Who are these Q&As for?

These Q&As are for health professionals.

What is an IGRA test?

The IGRA (Interferon Gamma Release Assay) test is a blood test that has been developed to help in the diagnosis of both active tuberculosis and latent tuberculosis infection. There are two tests currently available: the QuantiFERON-TB Gold In-Tube assay and the T-SPOT.TB test.

How do they work?

Both methods involve a single blood test that exploits the body's immune response to determine whether a person has been infected with Mycobacterium tuberculosis. T-cells, that have been in previous contact with the bacterium, release the cytokine, interferon gamma (a chemical messenger) when they are stimulated with synthetic peptides which are specific to a small number of mycobacteria, including human M. tuberculosis, but not the BCG vaccine strain of M. bovis. The amount of interferon gamma or the number of M. tuberculosis sensitive T-cells in the blood is then estimated by the tests. T-cells that have not been in contact with the bacterium, will not release the cytokine.

When should you use the test?


1. Diagnosis of Latent Tuberculosis Infection (LTBI). The need to investigate individuals for LTBI may arise in the following settings:

1.1 Contact Tracing: The HPA recommends a two step strategy as outlined in the NICE guidelines for screening for LTBI. This involves using a Tuberculin Skin Test (TST) and, if this is positive, an IGRA test. The NICE guidelines used the terminology “to consider” an IGRA test. This was done because at the time of writing, IGRA tests were not widely available in laboratories in England. 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 immunocompromisation.
(b) when screening large numbers of individuals as part of a public health investigation where logistic issues make repeated visits for sequential testing impractical.
(c) where TST is not available.

1.2 New Entrants: New entrant screening for tuberculosis should be incorporated within larger health screening programmes for new entrants, linked to local services as recommended in the NICE guidelines. The HPA recommends the use of IGRA tests following a positive TST for new entrant screening.

1.3 Healthcare Workers: New health care workers are recommended for testing for LTBI if they do not have symptoms suggestive of active disease and do not have evidence of prior BCG immunisation. NICE recommendations state that IGRA testing can be used as an alternative to TST in these individuals. The HPA supports the use of IGRA testing in health care workers as an alternative to TST. This is based on the importance of detecting latently infected health care staff who may go on to develop active disease potentially exposing vulnerable patients to the risk of infection and the logistical simplicity of IGRA testing.

1.4 Individuals going to undertake immunosuppressive therapy e.g. anti-TNF-α treatment: There is no NICE guidance relating to the use of IGRA tests for this purpose. British Thoracic Society guidelines relating to this published in 2005.
IGRA (go to http://www.brit-thoracic.org.uk/ click on guidelines/ guidelines since 1997 / tuberculosis / anti TNF). These guidelines, however, discuss the need to exclude active TB and the role of TST including detailed criteria for risk assessment based on pre-test probability, risks of drug induced hepatitis and consequences of LTBI reactivating. IGRA tests may be a suitable alternative in BCG vaccinated individuals within the context of this risk assessment.

2 Diagnosis of Active TB. This test should not be used in the first instance for diagnosis of active TB. IGRA should not replace appropriate microbiological and molecular investigation. Culture remains the gold standard. The HPA advises that these tests are only considered in the primary diagnosis of active tuberculosis if diagnosis is proving difficult and treatment options hinge upon a diagnosis. IGRA have no benefits in known pulmonary TB cases with bacteriological/molecular confirmation.

Can IGRA tests be used as a first line test for occupational health reasons? Yes - new health care workers are recommended for testing for LTBI using either TST or IGRA test if they do not have symptoms suggestive of active disease and do not have evidence of prior BCG immunisation.

How useful is the gamma interferon test in diagnosing active TB?

In some patients with tuberculosis it is not possible to isolate *M. tuberculosis* from clinical specimens, or obtain clinical specimens, despite the individual having symptoms, signs and/or radiological changes consistent with the diagnosis of tuberculosis. In these circumstances, a positive IGRA may increase confidence in the diagnosis. In those with symptoms or signs compatible with, but not indicative of the diagnosis of TB, a positive IGRA test may suggest more strongly the possibility of a TB 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 tuberculosis antigens can be reduced as a result of tuberculosis activity itself or the immunocompromising condition that underlies tuberculosis reactivation. For this reason IGRA testing can produce false negative results. It can also produce a ‘false positive’ result in an individual who has latent TB infection but a non-tuberculous cause of their current illness.

Can IGRA tests distinguish between active and LTBI?

No, the tests cannot distinguish between active TB and LTBI.

Can IGRA tests be used instead of the TST for contact screening and new entrant screening?

a) Contact screening. No. The HPA advises a two step testing strategy as recommended by NICE. A TST should be undertaken, and, if this is positive, it should be followed by an IGRA test. TST can give a false positive as a result of BCG vaccination. Interpretation of the TST result depends upon the clinical circumstances, further information can be obtained from www.immunisation.nhs.uk/files/mantouxtest.pdf, accessed 01.08.07. IGRA tests have a higher specificity, especially for previously BCG vaccinated individuals, so a negative IGRA may aid in ruling out a diagnosis of LTBI.

b) New Entrant screening. No. The HPA recommends the use of IGRA tests following a positive TST for new entrant screening. New entrant screening for tuberculosis should be incorporated within larger health screening programmes for new entrants, linked to local services as recommended in the NICE guidelines.

Should the IGRA tests be used for LTBI screening before immuno-suppressive therapy such as anti-TNF-α treatment?

Individuals going to undertake immunosuppressive therapy with anti-TNF-α treatment may require assessment for LTBI after the exclusion of active TB. There is no NICE guidance relating to the use of IGRA tests for this purpose. British Thoracic Society guidelines relating to this (go to http://www.brit-thoracic.org.uk/ click on guidelines/ guidelines since 1997 / tuberculosis / anti TNF) do not specifically mention IGRA. These guidelines, however, discuss the need to exclude active TB and the role of TST including detailed criteria for risk assessment based on pre-test probability, risks of drug induced hepatitis and consequences of LTBI reactivating. The HPA recommends that IGRA tests may be a suitable alternative in BCG vaccinated individuals within the context of this risk assessment.

This view is consistent with the consensus statement from the Wolfheze Workshop in 2006 which states that IGRA tests do have value for diagnosing/excluding LTBI for individuals going to receive anti-TNF-α.
Should IGRA tests be used for diagnosing extra-pulmonary TB?

IGRA tests should currently not be used as a routine diagnostic tool for active TB. The HPA advises that these tests are only considered in the primary diagnosis of active tuberculosis when it has not been possible to confirm the diagnosis of tuberculosis 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 an IGRA test is supported. The final decision should be based upon clinical judgement. IGRA tests can not distinguish between active TB and LTBI. Further research of their role in extra-pulmonary TB is currently being undertaken.

Can the test be used when someone is already on anti-TB therapy?

No, the evidence base is still unclear regarding how gamma interferon levels are affected by treatment. Currently, it should not be used for monitoring response to treatment.

How reliable are the results of IGRA testing?

There is limited evidence available but there appears to be high reliability for producing the same results following repeated testing. Studies have examined repeated testing in the same individual during treatment for active disease. In some instances the IGRA test result has either remained constant, or increased or decreased. The reasons for this remain unclear.

How does sensitivity and specificity compare with that for Mantoux (tuberculin) skin testing?

There is no gold standard for the diagnosis of LTBI. This means that the sensitivity (proportion correctly identified with disease) and specificity (proportion correctly identified as disease free) cannot be accurately calculated. Different methodologies are being used to attempt to address this:

1. Using the results of the tests obtained with blood specimens from patients recently confirmed with active tuberculosis as the basis for identifying truly positive results. The immunology underpinning active TB may be different from LTBI so the validity of approach is undetermined at present

2. Determining true negative test 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 been tested IGRA positive and ascertaining if they subsequently develop disease, to determine positive predictive values. These sorts of longitudinal study will ultimately provide the most useful information about the validity of IGRA tests in diagnosing LTBI.

The results from a number of studies suggest that IGRA tests are more specific than TSTs. They may also be more sensitive especially in subgroups of the population such as HIV infected individuals. A number of systematic reviews have been published which support this view. The results of a meta-analysis, however, carried out in 2007 are not so clear cut. While both IGRA tests were more specific than TSTs when applied to all patients, the difference between IGRA tests and TSTs disappeared when patients known to have had BCG were excluded. Both IGRA tests appeared more sensitive than TSTs.

What is the positive predictive value of a positive IGRA test for the subsequent development of TB?

This has not been determined because of a lack of a gold standard for diagnosing LTBI. The positive predictive value of any TB test varies with the prevalence of TB in the tested population. Longitudinal studies should provide the evidence to allow the calculation of positive and negative predictive values. Studies are in progress.

Does a positive IGRA result mean that an individual with latent TB is at greater risk of developing disease in the future?

The answer is unclear currently; longitudinal studies are examining this issue.
Can the level of a positive result from an IGRA tests be used to give an indication of the likelihood of reactivation of active disease in the future?

No, but studies are examining the level of response of a positive test result and whether this correlates to reactivation in the future. This is an area of future research.

Can IGRA tests be used for infants, children and adults?

Yes. The diagnostic accuracy of IGRA tests in children is, however, thought to be less than in adults due to a relatively immature immune system. Research is being undertaken on this subject and these Q & As will be revised as further evidence for their diagnostic accuracy in children accumulates.

Can the IGRA test be used in immunocompromised individuals for example individuals with HIV or on immunosuppressive drugs?

Yes. IGRA tests may be more sensitive than TST in immunocompromised individuals. Currently, the effectiveness of IGRA tests in immunocompromised individuals is being evaluated in several studies.

Are the results affected by pregnancy?

No information is currently available on whether the results of IGRA tests are affected by pregnancy.

Which IGRA test should I use?

This depends upon:

a) Laboratory - which test your local laboratory utilises. You will need to contact them directly to determine this. This will be the primary determining factor as to which test you use.

b) Clinical circumstances. Evidence to date suggests that T-SPOT.TB may be more sensitive in children under five years of age and immunocompromised patients although there maybe little to distinguish between the tests.

c) Logistics. The QuantiFERON Gold has the advantage of being more automated and can be stored for batch testing which may be advantageous in the case of a large outbreak. The T-SPOT.TB test has to reach the laboratory within a shorter time period, 8 hours. This may prove logistically difficult if large distances are to be travelled e.g. rural areas. The similar value for QuantiFERON is 16 hours, however, it can be incubated locally and transferred to the testing laboratory increasing the maximum transfer time to 3 days.

Can the IGRA test be done in my local laboratory?

Availability of IGRA testing is likely to vary from location to location. Check with your local laboratory and/or local unit of the Health Protection Agency, to find your local unit use the following link, www.hpa.org.uk/lars_homepage.htm, accessed 02.08.07.

My local laboratory does not provide IGRA tests. Where should I get them from?

If your local laboratory does not provide an IGRA testing service then contact your local unit of the Health Protection Agency.

What are the costs of IGRA testing?

The cost will vary between laboratories, and will be affected by the number of tests being carried out and how soon the test needs to be processed. As a rough guide, based on data provided by various laboratories, the cost of QuantiFERON Gold test is £35-70 and T-SPOT TB £50-80 per test.

Who is going to pay for IGRA tests?

Can the HPA advise what needs to go into local delivery plans for requesting funding allocation for IGRA tests?

It is essential for the local unit of the HPA to engage with the Director of Public Health of the local Primary Care Trust with respect to IGRA testing. Information that could be in local delivery plans includes: indication for funding (contact tracing, outbreaks and incidents), funding of transport of samples to the laboratory and an estimation of the annual number of individuals who would be eligible for IGRA testing (based on those who had a positive TST result in the previous year following contact tracing) plus an increase of 5-10% to cover any outbreaks or incidents that may occur in the local area in the following year.

What are the disadvantages and limitations of the IGRA test?

The TST is cheaper than IGRA test. Some patients may find a blood test less acceptable than an intradermal test. NICE has recommended further research into the patient acceptability of IGRA tests. The blood must be received by the laboratory within 8 hours of being taken for the T-SPOT.TB test and 16 hours for the QuantiFERON Gold test. This may introduce logistical difficulties.

What does the test involve? Will I have to take the blood?

The test involves a single blood test. Who actually takes the blood must be determined locally. The specimen must reach the laboratory within 8 hours of being taken for processing for the T-SPOT TB test and 16 hours for the QuantiFERON Gold test and be collected into special test tubes. Transportation of samples will also have to be determined locally. For instance, a courier or a health care professional may need to take the sample to the laboratory. The individual requesting the test will need to contact the laboratory before taking the blood to ensure that the laboratory is aware that the test is being requested and that the sample can be processed. Some laboratories only run the test once per month. It is strongly advised that each local unit of the Health Protection Agency and TB Service determine how to access these tests in their local area prior to an outbreak situation occurring. For areas where a larger distance needs to be travelled to reach a laboratory, the option of utilizing the hospital’s own phlebotomy service could be explored.

How are the results interpreted?

Laboratories will help with the interpretation of results. There are two types of test. The QuantiFERON TB Gold In-Tube assay reports a value of 35 i.u. and above as a positive test. An indeterminate result may be reported if there are high levels of background gamma interferon or the mitogen control tube result is negative indicative of poorly functioning immune system. The T-SPOT.TB reports a value of six or more spots as a positive value. An ‘indeterminate’ is also possible with the T-SPOT.TB test. Further details on the interpretation are available at:

What should I do if the IGRA test result is indeterminate?

Indeterminate results may arise either because the patient’s immune system is not functioning well or due to failure to follow appropriate procedures such as delays in sending samples or over/under filling of specimen tubes. A retest is possible, however, further action need to be determined by clinical opinion. Results should be discussed with the laboratory providing the test. There is currently no information on the benefits of repeatedly testing individuals whom have had a previous negative IGRA.

What do I do if the Mantoux (TST) test is positive and the IGRA test negative or vice versa?

a) Mantoux test positive and IGRA test negative. This is likely to be the result of a falsely positive Mantoux test result, for example, due to prior BCG vaccination. This should be considered as a negative result. Any further action will depend on the clinical circumstances.

b) Mantoux test negative and IGRA test positive. IGRA testing following a negative Mantoux test is not recommended by NICE or the HPA. In circumstances where this has been carried out, discordant results do occur. They may be the result of a falsely negative Mantoux test due to immunosuppression. These should be considered as a positive result. Any further action will depend on the circumstances in which the patient is being tested.

Do IGRA tests cross-react with any other non-tuberculous mycobacteria, or any other infections leading to possible false positive results?

Positive results can occur as a result of cross-reactivity with Mycobacterium kansaii, Mycobacterium szulgai and Mycobacterium marinum. Infection or colonisation with these organisms is rare and very unlikely to be the explanation of a positive result in most patients. No other infections are known to cross-react with IGRA tests, including M. bovis BCG.

Do the IGRA tests detect infection with M. bovis?

The tests cannot distinguish between members of the M. tuberculosis complex (M. bovis, M. tuberculosis and M. africanum) and therefore, it should be positive with M. bovis infection.

If this test helps to identify LTBI and NICE guidance states such individuals should be treated, who is going to prescribe/monitor/supervise these patients?

The patient pathway needs to be determined locally. Treatment of LTBI needs to be discussed with the patients and supervised by either the local TB service or an infectious disease consultant or a respiratory physician.

When is the optimum time post-TB exposure that an IGRA test should be carried out on TB contacts?

It is recommended that for close household contacts of a sputum smear positive individual, even if their TST is negative, an IGRA test should be undertaken 6 weeks or more after exposure.

Should contacts of a TB case who are under 2 years of age automatically receive IGRA testing irrespective of BCG status?

No. NICE provide algorithms in appendix E of the guidance (http://guidance.nice.org.uk/CG33) to determine the screening pathway for children under 2 years of age.

Can a BCG vaccination be administered to appropriate contacts on the strength of a negative IGRA test or does there need to be a TST?


Are there any systems in place for monitoring IGRA test usage?

No systematic surveillance of the use or the results of these tests is currently in place.
Who is the HPA team putting together this guidance?

This Q&A pack has been devised following questions generated by front-line staff. Answers were drafted by a Specialist Registrar in Public Health and amended and agreed by the Health Protection Agency Tuberculosis Programme Board.

Where can I find out more information about IGRA tests?


3) Centre for Disease Control and Prevention, Guidelines for using the QuantiFERON TB Gold test for detecting Mycobacterium tuberculosis infection, United States. www.cdc.gov/mmwr/preview/mmwrhtml/rr5415a4.htm, accessed 03.08.07.


7) Oxford Immunotec developed the T-SPOT test, www.oxfordimmunotec.com/, accessed 04.07.07


Who do I contact for further information?

Your local unit of the Health Protection Agency will have more information on the use of these tests and will be able to advise on further sources of more specialist advice if required.

Questions about the laboratory aspects of the test, or interpreting the results, should be directed to the laboratory.