



Public Health
England

**Position statement: Direct molecular
testing for tuberculosis in England,
Scotland and Wales**
July 2013

About Public Health England

We work with national and local government, industry and the NHS to protect and improve the nation's health and support healthier choices. We address inequalities by focusing on removing barriers to good health.

We were established on 1 April 2013 to bring together public health specialists from more than 70 organisations into a single public health service.

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1. Background

- 1.1 This position statement is intended to provide information and advice for clinicians, microbiologists, public health practitioners and commissioners on the implementation of molecular testing performed directly on samples for the diagnosis of tuberculosis.
- 1.2 The statement was produced by a working party consisting of members from Public Health England, the Royal College of Pathologists, British Infection Association, British Thoracic Society, Imperial College London, Public Health Wales, Scottish Mycobacteria Reference Laboratory and University of St Andrews. In order to produce this statement, the working party considered:
- the current status of TB diagnostic laboratories in England, Scotland and Wales, as determined by national audit in 2011-2
 - a summary of the published evidence on performance of the best performing direct molecular tests
 - detailed published [1] and unpublished data from NHS trusts in England and Scotland that have started to use direct molecular tests

2. Statements

- 2.1 Molecular testing for detection of *M. tuberculosis* complex performed directly on respiratory samples is superior to smear microscopy for the diagnosis of tuberculosis.
- 2.2 Molecular testing performed directly on respiratory samples is likely to be appropriate for the assessment of infectivity, but more UK-specific data relating molecular test results to smear positivity is required before a recommendation can be made.
- 2.3 Molecular testing cannot replace mycobacterial culture and this must still be done on all samples.
- 2.4 Direct molecular testing should be accessible for the diagnosis of tuberculosis for patients in all areas of England, Scotland and Wales. The test result should ideally be available within one working day of the sample being taken and within two working days at the most.
- 2.5 No statement can be made on the use of direct molecular tests for use in children or extrapulmonary tuberculosis as the evidence is still insufficient for unequivocal advice.

3. Discussion

Performance of direct molecular tests

- 3.1 The World Health Organization has approved the use of two types of direct molecular tests globally. The first type is a line probe assay (LPA); three main tests of this kind are commercially available (INNO-LiPA Rif.TB (Innogenetics, Belgium), Genotype MTBDR/MTBDRplus and Genotype MTBDRsl (Hain Lifescience GmbH, Germany). The second is the fully automated Xpert MTB/RIF assay (Cepheid, US). All these assays are based on targeted amplification (PCR) of specific fragments of the *M. tuberculosis* genome.
- 3.2 Four reviews summarising the performance of all of these assays have been published recently [2,3,4,5]. The overall pooled sensitivity and specificity from recent studies [6-17] for TB diagnosis in sputum smear positive samples ranged from 93-98% and pooled specificities of 83-99%.
- 3.3 LPAs have been extensively evaluated. One large national study [15], which was included in the pooled analysis, examined 7836 consecutive patient samples using a LPA compared to culture and molecular identification. For all sputum specimens the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy for MTBC detection compared to culture were 93.4%, 85.6%, 92.7%, 86.9% and 90.7%; the equivalent values for smear-positive sputum specimens (n=2606) were 94.7%, 80.9%, 93.9%, 83.3% and 91.3%.
- 3.4 The most commonly used test in the UK at present is the Xpert MTB/RIF assay. This has an overall sensitivity of 90% (95%CI 89-91) and specificity of 98% (95%CI 98-99) in respiratory samples compared to culture [4]. The sensitivity is 99% (95%CI 98-99) in smear microscopy positive and 76% (95%CI 72-78) in smear microscopy negative culture positive samples.
- 3.5 On the basis of these and related results, it was agreed that a molecular test performing at equivalent or better standards would be superior to smear microscopy for the immediate diagnosis of tuberculosis.

Specific limitations of direct molecular tests

- 3.6 Two studies from Uganda and Tanzania evaluated the association between smear positivity and cycle threshold (CT) values obtained using the Xpert MTB/RIF assay [8,18]. There was a good correlation between smear grading and CT values. The consensus was that molecular testing performed directly on respiratory samples is

likely to be appropriate for the assessment of infectivity. However, data from low prevalence areas such as the UK is currently insufficient to add to this analysis.

- 3.7 The use of smear testing for the diagnosis of non-tuberculous mycobacteria (NTM) was also discussed. Some molecular tests for *M. tuberculosis* are also able to detect and differentiate NTM, however the most common currently used tests do not. Smear tests remain relevant for the diagnosis of NTM at present, but cannot distinguish NTM from *M. tuberculosis*.

Continuing requirement for culture

- 3.8 The overall sensitivity of the currently best-performing molecular test is only 90% compared to culture. Molecular drug susceptibility testing provides data on a few antibiotics only and does not provide a comprehensive assessment of resistance. Isolates are required for strain typing, which underpins control of infection in the community. Therefore culture remains an essential component of TB microbiology. It is also required for the diagnosis of NTM infection.

Accessibility of direct molecular testing

- 3.9 It was the consensus opinion of the working party that direct molecular tests should be accessible for the diagnosis of tuberculosis in all regions of England, Scotland and Wales. Incremental improvements in early diagnosis may contribute to the continued improvement of TB control in the UK, as well as to individual patient management. A number of considerations were identified to take into account when planning service provision, including: local TB incidence, drug resistance, clinical service provision arrangements, safety and quality assurance.

4. Knowledge gaps identified

- 4.1 Infectivity: There is incomplete evidence to determine how molecular test results relate to infectivity. For this reason a smear is likely to be required at present to determine public health actions, based on the traditional approach to infectivity assessment. This could be done only on molecular test positive patients, reducing the requirement for smears. The knowledge gap can be addressed in the first instance by a UK study linking smear and quantitative molecular test results. It was also noted that molecular test positive, smear negative patients have a lower, but not non-existent, risk of transmitting disease. Therefore alternative approaches to isolation and contact screening may become required as the evidence base develops.
- 4.2 Clinical impact: There is limited evidence on the impact of introducing molecular testing on clinical management or outcome of patients. The theoretical benefit of an earlier diagnosis using a more sensitive test may not translate into change in management due to other factors such as administrative delay. A prospective evaluation of molecular diagnosis is required.
- 4.3 Cost effectiveness: There is no published study capturing both laboratory and clinical costs and savings associated with the introduction of a molecular TB test. Specifically, the cost effectiveness of replacing smear testing with a molecular test should be evaluated. The working party identified occult costs and savings that may be difficult to capture, such as change in isolation requirements and use of PPE, investigations for alternative diagnoses or radiological investigations for TB which are cancelled, and change in requirements for admission or clinic appointments. Part of this assessment is being undertaken by an NIHR Health Technology Project (No 10/96/01) with an estimated publication date of 2013.
- 4.4 Available assays: The need for alternative commercial options for direct molecular diagnosis was recognised by the group.

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Conflicts of interest

No conflicts of interest were declared by the members of the working party.