Health Protection Agency position statement on the use of Interferon Gamma Release Assay (IGRA) tests for Tuberculosis (TB)

Draft Interim HPA Guidance
HPA Tuberculosis Programme Board

Withdrawn

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Who is this position statement for?

- Communicable disease control professionals
- Clinical staff involved with the diagnosis and treatment of TB
- TB nurse specialists
- Laboratory staff involved with IGRA testing
- Primary Care staff

What does this add?

Following recent additions to the evidence base on IGRA testing the Department of Health commissioned NICE to produce a partial update of the management of TB guidelines, published in March 2011 [1]. This position statement has been revised in response to this updated guidance.

Objectives

- To provide information on IGRA tests and their role in the diagnosis of TB
- To support frontline clinical staff in deciding whether IGRA tests should or should not be used
- To clarify and expand on the National Institute of Health and Clinical Excellence (NICE) [1] guidance on the use of IGRA tests

Introduction and background

The World Health Organization Stop TB strategy [2] aims to reduce the global burden of TB by 2015. In order to achieve this goal, patients with infectious (active) TB need to be diagnosed and treated and those with latent infection identified, so they can be offered prophylaxis to reduce the risk of developing active TB later in life. Approximately 5-10% of those with latent tuberculosis infection (LTBI) will subsequently develop disease [3]. The global reservoir (LTBI) is thought to be one third of the world's population(3) and reactivation causes over 70% of tuberculosis in England and the UK [4]. It therefore remains essential for diagnosis and treatment of LTBI to be a key control measure of TB in the UK.

Various clinical symptoms and signs, radiological and histopathological findings are suggestive of active TB, but the gold standard for the confirmation of active disease is the culture of *Mycobacterium tuberculosis*. There are no clinical symptoms or signs in LTBI and no gold standard laboratory test is available. In asymptomatic patients LTBI is currently being diagnosed by administration of a tuberculin skin test (TST), a two step approach of TST then IGRA or in some circumstances IGRA alone.

IGRA tests

There are currently two interferon gamma release assays commercially available: QuantiFERON-TB Gold In tube (Cellestis, Australia) and T.Spot.TB (Oxford Immunotec, UK). Both tests determine from an individual's immune response whether they have been infected (currently or previously) with *M. tuberculosis*. All the tests are based on the same immunological principle. The patient's blood is stimulated with synthetic antigens and the amount of, interferon gamma (a cytokine) produced by the T cells, or number of activated T cells is measured. Both tests have been developed using antigens found in strains of *M.tuberculosis*, absent from the BCG vaccine-strain *Mycobacterium bovis*. Therefore these tests are less influenced by prior BCG vaccination.

Interpretation of the current evidence on the diagnostic accuracy of IGRA remains problematic. The majority of research has focussed on the sensitivity and specificity of IGRA tests in diagnosing LTBI, in the absence of a gold standard test.

The absence of a gold standard for the diagnosis of LTBI requires other methodologies for comparisons to be made:

1. Using the results of the tests obtained with blood specimens from patients recently confirmed with active TB as the basis for identifying truly positive results.
2. Determining true negative results by testing healthy volunteers from low prevalence areas who have had no known contact with a case of active TB and assuming them to be LTBI free.
3. Examining the correlation of a positive IGRA test with levels of exposure among individuals recently in contact with a known case of sputum smear positive TB (level of exposure studies).
4. Measuring the degree of concordance with TST, recognising the sub-optimal validity of TST (degree of concordance studies).
5. Following up groups of individuals over time who have tested IGRA positive and ascertaining if they develop disease, to determine positive and negative predictive values. (longitudinal studies).

Evidence from recent reviews indicates the sensitivity of IGRA is at least equal to TST in various at risk groups whilst the specificity is consistently greater than TST in all groups [5,6,7,8]. A higher level of concordance between IGRA and TST was observed in non BCG vaccinated populations than in those who were BCG vaccinated [1].

Only 2 studies of IGRA predictive value have included UK populations [9,10]. Results from ongoing prospective studies in the UK [11] will inform the future use of IGRA in the UK.

Evidence of the cost effectiveness of IGRA testing remains sparse, published studies have little generalisability to a UK situation. The guidance developed by NICE [1] has incorporated models based on cost effectiveness papers for adult contacts and screening people from high prevalence populations. No cost effectiveness models have been incorporated for other risk groups. Any conclusions thus involve a degree of assumption in relation to disease prevalence and test predictive value.

The immunology underpinning active TB may be different from LTBI so the results of these studies cannot be assumed to apply to the diagnosis of active TB.

Use of IGRA tests for the diagnosis of active TB

Various clinical symptoms and signs, and radiological and histopathological findings are suggestive of active TB. The gold standard for confirmation of active TB remains culture of *M.tuberculosis*. There is little place for IGRA tests in the diagnosis of active TB in adults. This provides a definitive diagnosis and permits the identification of drug resistance. In some patients with TB it is not possible to obtain clinical specimens or isolate M. tuberculosis from clinical specimens obtained, despite the individual having symptoms, signs and/or radiological changes consistent with the diagnosis of TB. In these circumstances a positive **IGRA test may increase confidence in the diagnosis.**

A negative IGRA test result may contribute to the confidence with which the diagnosis can be ruled out and may allow more complex or invasive investigations to be deferred or avoided. T cell responsiveness to TB antigens can be reduced as a result of an active TB infection or any immunocompromise that underlies TB reactivation. For this reason IGRA testing can produce false negative results. Rarely, it can also produce a false positive result in an individual who has latent TB infection but a non TB cause of their current illness. IGRA tests cannot distinguish between active and latent TB.

Due to the limited evidence for the effectiveness of IGRA testing in the diagnosis of active TB the cost effectiveness of their use for this purpose has not been adequately researched. **IGRA tests should not replace diagnostic methods for diagnosing active TB** [12]. It is important that resources should not be diverted from the conventional diagnostic approaches which are the most clinically useful and cost efficient method of making the diagnosis.

NICE Guidance for IGRA testing in the diagnosis of active TB

NICE conclude that 'interferon gamma tests may have a role in ruling out infection with M tuberculosis', an update on this area is awaited. Guidance on the methods for diagnosis of active TB is detailed in the NICE guidelines [1] and has not been updated in the 2011 guidance revision.

HPA recommendation for IGRA testing in the diagnosis of active TB

IGRA tests should not be used as a routine diagnostic tool for active TB. The HPA advises that IGRA tests are only considered in supporting the primary diagnosis of active TB when it has not been possible to confirm the diagnosis by culture and when strong support for the diagnosis is lacking from radiological and histopathological tests. If the diagnosis remains in doubt and a subsequent management decision on whether or not to treat will be influenced by the result, then the use of IGRA test is supported. The final decision should be based on clinical judgement. The diagnosis of active TB is rarely made from the result of any one single test.

Use of IGRA testing in the diagnosis of LTBI

There are no signs and symptoms in LTBI and no gold standard laboratory test is available. At present LTBI is diagnosed using the Mantoux test alone, or an IGRA test alone or a two step strategy of Mantoux then IGRA. The Mantoux method of TST requires intradermal injection with tuberculin, results read 48-72 hours later. The technique requires an experienced operator and the patient to return for a second visit. Despite the low cost and availability of this method it is subject to a great deal of inter and intra observer variation. False positives can occur due to previous vaccination with BCG and false negatives whenever the individual is immunocompromised, whether drug induced or as a component of an underlying condition. Given the current evidence it is reasonable to assume that IGRA tests are at least as sensitive as TST and more specific in BCG vaccinated populations.

IGRA offers an advantage over TST by reducing the number of individuals offered chemoprophylaxis due to its ability to distinguish between previous BCG (where there is no reliable vaccination record and/ or no scar) and LTBI.

NICE guidance for IGRA testing for the diagnosis of LTBI

NICE guidance reflects both the growing evidence base from longitudinal studies on the sensitivity and specificity of IGRA and cost effectiveness studies. The use of a step wise approach of Mantoux TST then IGRA if TST positive remains the most cost effective option in the UK; NICE recommends this strategy for new entrants to the UK from high incidence countries, healthcare professionals with high risk of TB contact or previous BCG and children identified as contacts of TB cases.

NICE recommends IGRA to be considered as the first line diagnostic test in specific circumstances:

NICE recommends that a single IGRA test can be performed to diagnose LTBI in people in hard to reach groups.

NICE recommends consideration of IGRA testing for people aged 5 years and older in an outbreak situation where a large number of contacts need to be tested.

NICE recommends that new healthcare workers who are NHS employees are offered IGRA testing if they have recently arrived from high incidence countries or if they have had contact with patients in settings where TB is highly prevalent.

NICE guidance for immunocompromised adults is divided according to the nature of immunocompromise:

- For people with **HIV and CD4 counts less than 200 cells/mm** an IGRA should be performed concordantly with a Mantoux. If either test is positive further clinical assessment is needed to exclude active TB and consideration of prophylaxis for LTBI if appropriate.

- For people with **HIV and CD4 counts of 200-500 cells/mm** NICE recommend that a IGRA test alone or a IGRA with concurrent Mantoux. If either test is positive further assessment should be made to exclude active TB and consideration of prophylaxis for LTBI as appropriate.

- **All other people who are immunocompromised,** including people with prolonged steroid use, use of TNF alpha antagonists and drugs used to prevent rejection of transplanted organs are recommended to be offered a IGRA test alone or a IGRA with concurrent Mantoux. If either are positive further clinical assessment for active TB and consideration of prophylaxis for LTBI as appropriate is advised.

HPA recommendation on testing for LTBI

This section reiterates the details of the NICE guidelines and provides further clarification for the local application of IGRAs.

The HPA recommends that Mantoux test be used at the first line test for LTBI in contacts of infectious cases and others considered at increased risk of LTBI. Mantoux testing should be performed in line with the Green book guidance [13]. Those with positive TST results (based on the Green Book criteria) should then be considered for IGRA testing. Indeterminate results should be discussed with a TB specialist.

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

1. New entrants from high incidence countries aged 16-35

2. New entrants from high incidence countries or in contact with high risk individuals being screened as part of new NHS employee checks

3. Patients identified as contacts to a case in a large outbreak of TB

In all situations availability and applicability to the local population should be considered in deciding and offering the most appropriate test. Opinion and advice of TB specialists should be sought in indeterminate cases.

Testing for LTBI in new entrants from high incidence countries

New entrant screening should be incorporated within larger health screening programmes for new entrants to England and Wales, linked to local services as recommended in the NICE guidelines [1].

The HPA recommends that new entrants under 35 years are offered Mantoux testing followed by IGRA if positive. New entrants with positive Mantoux test under the age of 5 should be referred to a TB Specialist. IGRA alone can be used if local facilities are available in new entrants aged 16-35. If over 35 consideration of risk should be taken prior to the use of Mantoux or IGRA testing. It remains paramount in all cases to consider the presence of signs and symptoms of active TB.

Testing for LTBI in household contacts under 5 years

The HPA recommends that household contacts of TB under 5 years are offered Mantoux testing. If the test is positive referral should be made to a TB specialist for exclusion of

active TB. In those children who are negative but who are a contact of a sputum smear positive TB case, a IGRA should be offered 6 weeks after the initial test with a repeat mantoux

Testing for LTBI in contacts in an outbreak situation

The HPA advises that in the context of an outbreak situation the Outbreak Control Team should consider the use of IGRA as a diagnostic test for LTBI in people aged 5 and older, if facilities are available. Signs and symptoms of active TB need to be excluded prior to interpretation of the test result and the ongoing investigation should incorporate advice from local TB multidisciplinary teams.

Testing for LTBI in new health care workers

The HPA recommends that healthcare workers should be offered an IGRA test if they have significant exposure to TB, either from a high incidence country of origin through occupational exposure or have evidence of previous BCG vaccination. It is important to note that some healthcare workers may also be immunocompromised individuals and in these cases the guidance in the related sub category is advised.

Healthcare workers not in the high risk categories should be offered Mantoux followed by IGRA if Mantoux test positive.

Testing for LTBI in individuals who are immunocompromised or undertaking immunosuppressive therapy:

The risk of developing TB following a diagnosis of LTBI increases in those who are significantly immunocompromised. Individuals with HIV or those due to commence immunosuppressive therapy including anti TNF alpha agents may require assessment for LTBI after exclusion of active TB.

The HPA recommends that all immunocompromised children with suspected LTBI are referred to TB Specialists for further management. The HPA recommends that for adults with HIV with a CD4 cell count less than 200 cells/mm that both an IGRA and Mantoux test be performed to diagnose LTBI. For other immunocompromised adults (HIV with CD4>200cells/min, drug induced) at risk of LTBI an IGRA test can be used solely or in concordance with a Mantoux test. Any indeterminate results should be discussed with a TB specialist.

The HPA advises that an assessment of the degree and nature of immunocompromise, including tests for HIV infection, should be made on any individual considered to be high risk for developing TB.

Testing of individuals in hard to reach groups:

The HPA recommends that the use of single IGRA can be considered in hard to reach populations if appropriate testing facilities and treatment programmes are available. The use of this strategy should be guided by data on local knowledge of at risk groups and epidemiology of TB.

Update of this guidance

The use of IGRA testing for LTBI is a rapidly progressing area of research with a continuing and expanding evidence base. This position statement is accompanied by a set of questions and answers developed following informal consultation with HPA local and regional services, Regional Microbiology Network and HPA Colindale staff.

Guidance prepared by Dr Rachel Weston, Dr Helen Stagg, Professor Francis Drobniewski, Dr John Magee and Professor Ibrahim Abubakar on behalf of the Health Protection Agency Tuberculosis Delivery Board.

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