

### **10.3.1 Working Group on New TB Diagnostics: summary strategic plan, 2006–2015**

The Working Group on New TB Diagnostics was established in 2001 with the aim of coordinating and facilitating the development of a toolbox of widely accessible diagnostic tests to augment control of the global TB epidemic. Over the coming decade the Working Group plans to bring through a portfolio of such diagnostic tests, with implementation level ranging from the district level laboratory to first point of care (POC).

#### **Strategic vision: 2006–2015**

More than a century after its original development, the microscopic examination of sputum is still the only widely available diagnostic tool for identifying TB in most developing countries. Unfortunately, the test has a sensitivity of only 40–60% under field conditions, falling as low as 20% in the presence of HIV coinfection. Yet even this unremarkable diagnostic test remains beyond the reach of the majority of TB patients.

In resource-limited settings drug susceptibility testing, if available, is usually performed only after treatment failure, missing an opportunity to interrupt transmission. In contrast the standard of care in industrialized nations is universal susceptibility testing.

One third of the population of the world has a latently infection with *M. tuberculosis*. Preventive therapy effectively reduces progression to active disease, but there is currently no way to predict which subjects are at greatest risk of progression, with most to gain from such therapy.

These three issues dominate the current strategic direction of the Working Group on New TB Diagnostics.

The vision of the Working Group is to develop and introduce cost-effective and appropriate new diagnostic tools that are accessible to patients and will contribute towards improved control of the global TB epidemic and improve the quality of patient care.

The ideal toolbox would contain diagnostic technologies that perform equally well in HIV-infected subjects, to

1. improve TB case detection, through high sensitivity and specificity and improved accessibility – simple, accurate, inexpensive products that produce results on the same day, and can be applied at low levels of care, are the ultimate goal;
2. rapidly and inexpensively identify drug-resistant TB, allowing timely effective treatment to reduce both individual morbidity and transmission;
3. reliably identify latent TB infection and define the risk of future progression to active disease, allowing rational use of preventive therapy in appropriate subjects.

*See Objectives on opposite page*

#### **Activities**

##### ***Discovery biology and basic technology***

The greatest impact on public health in the TB diagnostics area is expected from a highly accurate and field-usable testing device. The most prominent barrier to the development of suitable antigen or antibody assays is the lack of suitable targets. In existing serological tests, sensitivity is relatively high

only in patients with smear-positive disease, and much lower in children, patients with extrapulmonary or smear-negative disease, or HIV coinfection, thus offering little additional benefit over sputum smear. During 2005, the Working Group, in collaboration with TDR, will complete an assessment of a wide range of commercially available rapid serological tests.

In 2005–2006 FIND will select more promising antigen combinations, on the basis of available research data and expert knowledge and opinion. The Working Group plans to foster and finance additional research in this area, building on advances in mycobacterial genome sequencing and expression profiling. It is anticipated that this information will facilitate the development of subsequent generations of improved test strips suitable for use at point of care, and that during 2006–07 an improved POC test (for blood, serum, urine or saliva) will be developed.

Research on predictive markers for the conversion of latent infection into active disease is still in its infancy. The Working Group estimates that basic research at academic sites will be needed for at least three more years before product development can be initiated. The market for such products will be broad, thus a reasonable drive for resource allocation in competent research centres can be assumed, which will be monitored and supported by the Working Group.

Nucleic acid amplification tests (NAAT) show promise for rapid and reliable detection of *M. tuberculosis* in sputum and other samples. The key challenge for harnessing the benefit from these technologies in the public health sector of developing countries is discovering highly integrated, user-friendly solutions that are affordable. During 2005–06 FIND will assess the technical feasibility of several candidate system concepts with a view to selecting development partners for a highly integrated NAAT product for use at the first referral level (district laboratory) or at the peripheral level (currently microscopy centre) by 2008.

##### ***Product development***

The Working Group will support product development both directly, through product-specific development partnerships, and indirectly, through the creation of a stimulating and enabling framework.

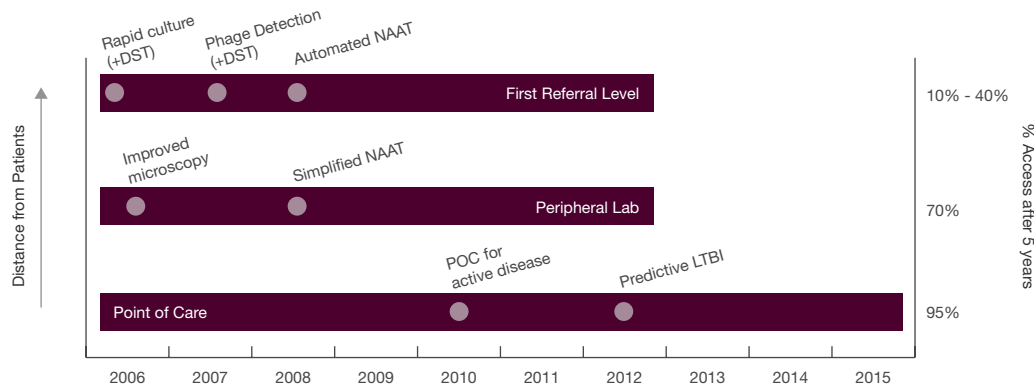
The direct measures will include financial and logistic support for a portfolio of projects that respond to the specific needs of the different levels of the public health system in high-burden countries (first referral level or district laboratory, peripheral laboratory or microscopy site, and point of care or rural health post). Different products will be needed for case detection, diagnosis of MDR-TB, and latent infection. The essential targets for product introduction at the different levels of the health system are outlined in Figure 34.

*See Figure 34: Targets for introduction of tests, leading to sustainable adoption, 2006–2015*

The indirect measures, comprising an enabling infrastructure, are: (1) the release in 2005 of the first comprehensive market report with special emphasis on the public health markets in developing countries; (2) the detailed identification and description of customer requirements – these customer requirements are specific for the different segments of the public health system and serve as a basis for more detailed product

OBJECTIVE 1: Address existing gaps in knowledge that are obstructing development of new diagnostic tools	
TARGETS	INDICATORS (APPLY TO ALL 3 TARGETS)
<ul style="list-style-type: none"> <li>• Sensitive early detection of active disease Discovery science to identify new markers (also in HIV-infected subjects) with improved discriminative power for active disease (may be antigenic, immunological, proteomic or other) Validation of candidate targets in suitable screening format (e.g. enzyme-linked immunosorbent assay (ELISA)) with patient samples from target populations Exploration and further refinement of understanding of transmission dynamics and natural history to inform mathematical modelling of potential impact of new diagnostic tools</li> <li>• Identification of latent TB infection at risk of progression Discovery science to identify new markers (also in HIV-infected subjects) with improved discriminative power for predicting future progression to active disease (may be antigenic, immunological, proteomic or other) Evaluation of predictive value, in identifying subjects at risk of progression, of next generation of existing tools for detection of latent TB infection</li> <li>• Simple, rapid identification of drug resistance Discovery science to identify novel markers of drug resistance for first- and second-line drugs in cultured isolates Discovery science to improve detection of drug resistance direct from patient samples Validation of marker candidates in suitable screening format with patient samples from target populations</li> </ul>	<ul style="list-style-type: none"> <li>• Number of studies received and financed through "requests for applications"</li> <li>• Number of agencies having announced related funding opportunities</li> <li>• Number of related peer-reviewed publications</li> <li>• Number of new promising technologies reported</li> <li>• Number of new diagnostic reagents/targets identified</li> <li>• Number of new promising technologies identified through landscape-mapping</li> <li>• Number of requests for reference material received by sample and strain banks</li> <li>• Number of publications associated with use of sample and strain banks</li> <li>• Number of target validation studies performed under the auspices of the Working Group on New TB Diagnostics</li> <li>• Number of new targets with contractually assured affordable and sustainable product access</li> </ul>
OBJECTIVE 2: Development and evaluation of a portfolio of new diagnostic tools and demonstration of impact	
TARGETS	INDICATORS (APPLY TO ALL 3 TARGETS)
<ul style="list-style-type: none"> <li>• Sensitive, early detection of active disease Conceptualization and development initiation of simple rapid-format tests for TB in sputum, serum, saliva or urine based on improved targets Introduction of at least one product for use in district laboratories by 2007 Introduction of at least one product for use in peripheral laboratories by 2008 Introduction of at least one POC product for health centres by 2010</li> <li>• Identification of latent TB infection at risk of progression Conceptualization and development initiation of test for risk of disease progression in a suitable platform based on best candidates Introduction of at least one product for point of care use by 2012</li> <li>• Simple, rapid identification of drug resistance Conceptualization and development initiation of tests for drug resistance requiring equal or less infrastructure and training than current technologies Introduction of at least one product at first referral level by 2006 and at peripheral laboratory by 2008</li> </ul> <p>For all three targets:</p> <ul style="list-style-type: none"> <li>• Inclusion of related goals in research funding calls by major funding agencies <ul style="list-style-type: none"> <li>• Public sector product development agreements with industry</li> <li>• Coordinated evaluation and demonstration projects</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Number of agencies announcing relevant funding opportunities</li> <li>• Defined customer requirements and product specifications</li> <li>• Number of product development agreements with industrial partners</li> <li>• Number of successfully completed development and technical evaluations according to product specifications</li> <li>• Number of clinical evaluation and demonstration sites developed and authorized</li> <li>• Number of evaluation projects initiated</li> <li>• Number of evaluation projects completed</li> <li>• Number of peer-reviewed publications reporting results from evaluation projects</li> <li>• Agreement on empiric design of demonstration studies with selected NTPs</li> <li>• Number of demonstration studies initiated and completed</li> <li>• Number of peer-reviewed publications reporting results from demonstration studies</li> <li>• Number of new targets with contractually assured affordable and sustainable product access</li> </ul>
OBJECTIVE 3: Implementation of new diagnostic tools and ensuring access	
TARGETS	INDICATORS
<ul style="list-style-type: none"> <li>• Definitive predictions of impact from the use of improved diagnostics on TB detection rate and transmission</li> <li>• Operational studies to demonstrate epidemiological and economic impact of new tools in high-burden settings</li> <li>• Accelerated registration of products with proven utility</li> <li>• National and international policy changes reflecting impact of new diagnostics</li> <li>• Creation of demand through communication to stakeholders (NTPs, MOH, technical and funding agencies.)</li> <li>• Ensured access to proven technologies through inclusion in GDF or other procurement mechanisms</li> </ul>	<ul style="list-style-type: none"> <li>• Completion of mathematical model defining impact and cost-effectiveness</li> <li>• Number of countries with streamlined regulatory procedures for TB diagnostics</li> <li>• Number of market analysis updates</li> <li>• Number of new diagnostic tools included in TB policy recommendations of international technical agencies</li> <li>• Number of new diagnostic tools included in national TB policy recommendations</li> <li>• Number of NTPs using new diagnostic tools at district level</li> <li>• Number of NTPs using new diagnostic tools at local level</li> <li>• Number of NTPs using new diagnostic tools at point of care</li> </ul>

**FIGURE 34:** TARGETS FOR INTRODUCTION OF TESTS, LEADING TO SUSTAINABLE ADOPTION, 2006–2015



specifications; (3) further expansion and maintenance of the sample and strain bank to support product development with selected partners and in other qualifying centres; (4) laboratory strengthening for clinical trials; (5) development of diagnostic trial design and monitoring tools; (6) generation of an inventory of clinical trial sites; (7) collation of information on regulatory and procurement policy.

#### Evaluation

All products sponsored by or developed under the auspices of the Working Group and FIND will undergo detailed technical evaluation, facilitated by the availability of well characterized clinical samples and strains from the TB sample and strain banks, and field studies performed in well established and qualified research sites in high-burden countries.

#### Demonstration

Products that successfully complete the development process and technical evaluation studies will subsequently be tested and further characterized in demonstration studies. The first such studies, which are already under way, involve a rapid culture method for case detection and detection of drug resistance that is already in widespread use in the developed world, and offers significantly higher sensitivity than smear microscopy. Optimizing the translation of these technologies into improved TB control and patient care is the focus of the demonstration projects under way in several African countries with high HIV/TB coinfection rates, and in Eastern Europe for the management of MDR-TB. Other demonstration projects will be initiated in the near future to evaluate improved microscopy.

#### Regulatory issues

In recent years the Working Group has undertaken a comprehensive survey of the regulatory situation for TB diagnostics in high-burden countries, identified local stakeholders and gained insights into likely future trends in the regulatory environment. The Working Group will contribute to the harmonization of regulatory requirements by assembling a team of representatives from all affected stakeholders (regulatory bodies, manufacturers

and public health agencies) and supporting studies that create confidence in a harmonized approach.

#### Monitoring and evaluation

Progress towards the overall goals of producing new diagnostic tools, as envisaged above, will be reviewed against the targets and timelines described at annual meetings of the Working Group. Dedicated secretariat staff will continuously monitor progress and highlight bottlenecks and problems at the annual meetings of the Working Group, or to appropriate individuals or subgroups.

#### Key risk factors

- Insufficient financial investment and delayed investment  
Adequate investment early on is required to fund discovery and early-stage technologies. Product-specific development agreements require financial commitments covering the entire planning phase of the project (until introduction) – otherwise attractive financial terms for the public health market cannot be achieved.
- Technologies fail  
Technologies can fail during the discovery phase or development phase, or during evaluation or demonstration studies, although the risk of failure decreases as projects reach later phases. To offset the risk of failure, the breadth of the development portfolio is risk-balanced comprising multiple options at each level.
- Inadequate laboratory strengthening  
Many of the new diagnostic technologies require improved laboratory capacity and development of laboratory infrastructure, which will vary according to the technology to be implemented. Collaboration with the DOTS Expansion Subgroup on Laboratory Strengthening will ensure the timely and appropriate strengthening of laboratory services to meet the requirements for implementation of new diagnostics.

- Inadequate access to new products

The introduction of improved diagnostic tools based on positive outcomes in evaluation and demonstration studies does not necessarily guarantee broad access and use. Potential constraints include high product or infrastructure costs, regulatory hurdles, lack of local or NTP "buy-in", and unreliable distribution and product support systems. The Working Group on New TB Diagnostics has developed a range of approaches to overcome these constraints, including contractually agreed affordable product pricing in development partnerships, regulatory harmonization activities, early involvement of local stakeholders in demonstration projects, and drawing on the experience of the Global Drug Facility.

- Interrupted product supply

The Working Group plans to make significant investments in discovery, product development studies and supporting activities, the return for which must be a reliable and uninterrupted supply of high-quality product. This, in turn, depends on careful selection of development partners and manufacturers. To address the risk that manufacturers and suppliers might change their business focus, sell out, default or collapse, the Working Group, through FIND, has developed an intellectual property strategy that ensures access to the know-how built into all sponsored products, through a royalty-free licence scheme that allows the transfer of the manufacturing process to more appropriate business partners if necessary.

prequalification of manufacturers, market analysis updates, regulatory harmonization, Working Group operations).

This amounts to a total budget need of US\$516 million. The estimated total financing available among all stakeholders is US\$80 million, some of which may be shared costs with industry. The funding gap is therefore estimated at US\$436 million.

*See Table 25: Research and development costs for specific technologies*

### **Modelling the predicted impact of novel diagnostics for detection of active TB**

It is expected that new diagnostics will improve TB control by improving the accuracy of detection of active TB cases in all patient groups, with tools that are widely accessible logistically, financially and technologically. A mathematical model is being developed to test this hypothesis, and to generate predictions of the potential impact on TB epidemiology. The model will be used to investigate the potential impact of a range of tools, with varying sensitivity for detection of smear-positive and smear-negative disease, and will take into account the predicted reach (or penetration) of each tool (e.g. district laboratory, local microscopy unit, POC) as well as performance compared with existing tools in both HIV-infected and uninfected subjects. The interaction between these predicted impacts and the anticipated epidemiological effects of the measures described in the strategic plans of the implementation working groups (on DOTS expansion, TB/HIV, and DOTS-Plus for Multidrug-resistant TB) will also be investigated.

### **Budget requirements for the Working Group on New TB Diagnostics: 2006–2015**

The funding required to support basic science and the development, evaluation, and demonstration of the proposed tests is US\$497 million. An additional US\$19 million is required for enabling and supporting infrastructure (reference material banks, clinical trial training, laboratory strengthening,

**TABLE 25: RESEARCH AND DEVELOPMENT COSTS FOR SPECIFIC TECHNOLOGIES FOR NEW TB DIAGNOSTICS, 2006–2015 (US\$ MILLIONS)**

	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	All years	% total
<b>Early-Stage Diagnostic Development and Research</b>	24	24	25	24	23	21	20	18	14	14	206	40%
Discovery Science (to include POC, Phage, predictive LTBi)	8.6	8.8	9.1	8.7	8.2	7.7	7.1	6.5	5.0	5.2	75	14%
Development (to include above plus simplified and automated NAAT, rapid culture and improved microscopy)	15	16	16	15	14	13	12	11	9	9	131	25%
<b>Clinical Trials</b>	35	36	37	35	33	31	29	26	20	21	303	59%
Clinical trial training and laboratory strengthening	0.4	0.4	0.4	0.4	0.4	0.3	0.3	0.3	0.2	0.2	3	0.7%
Reference material banks	0.4	0.4	0.4	0.4	0.4	0.3	0.3	0.3	0.2	0.2	3	0.7%
Pre-qualification of manufacturers	0.5	0.5	0.6	0.5	0.5	0.5	0.4	0.4	0.3	0.3	5	0.9%
Market analysis updates	0.0	0.2	0.2	0.2	0.0	0.0	0.0	0.0	0.0	0.0	1	0.1%
Evaluation projects (all tools listed above)	9.2	9.5	9.8	9.3	8.8	8.2	7.6	7.0	5.4	5.6	80	16%
Demonstration projects (all tools listed above)	24.2	24.9	25.7	24.4	23.1	21.6	20.0	18.3	14.1	14.6	211	41%
<b>Regulatory Approval and Registration</b>	0.2	0.2	0.2	0.2	0.2	0.0	0.0	0.0	0.0	0.0	1	0.2%
Regulatory harmonization	0.2	0.2	0.2	0.2	0.2	0.0	0.0	0.0	0.0	0.0	1	0.2%
<b>WG Operations</b>	0.5	0.5	0.5	0.5	0.6	0.6	0.6	0.6	0.6	0.7	6	1%
Meetings, Secretariat, Coordination	0.3	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.4	0.4	3	0.7%
Advocacy	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.3	0.3	2	0.4%
<b>TOTAL</b>	59	61	63	60	56	53	49	45	35	36	516	