



TB molecular diagnostics: a call to action

Over 60 medical professionals, researchers, healthcare scientists and patient advocates representing key stakeholders across the UK with an interest in tuberculosis (TB) came together at University College London (UCL) **to debate the current approach to diagnosing and treating TB, and how new methodology might impact on this.** The event was divided into a series of presentations and panel discussions, followed by breakout groups and patient insights.

Throughout the day, delegates debated the role of molecular diagnostics in resource rich, low TB incidence settings, with the objective of developing a consensus on how strategies for the rapid identification of active TB cases could be implemented more widely. This included discussion on the pros and cons of molecular diagnostic testing services being located within local hospitals or at regional and national reference laboratories.

The following sections detail the formal presentations and describe the wide-ranging perspectives and experiences reported by the delegates during the open discussion.

UCL-TB



TB molecular diagnostics: a call to action

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UCL Institute of Child Health
30 Guilford Street
London
WC1N 1EH
United Kingdom

SUMMARY OF THE PRESENTATIONS

Next generation TB diagnostics: test and treat

Dr Elisa Tagliani, Ospedale San Raffaele, Italy

Near-patient molecular diagnostic testing using the Cepheid GeneXpert® is at the heart of the EDETECT TB (early detection and integrated management of tuberculosis in Europe) project, which is employing a test and treat strategy to screen migrants arriving in Italy for TB. **The new Xpert® MTB/RIF Ultra test showed increased sensitivity compared to its predecessor.**

Implications of quantification of TB in molecular diagnostics

Dr Jim Huggett, LGC & University of Surrey, UK

Molecular quantification offers the potential for rapid monitoring of bacterial load and viability to monitor response to treatment. While this could help increase the pace of clinical trials, further studies are necessary to understand the sources of technical, biological and clinical noise. Metrological approaches offer a route to better understand the origin of these errors, which could improve the identification and translation of quantitative biomarkers to assist the treatment of TB.

Past lessons and implications for future testing strategies

Professor Onn Min Kon, Imperial College London, UK

An examination of the data from the London Multi-Drug Resistant (MDR) TB Cohort review (2000-2016)* indicated that, had NICE (National Institute for Health and Care Excellence) guidelines been strictly adhered to, 58 % of smear-positive MDR cases and 63 % of all cases, regardless of smear result, would have been missed as the current criteria are not sufficiently sensitive for MDR TB. **Rapid identification of active cases requires diagnostic tests with a turnaround time of less than one day.**

The solution may lie in a synergistic approach to screening, with smear-positive samples undergoing rapid molecular diagnostics confirmation testing, complemented – but not replaced – by culture and/or WGS at a reference laboratory to obtain the drug-resistance profile and further inform treatment.

**Data courtesy of Charlotte Anderson and Oliver McManus, Public Health England Health Protection Directorate: Field Epidemiology Service*

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Horizon scanning for whole genome sequencing

Dr Adam Witney, Institute for Infection and Immunity, St George's, University of London, UK

Whole genome sequencing (WGS) applications and resistance genotyping have the potential to benefit TB infection control, by enabling more informed treatment choice by direct prediction of resistance and indirect association of genotypes to patient outcomes. It will also aid surveillance, helping to identify transmissions and outbreaks, and allowing direct public health interventions. In the future, WGS could become a standard diagnostic approach, which would be further enhanced by eliminating the culture step from the TB diagnostic workflow, drastically reducing the time to results.

Past lessons and implications for future testing strategies for children

Dr Norbert Heinrich, University of Munich, Germany

The inherent disease characteristics of paediatric TB differ from those seen in adults, making detection difficult. It is also hard to obtain samples from infants, and so **new 'child-friendly' diagnostic tests need to be developed that work on samples that are easy to obtain from children**, for example, blood, urine or stool samples. To help overcome this issue, the RaPaed TB project is currently validating 10 new diagnostic assays that are independent of sputum.

Cost effectiveness – what does the future look like?

Dr Hassan Haghparast-Bidgoli, University College London, UK

In any diagnostic pathway, evidence relating to cost, cost effectiveness and affordability are essential for decision makers. **Rapid molecular diagnostic testing is a potentially cost-saving and cost-effective route to early diagnosis**, allowing patients to be isolated and treatment to be initiated promptly. This helps to prevent transmission, reduces hospital stays and clinic visits, and enables more targeted contact investigations.

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BREAKOUT GROUPS AND PATIENT PANEL DISCUSSIONS

Participants in the breakout groups discussed two key questions:

- **What are the perceived benefits of local site testing compared to centralised molecular testing for initial TB diagnosis?**
- **What are the barriers to effective implementation of local site testing?**

The outcomes of the discussions are summarised below.

The current situation

Clinicians and hospitals across the UK have adopted a variety of approaches for diagnosing and treating TB, taking advantage of rapid molecular diagnostics where available, to provide results within hours. However, many hospitals are still reliant on reference laboratories and centralised testing for initial confirmation of TB.

Current NICE guidelines suggest nucleic acid amplification tests (NAAT) if there is clinical suspicion of TB and:

- the person has HIV; or
- rapid information about mycobacterial species would alter the person's care; or
- the need for a large contact-tracing initiative is being explored.

It was widely felt that in nearly every case of suspected TB, rapid molecular diagnostics would alter the course of care, particularly for MDR TB.

Drug susceptibility testing (DST) is key to ensuring that a patient receives the appropriate treatment, and hospitals rely on reference laboratories for this service, which can prolong the time spent on standard therapy (rifampicin, isoniazid, pyrazinamide and ethambutol) due to the practical delays in logistics when the sample is sent from local to regional or reference laboratories. Given the potential toxicity of these drugs, it is important that they are prescribed with care. **It is essential to select the best drug combination backed up by high-quality information at the earliest opportunity.**

Benefits of local site testing

Speed

Short turnaround times are a clear advantage of local site testing. **Rapid molecular diagnostic platforms can provide results in under 80 minutes, including an indication of rifampicin resistance.**

In the absence of molecular diagnostics, most hospitals use smear microscopy and many delegates reported long turnaround times – from 24 hours to as much as a week – largely due to the time taken to transport samples to and from the reference laboratory. In addition, one of the complexities of centralised testing is ensuring that the infrastructure and internal hospital communication channels are in place to support as fast a diagnosis as possible; communication breakdown between departments can introduce unnecessary diagnostic delays that would be avoided with local site testing. Finally, problems arise when sputum samples sent for testing have insufficient biomass, and the bacterial load is too low to provide a conclusive result. In these instances, requests for more samples and a second round of transportation can significantly lengthen the time to result for the patient.

Targeting hard-to-reach populations

TB is over-represented in under-served and hard-to-reach populations, such as the homeless or immigrants, groups that historically can lie outside of conventional healthcare service delivery. Rapid reporting of diagnostic results is particularly important in these circumstances, as **short turnaround times increase the chance of ongoing engagement while waiting for test results**, making it much easier to ensure they receive appropriate care. Outreach programmes using a ‘find and treat’ approach, and mobile labs that visit homeless hostels or prisons, benefit significantly from near-patient diagnostics.



“Find and Treat” van from the NHS. To offer a high standard of TB care the team integrated a molecular testing platform to confirm the X-ray diagnosis, thereby enabling the care pathway at the same time.

Reduced pressure on hospitals

Rapid molecular diagnostic testing is a potentially cost-saving and cost-effective route to early diagnosis, allowing patients to be isolated and treatment to be initiated promptly when there is a positive result. Fast turnaround times lead to improved case management, enabling patients who screen negative for TB to come out of isolation sooner. This frees up beds for other patients, with an additional benefit for local infection control. Earlier initiation of treatment also reduces transmission, relieving hospitals of the burden of managing preventable cases of TB.

Placing patients at the centre of care

For many patients, waiting days or weeks for a diagnosis is a stressful experience. Patients with suspected TB may be in isolation and off work; the financial ramifications can be particularly difficult for the self-employed or people on zero-hour contracts. Combined with the standard two weeks of prescribed treatment following diagnosis, some patients are looking at up to a month off work. Many struggle with isolation during this period, avoiding potentially infecting others, and being careful around family members and children. Local site diagnostics and the rapid availability of results – within a day of collecting a sputum sample – could significantly reduce this time, benefitting the patient, their family and carers, as well as the healthcare team treating them.

Patients want a rapid diagnosis, and some delegates reported experiencing tension when patients felt let down by the speed of the system. Treatment often starts before the culture results are received which, understandably, creates some challenges; patients may refuse to take medication until they are confident they have TB. Medical practitioners may also be reticent to begin treatment, having been caught out previously when they wrongly suspected TB, which turned out to be something else.

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OVERCOMING BARRIERS TO IMPLEMENTATION OF LOCAL SITE TESTING

Centralised testing means many different things to different individuals, with some smaller hospitals having much longer transit times than those in cities. A number of barriers to the implementation of local site testing were identified:

Financial resource allocation

This remains one of the chief barriers to successful implementation of molecular diagnostics. At first glance, compared to smear microscopy, molecular diagnostics is more expensive on a per sample basis. However, **it is vital that hospitals consider the total cost of patient treatment, including isolation of MDR patients.** Budget constraints make it more important than ever that departmental managers work together to see how segregated financial resources can be combined to fund molecular diagnostics. The debate over cost effectiveness continues, and it is often assumed that moving towards centralised testing will be the most efficient use of resources. However, the downstream costs associated with late diagnosis and treatment, delayed patient discharge and the potential for transmission are not always considered.

It was suggested that some cost savings could be introduced by eliminating smear microscopy altogether and going straight to rapid molecular TB diagnostics, as is the practice in South Africa. Testing for multiple diseases on a single platform may also reduce costs and enhance cost effectiveness by streamlining workflows. Further research in a low TB prevalence setting, such as the UK, would likely be required.

Human and laboratory resources and quality control

Implementing local site testing may sometimes be less than straightforward, due to quality control requirements and, on occasion, resistance to changing protocols because of the increased workload to validate new platforms or tests. Ensuring adequate staffing over the weekend to accommodate an increase in on-site testing may also be difficult. Ultimately, **the benefits of local site testing will only be realised if there is a willingness to alter treatment pathways in light of faster diagnostics.**

One of the challenges facing TB diagnostics is working with potentially infectious samples, requiring a Category 3 laboratory for culture. Hospitals may not have adequate facilities to meet this need, sending suspected TB samples to a reference laboratory instead. However, testing using a GeneXpert platform can be performed in a Category 2 laboratory, which is a significant advantage. Anecdotally, hospitals with a research arm are some of the first to adopt local on-site molecular diagnostics, in part due to instrument manufacturers being eager to collaborate and see research undertaken on their platforms.

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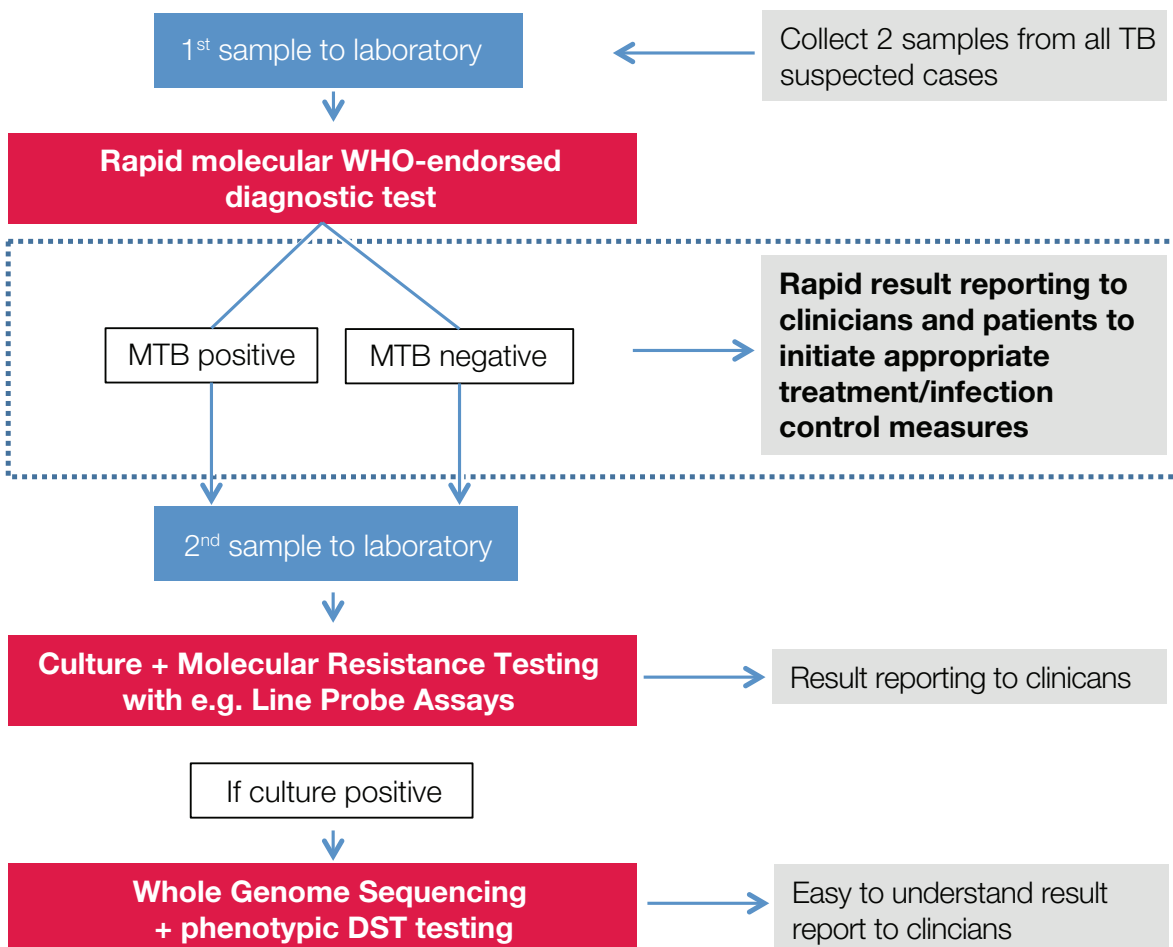
Generating awareness at all levels of care

Delegates were privileged to hear the stories of two patient advocates, Amy McConville and Steve Bradley. Neither Amy nor Steve fitted the typical TB patient profile – often thought to be one of someone who has migrated from, or spent a long time in, a high-incidence country – resulting in misdiagnoses and considerable delay before the disease was even suspected. **Limited awareness among GPs of the prevalence of TB is likely to contribute to a lack of focus on targeting the disease and improving diagnostics.** In the first instance, a delay in suspecting TB can often be a bottleneck in treating the disease. For example, a suspicious lump may require examination by both microbiology and histology to rule out TB. Without GP awareness and referral, the fastest diagnostics in the world are unlikely to make much difference.

The ideal workflow

Throughout the day, there was much discussion about the ideal protocol for diagnosing TB, given the right resources and funding. **The preference is for sputum samples to be immediately tested using more sensitive, rapid, WHO-endorsed molecular diagnostics, followed by culture confirmation and subsequent whole genome sequencing.**

WGS offers a complete resistance profile, which is essential for improving prescriptions and highlighting related strains, enabling a possible outbreak to be identified. However, there is a need for software developers to work with WGS providers to present the results in a way that is easy to understand, allowing non-specialists and frontline clinicians to respond and adapt patient treatments accordingly.



Ideal diagnostic workflow to support rapid active case finding. For all people thought to have TB, at least two samples should be collected. The first should be tested with a WHO-endorsed, rapid molecular test. The initial result from this test can be used to enable prompt clinical and infection prevention decision making while awaiting smear. If positive, the second sample should then go on to receive further resistance testing, e.g. at a genotypic or phenotypic level.

MOVING FORWARDS – A CALL TO ACTION

Bringing together healthcare professionals, researchers, scientists and patient advocates from key stakeholders across the UK highlighted the complexity of TB diagnosis. **Delegates were unanimous in calling for the adoption of rapid diagnostic tests for all people suspected to have TB.**

For many, understanding the prevalence of TB in the local population is central to developing improved diagnostic workflows and patient support. Simply raising awareness among GPs will go a long way towards decreasing the time to sample collection and, hopefully, catching TB in the early stages of disease. **Regional TB networks also have a role to play in providing a unified voice and building on NICE guidelines to develop an agreed response, including the provision of local site and/or centralised testing.**

Downstream costs associated with either late or misdiagnosis and treatment must additionally be factored into any discussion concerning adoption of local site testing.

There was consensus among the delegates that local site molecular testing in every hospital is an ideal, though possibly uneconomic, solution. If molecular testing at a local site is not possible, hospitals must review and revise existing testing protocols, making the most of the available resources, and initiating the all-important conversations that need to take place, whether that is to increase awareness of a rapid diagnosis or tackle breakdowns in communication.

“In summary, molecular diagnostics for TB have a central role at the heart of patient care and in contributing to the overall TB elimination efforts in the UK through rapid active case finding.”