AAP), UK, Switzerland, Australia, Slovakia, Japan (children >12 years of age), Saudi Arabia, the Netherlands, Norway, Bulgaria, Portugal, Croatia, Denmark, Austria
Against the use of IGRAs	In adults	WHO, Canada, Switzerland, Saudi Arabia, Croatia, Ireland, South Korea, Brazil
	In children	WHO, France, Ireland, South Korea, Brazil
No recommendations		Germany, Italy, Spain, Finland, Poland, Czech Republic

AAP, American Academy of Pediatrics; CDC, US Centers for Disease Control and Prevention; ECDC, European Centre for Disease Prevention and Control; IGRA, interferon-gamma release assay; TST, tuberculin skin test; WHO, World Health Organization.

<sup>a</sup>Some countries/organizations are listed more than once because their recommendations vary across risk groups.

**TABLE 2. Guidelines on IGRAs: recommendations for contact investigation in adults**

Recommendation	Guideline or position statement <sup>a</sup>
TST alone	WHO, Brazil, ECDC (high-incidence countries)
TST followed by IGRA, if TST positive (either IGRA only in BCG-vaccinated persons or independent of BCG vaccine)	Canada (low-risk contacts), Germany, Italy, Switzerland, Spain, Saudi Arabia, the Netherlands, Norway, Bulgaria, Portugal, Ireland, ECDC (low-incidence countries), and for UK and South Korea only in adults <35 years old
Both TST and IGRA	Canada (high-risk contacts), Czech Republic, Croatia, Austria, Australia (IGRA may be considered in addition)
Either TST or IGRA	USA, Denmark, Finland (IGRA preferred if BCG-vaccinated in all three countries), South Korea (only in adults <35 years old), Austria
IGRA alone	Slovakia, Japan, France

BCG, bacille Calmette–Guérin; CDC, US Centers for Disease Control and Prevention; ECDC, European Centre for Disease Prevention and Control; IGRA, interferon-gamma release assay; TST, tuberculin skin test; WHO, World Health Organization.

<sup>a</sup>Some countries/organizations are listed more than once because their recommendations vary across risk groups.

is primarily intended to increase specificity in individuals with prior BCG vaccination, and also to reduce costs incurred by the follow-up and LTBI treatment of TST false positives. Some countries recommend only IGRAs for persons with previous BCG vaccination, whereas others favour the IGRA in a second step independent of a history of BCG vaccination. A few country guidelines acknowledge the possibility that a TST can boost subsequent IGRA results [56] (i.e. Canada, USA, the Netherlands, Germany, Ireland) and some make specific recommendations on when the IGRA should be performed in relation to the TST (i.e. on the day of reading of the TST or within 3 days of the TST placement).

Some guidelines suggest that either an IGRA or a TST should be used for contact investigation (USA, Denmark, South Korea, Finland, Austria). Some of these (i.e. USA, Denmark, Finland) specify certain subgroups in which the IGRA should be used preferentially (i.e. persons who refuse to accept the TST, BCG-vaccinated individuals and individuals who are unlikely to return for the second visit required for a TST). Some countries suggest using the IGRA only (Slovakia, Japan, France) or in addition to the TST (Czech Republic, Austria, Croatia). The Australian guidelines suggest using the IGRA “as a supplementary test in individualised clinical assessment” [30]. Similarly, Canada uses a differentiated approach based on the risk of the patient [7]. For individuals with a high-risk exposure or a high-risk for progression to active TB, both tests are carried out to increase sensitivity, whereas for all others the sequential approach is taken with the TST performed first.

The WHO issued a recommendation against the use of IGRAs and for the use of TST, but only in low- and

middle-income settings, regardless of HIV status [35,36]. The ECDC has a differentiated approach based on TB-incidence. In a high-incidence setting, the ECDC concurs with the WHO and suggests only a TST, whereas for low-incidence settings a two-step approach is recommended [37]. Overall, the recommendations for contact tracing in adults appear to suggest a clear trend towards an increased use of IGRAs, especially in low-incidence countries, mostly as a two-step strategy.

### Contact tracing in children

There are limited data on the use of IGRAs for the diagnosis of LTBI in children. The data are especially sparse in the very young children, and very few studies have assessed the predictive value of IGRAs in children. Two recent meta-analyses concluded that TST and IGRAs have similar accuracy for the detection of TB infection or the diagnosis of disease in children [43,57].

Guidelines regarding children are very heterogeneous and reflect the uncertainties in the evidence base (Table 3). Many continue to prefer a TST alone, either for all children (WHO, ECDC, Brazil, Switzerland, France) or only for children under 5 years of age (Canada, Japan, Ireland, USA-CDC and USA-AAP). Treatment for LTBI based on a positive TST result only, regardless of BCG vaccination or even if a TST

**TABLE 3. Guidelines on IGRAs: recommendations for contact investigation in children**

Recommendation	Guideline or position statement <sup>a</sup>
TST alone	WHO, ECDC, France, Brazil, Switzerland (IGRA in addition only in case of doubt), Slovakia (in BCG non-vaccinated children), South Korea (for children <5 years old)
TST alone (in children 0–4 years old); TST followed by IGRA, if TST positive (for children 5–17 years old)	Canada (low-risk contacts), Japan, Ireland, USA-AAP (for children >5 years old, IGRA may also replace TST)
TST followed by IGRA, if TST positive	Germany, Italy, Spain, Saudi Arabia, the Netherlands (dependent on BCG vaccination status and result of TST, only TST might be sufficient), Bulgaria, and for children >5 years of age only in Portugal and UK
TST followed by IGRA, if TST negative	Portugal (for children <5 years old), UK (for children 2–5 years old)
Either TST or IGRA	Denmark, USA-CDC (but TST is preferred in children <5 years old), South Korea (for children >5 years old, but TST preferred), Finland
Both TST and IGRA	Canada (high-risk contacts), Czech Republic, Croatia, Australia (IGRA may be considered in addition for children >2 years old)
IGRA alone	Norway

AAP, American Academy of Pediatrics; BCG, bacille Calmette–Guérin; CDC, US Centers for Disease Control and Prevention; ECDC, European Centre for Disease Prevention and Control; IGRA, Interferon-gamma release assay; TST, tuberculin skin test; WHO, World Health Organization.

<sup>a</sup>Some countries/organizations are listed more than once because their recommendations vary across risk groups.

is negative but a high clinical suspicion persists, is justified by the fact that young children are at high risk for progression to active TB. Most other guidelines recommend a TST in combination with an IGRA if the TST is positive, especially for BCG-vaccinated children (Germany, Italy, Spain, Saudi Arabia, the Netherlands, Bulgaria).

Some statements limit the two-step testing to children over 5 years of age (Canada, Japan, Portugal, UK, Ireland and USA-AAP) given the limited amount of data on IGRAs in very young children. *The Red Book* (USA-AAP), while favouring a two-step approach, also allows the use of IGRAs replacing the TST for children older than 5 years of age. The guidelines using an approach with either a TST or an IGRA include the USA-CDC (TST favoured for children <5 years of age), Denmark, South Korea (TST only recommended for children <5 years of age and favoured for children >5 years of age) and Finland. A few countries recommend both tests together (Canada—for high-risk contacts, Czech Republic and Croatia) or suggest that an IGRA may be used as a supplementary test (Australia, for children >2 years of age) or if initial TST is negative (Portugal for children <5 years of age, UK for children 2–5 years of age).

#### Immunocompromised: individuals with HIV infection

Individuals who are HIV-positive are at high risk of progression from LTBI to active TB and therefore are an important group for LTBI screening [36,58]. Data on the use of IGRAs in people living with HIV were summarized in a recent systematic review [59]. The sensitivity estimate in HIV-infected patients with culture-confirmed TB was higher for T-SPOT.TB (72%) than for QFT-GIT (61%). However, neither IGRA was consistently more sensitive than the TST in head-to-head comparisons. The agreement between the two IGRAs and TST was higher in the high-income countries where BCG vaccination was used less frequently.

The meta-analysis also suggested that IGRAs, and especially the T-SPOT.TB assay, are less affected by HIV-related immunosuppression than the TST, but the differences between the tests were small and results varied substantially across individual studies. Limited data were available on the predictive value of IGRAs for active TB. Hence, the systematic review concluded that IGRAs perform in a similar way to the TST in identifying HIV-infected individuals who could benefit from LTBI treatment.

These equivocal data are also reflected in the wide array of different country recommendations (Table 4). The guidelines for low-resource and high-TB-incidence settings, the Brazilian and the WHO guidelines, recommend the TST. The other guidelines and position papers clearly show a trend towards a greater use of IGRAs. While the Swiss, French

**TABLE 4. Guidelines on IGRAs: recommendations for HIV-infected populations**

Recommendation	Guideline or position statement <sup>a</sup>
TST alone	WHO, Brazil
TST followed by IGRA, if TST positive (and BCG-vaccinated)	Spain
TST followed by IGRA, if TST negative	Canada, Italy, Saudi Arabia, Spain, Ireland
Either TST or IGRA	Denmark, South Korea, Austria
Both TST and IGRA	ECDC, Portugal, Croatia, Slovakia, the Netherlands, USA (if either initial test negative), South Korea, UK
IGRA alone	Switzerland, Bulgaria, France, UK (if CD4 200–500)
No specific recommendations	Germany, Czech Republic, Norway, Japan, Finland, Australia

AAP, American Academy of Pediatrics; BCG, bacille Calmette–Guérin; CDC, US Centers for Disease Control and Prevention; ECDC, European Centre for Disease Prevention and Control; IGRA, interferon-gamma release assay; TST, tuberculin skin test; WHO, World Health Organization.

<sup>a</sup>Some countries/organizations are listed more than once because their recommendations vary across risk groups.

and Bulgarian guidelines recommend use of IGRA alone, other countries and organizations (ECDC, Portugal, Slovakia, the Netherlands, USA, South Korea, Croatia and UK) suggest the use of both tests together (either up front or if the chosen initial test is negative) to increase the sensitivity. Yet others suggest a two-step approach with a negative TST followed by an IGRA to increase sensitivity (Canada, Italy, Ireland, Saudi Arabia and Spain).

#### Immunocompromised: individuals on anti-tumour necrosis factor- $\alpha$ therapy

Individuals on tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) inhibitor therapy are at high risk of progression from LTBI to active TB [60]. Screening for LTBI is recommended in many countries before starting TNF- $\alpha$  inhibitors for immune-mediated inflammatory disorders. Few studies have evaluated the performance of IGRAs in screening for LTBI in patients with these disorders.

Although no meta-analysis has been published, two recent reviews [61,62] have synthesized the data. Both reviews were hampered by the substantial heterogeneity between the studies. The differences in the studies relate to the level of immunosuppression (pre-TNF- $\alpha$  inhibitors, on TNF- $\alpha$  inhibitor and variable additional steroid use), the types of TNF- $\alpha$  inhibitors used, the immune-mediated inflammatory disorders treated (IMID), the tests that were evaluated, and the rate of BCG vaccination in the population. In addition, the small numbers of patients with confirmed TB disease and the lack of any data on the predictive value of IGRA limited the studies. The authors concluded that the current evidence does not suggest superiority of IGRAs over the TST in identifying latent TB in individuals with IMID [61].

Similar to HIV, the guidelines for LTBI screening for patients on TNF- $\alpha$  inhibitors reflect the lack of definitive data (Table 5) and a number of different strategies are recommended. While the Brazilian guidelines continue to rely on the TST, several others now favour the IGRAs as the only test (Germany, Switzerland, Bulgaria, Japan, France, Poland) and some suggest a TST in addition to the IGRA only if the IGRA is repeatedly indeterminate or negative (i.e. Germany). Many guidelines combine both tests to increase sensitivity (ECDC, USA, Portugal, Czech Republic, Croatia, Slovakia, the Netherlands, South Korea, Ireland and UK) either upfront or if the initially chosen test is negative. Alternatively, a two-step approach with an IGRA following a TST, if the TST is negative, is recommended to increase sensitivity but limit cost (Canada, Italy, Spain, Saudi-Arabia).

### Screening of immigrants

In low-incidence countries, a majority of the TB cases occur among recent immigrants and foreign-born persons [2,63], and immigrant screening is often a key component of TB control. Most guidelines that include recommendations are from countries with low-incidence (Table 6) and focus on immigrants from high-incidence settings but others also include recommendations for immigrants who are likely to develop active disease (i.e. children or persons with underlying disease that predisposes them to a reactivation of an LTBI) independent of their country of origin (e.g. Canada, the Netherlands).

All guidelines that do make recommendations for screening of immigrants incorporate IGRAs. The most common algorithm is a TST followed by an IGRA if positive (UK (for

**TABLE 5. Guidelines on IGRAs: recommendations for LTBI screening in persons on TNF- $\alpha$  inhibitors**

Recommendation	Guideline or position statement <sup>a</sup>
TST alone	Brazil
TST followed by IGRA, if TST positive	Spain, Norway
TST followed by IGRA, if TST negative	Canada, Italy, Spain, Saudi Arabia
Either TST or IGRA	Australia-ARA, Denmark (IGRA favoured), South Korea
Both TST and IGRA	ECDC, UK (alternatively IGRA alone), USA (if either initial test negative), Portugal, Croatia, Czech Republic, Slovakia, the Netherlands, South Korea, Ireland (TST preferred)
IGRA alone	Germany, Switzerland, Bulgaria, Japan, France, Poland, Austria
No recommendations	Finland, Australia-NTAC

ARA, Australia Rheumatology Association; CDC, US Centers for Disease Control and Prevention; ECDC, European Centre for Disease Prevention and Control; IGRA, interferon-gamma release assay; NTAC, National Tuberculosis Advisory Committee, Australia; TST, tuberculin skin test; WHO, World Health Organization.

<sup>a</sup>Some countries/organizations are listed more than once because their recommendations vary across risk groups.

**TABLE 6. Guidelines on IGRAs: recommendations for screening of immigrants**

Recommendation	Guideline or position statement <sup>a</sup>
TST followed by IGRA, if TST positive	UK (for children age 5–15 years), Italy, Switzerland, Spain, Norway, Ireland, Bulgaria, France (in children), Slovakia, the Netherlands (for children only; dependent on BCG vaccination status and result of TST, only TST might be sufficient)
Both TST and IGRA	Czech Republic, UK (for adults age 16–35 years; or IGRA alone alternatively)
Either TST or IGRA	USA (IGRA preferred in BCG-vaccinated persons), Canada, Australia
IGRA alone	France (in adults)
No recommendations/not recommended	Germany, Japan, Saudi Arabia, Brazil, Portugal, Croatia, Denmark, South Korea, Finland, Poland, Austria

BCG, bacille Calmette–Guérin; CDC, US Centers for Disease Control and Prevention; ECDC, European Centre for Disease Prevention and Control; IGRA, interferon-gamma release assay; TST, tuberculin skin test; WHO, World Health Organization.

<sup>a</sup>Some countries/organizations are listed more than once because their recommendations vary across risk groups.

children 5–15 years of age), Italy, Switzerland, Spain, the Netherlands, Norway, Ireland, France, Slovakia and Bulgaria). This algorithm is intended to increase specificity given the widespread use of BCG vaccination in countries where TB is endemic.

### Serial testing of healthcare workers

The value of IGRAs in the testing of healthcare workers has been investigated in over 50 studies, which are summarized in a recent systematic review [64]. The review differentiates between initial testing (e.g. pre-employment) and serial (repeated) testing of healthcare workers. Overall, the review concluded that the use of IGRAs instead of TST for one-time screening may result in a lower prevalence of positive tests and fewer healthcare workers who require LTBI treatment, particularly in settings where TB incidence is low. However, the use of IGRAs for serial testing is complicated by the lack of data on optimal cut-offs for serial testing and unclear interpretation and prognosis of conversions and reversions [64].

This uncertainty is also reflected in the guidelines (Table 7). Many guidelines and position papers do not make recommendations for the serial screening of healthcare workers (Australia, Czech Republic, Norway, Croatia, Denmark, Germany, UK, Finland and ECDC). Some countries suggest the use of IGRAs only (Slovakia, Japan, the Netherlands, Portugal, France) or as an alternative to the TST (USA, Switzerland, Italy) for serial healthcare worker screening.

Some of the guidelines comment on the limitations of the IGRAs for serial testing. For example, the Canadian guideline states that “there is insufficient published evidence to recommend serial IGRA testing in populations exposed to TB, such as healthcare workers or prison staff and inmates” [7]. The

**TABLE 7. Guidelines on IGRAs: recommendations for serial testing of healthcare workers**

Recommendation	Guideline or position statement <sup>a</sup>
TST alone	Brazil, South Korea, Canada, Saudi Arabia, Ireland, Austria
TST followed by IGRA, if TST positive	Spain, the Netherlands, Bulgaria
Either TST or IGRA	USA, Switzerland, Italy (in BCG-vaccinated IGRA preferred)
IGRA alone	Slovakia, Japan, Switzerland, the Netherlands, Portugal, France
No recommendations/not recommended	Australia, Czech Republic, Norway, Croatia, Denmark, Germany, UK, Finland, ECDC

BCG, bacille Calmette–Guérin; CDC, US Centers for Disease Control and Prevention; ECDC, European Centre for Disease Prevention and Control; IGRA, interferon-gamma release assay; TST, tuberculin skin test; WHO, World Health Organization.

<sup>a</sup>Some countries/organizations are listed more than once because their recommendations vary across risk groups.

CDC guideline states that “the criteria for interpreting changes in an IGRA that identify new infections remain uncertain” [5]. Because of such concerns, many countries actually favour a TST only (Brazil, South Korea, Canada, Saudi Arabia, Ireland, Austria), or a TST with a second-step IGRA if the TST is positive (Spain, the Netherlands, Bulgaria).

## Conclusion

A growing number of guidelines and position papers now address the use of IGRAs. Overall, the use of IGRAs is increasingly recommended, primarily in low-incidence settings, but there is considerable diversity in the recommendations on how exactly IGRAs should be used. In high-incidence and low-resource countries, the TST is still favoured because there is no strong evidence that IGRAs are superior to the TST in such settings, especially given the significantly higher costs associated with IGRAs. In low-incidence and high-resource settings, the higher specificity of IGRAs and their logistical advantages seem to enhance their adoption and usage.

One reason for the heterogeneity among guidelines is that conclusive data to inform these guidelines were often limited, particularly with the older guidelines. This is true especially with respect to the use of IGRAs in patients starting TNF- $\alpha$  inhibitors or in children younger than 5 years of age. Until recently, there were few cohort studies on the predictive value of IGRAs and this may have further influenced guidelines and statements.

Whereas most guidelines (78%) cited systematic reviews of available data, most (70%) did not use objective and transparent grading systems (e.g. GRADE [65]) for guideline development. A majority of the guidelines did not include

statements on conflict of interest. These findings are consistent with published data on poor methodological quality of TB guidelines [66]. On the positive side, several countries have attempted to update their guidelines, as the evidence base on IGRAs has steadily matured. To have an impact, future IGRA guidelines must be transparent, evidence-based, periodically updated and free of financial conflicts and industry involvement.

## Acknowledgements

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