Stop TB Partnership

New Diagnostics Working Group
Annual Meeting

13 November 2012
Kuala Lumpur

TB diagnostics: top 10 FAQs by test developers

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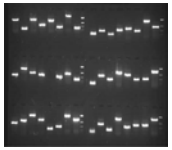
McGill

The TB dx landscape in 2012 is quite remarkable

Tuberculin		→		IGRAs
Conventional microscopy		→		LED/FM microscopy
Solid cultures		→		Liquid cultures
Conventional, phenotypic DST		→		Molecular DST (LPA)
Conventional PCR		→		Cartridge-based NAATs

But

- We still have big unmet diagnostic needs
- We need better and more affordable tools
- We need competition to increase affordability and diversity of options

Thankfully

- Fast-follower NAATs are rapidly emerging
- Big investments made in biomarkers for POC solutions
- Unprecedented industry interest
  - Revival of interest among established players
  - New players, including those from emerging economies
- We must encourage and support these product developers


HOLOGIC
GEN-PROBE
Roche
Akonni
Biosystems
BD
epistem
Genedrive
speed to result
Abbott
Diagnostics
Thermo
SCIENTIFIC
Alere
NANOLOGIX
Cepheid
Seegene
Fio Corporation
HAIN
LIFESCIENCE
KGI
molbio
ReaMetrix
Beta
Accelerating Innovation
CapitalBio
Corporation
GBD
Global BioDiagnostics
biohelix
QUIDEL
CORPORATION
MEDEX
Loncin S.A.
MENSSANA
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VISUAL SCIENCES
Oxford
Immunotec
BIOMÉRIEUX
Ocimum
Biosolutions
WAVE 80
Luminex
TwistDx
QIAGEN
veredus
laboratories
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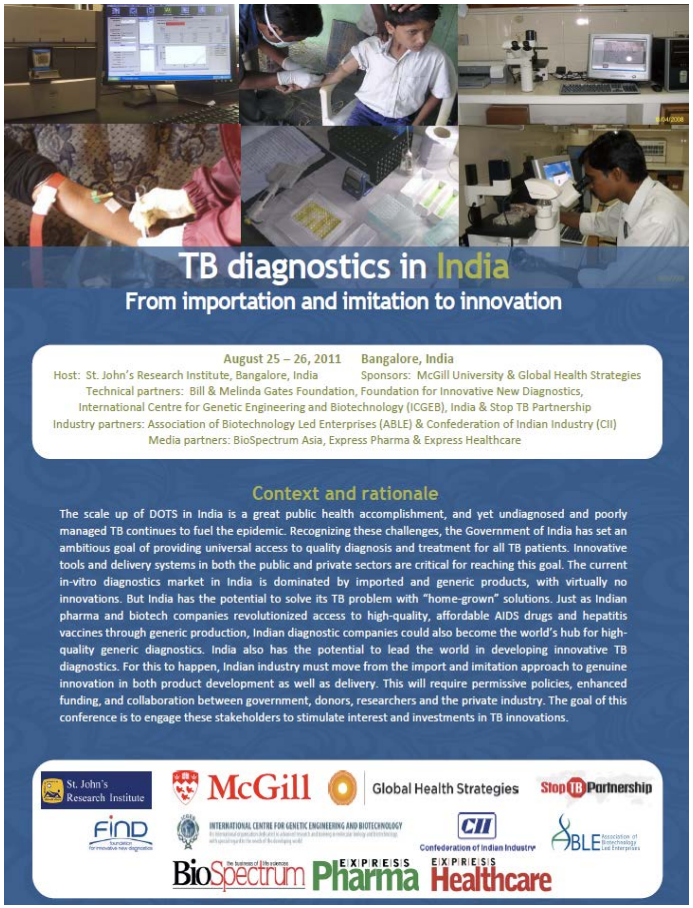
FOUNDATION FOR HEALTH
GenturaDx
FLUORESENTRIC
Nanosphere
BIOFIRE
ANTIGEN
DISCOVERY INC
CHEMBIO
DIAGNOSTIC SYSTEMS, INC.
microsens
med:tech
DNA genoTEK
enigmadiagnostics
m·bio
DIAGNOSTICS
HARDY
DIAGNOSTICS
SEQUELLA
SomaLogic

Engaging industries and donors in emerging economies



Bangalore 2011

http://gongyi.qq.com/zt2012/Diagnostics/

Shanghai 2012

http://tbevidence.org/2011/11/bangalore/

Test developers are asking important questions

- Based on input from over 25 companies and test developers (including academics), here are the top 10 FAQs
  - Follows a natural order: Current landscape, market, unmet needs, TPPs, product development, evaluation, regulation, policy and scale-up

I am very grateful to these individuals and companies for their candid and detailed responses!

#1. TB BURDEN AND Rx LANDSCAPE

What is the global burden of TB (including latent TB, TB/HIV and MDR/XDR-TB) and what is the current and future TB treatment landscape?

- What is the current burden and predictions for future, disease distribution (highest burden countries), current and future patient demographics, and trends over the next 5-10 years?
- What is the treatment landscape today and in 5-10 years? What is the level of access to current TB treatment?
- What TB drugs are currently important for drug susceptibility testing (DST), and which drugs will need to be considered for DST in the near future?

#2. CURRENT LANDSCAPE AND PIPELINE

What is the current testing landscape for TB (including latent TB and DST), and what diagnostics are in the pipeline? What is the level of access to current TB diagnostics?

- What TB diagnostic tests are currently on the market, and what products are likely to enter the market in the near future?
- Which tests are currently included in policy recommendations and widely used? What are the currently used diagnostic algorithms? Who develops them and what is the process for changing the algorithm?
- What is the current level of access to available TB diagnostics in high burden countries?

#3. MARKET SIZE, POTENTIAL, DYNAMICS

What is the market size and potential for new TB diagnostics, and what are the market dynamics around TB diagnostics?

- What is the current market size for TB diagnostics? What is the market potential for new tests? What is the expected market growth rate?
- How is the market segmented by low, middle vs. high income countries? By where the test might be utilized (i.e. reference lab, microscopy center, etc.)?
- How is the market served currently? What are the key market barriers for uptake? What will drive uptake?
- Will most high burden countries scale-up Xpert MTB/RIF? What needs does it meet? How much of the market will it address? What problems remain?
- Are market access barriers lower for 2nd or 3rd, rather than the 1st product in its class?
- What is the risk for new products that have to compete against entrenched competitors?

#4. TARGET PRODUCT PROFILES

What are the unmet diagnostic needs and target product profiles (TPPs) of greatest relevance?

- Which attributes within the TPP are the most important to focus on? What are the top 4-5 features that are needed in a TB diagnostic test for developing countries?
  - At what price/cost can a new TB diagnostics be sold? What is the current and projected pricing environment over the next 5-10 years? Is the $9.98 price the new benchmark?
  - What are the differences in the market opportunities for a screening test and separately for a DST? How is the price/cost affected if the new test is a screening (broadly used) test versus an “add-on” or reflex test?
  - How critical is it to include DST in the test? Which drugs are critical for DST now, and in the future? Is it advantageous to have a platform that can detect a large number of mutations? What is the cost-benefit ratio of having these additional elements in the test?

#4. TPP attributes

- Target cost
- Sensitivity/specificity (which is more important and minimum acceptable levels)
- Point-of-care versus centralized lab testing
- Manual versus automated
- TB only test versus multiplexed platform (e.g. + HIV, CT/NG)
- Integrated or reflex DST
- Rule-in or rule-out test?
- Infrastructure requirements (e.g. power, temperature control)
- Time to result (how important is same-day results?)
- Throughput
- Sputum versus other samples
- Requirements for reporting and connectivity
- Drugs to include in DST
- Importance of subgroups such as HIV-infected and children
- Shelf-life requirements, etc.

#5. PRODUCT DEVELOPMENT SUPPORT

Where and how can test developers get funding, technical assistance and secure necessary specimens/strains for test development?

- How do companies get funding for TB dx development?
- Which are the key funding/donor agencies (e.g. NIH, BMGF, USAID, DFID, Wellcome) and what are their funding priorities in product development?
- If donors support product development, what are their expectations in terms of pricing, global access, IP, etc.?
- Which are the PDPs (e.g. FIND, PATH, IDRI) that can provide support with TB dx development and what are their criteria/conditions for providing support?
- Where can test developers get well-characterized specimens (including non-infectious artificial sputum), strains, sequences for DR mutations and BSL3 facilities?

#6. PRODUCT VALIDATION SUPPORT

What kind of validation is required for a new TB diagnostic in order to enter the market and where can companies get support for such validation?

- How many validation studies will be required? Are test accuracy studies adequate, or clinical impact studies required? How much geographical diversity is needed for the clinical trials?
- What validation studies were required for, and conducted by Cepheid to bring their TB test to market? How much did it cost and who paid for it?
- Who can provide clinical trials and validation support to companies?
- What will it cost to conduct clinical validation studies? Will donors pay for product validation?
- Which academic institutions are capable of test validation and field trials?
- Which are the PDPs (e.g. FIND, PATH, IDRI) or agencies (e.g. CDRC, CHAI) that can provide support with validation and what are their criteria/conditions for providing support?

#7. REGULATION

What are the regulatory requirements for TB diagnostics, both in-country and globally?

- What is required for the registration of new diagnostics in the major, high TB burden countries?
- Will multiple regulatory approvals be necessary? What will it cost? Is there a pathway to get simultaneous approvals?
- How critical is FDA approval for global markets and what will it take to get FDA approval?
- What are the advantages and disadvantages of getting CE mark versus WHO PQ versus FDA approval and which of these is needed for major markets?
- How strong is the IP in the TB diagnostics area?

#8. POLICY

Are global policy endorsements required? If so, what kind of evidence is necessary for global policy endorsements and scale-up?

- What global policy endorsements or approvals are critical for success (e.g. WHO, CDC, FDA, others)?
- Is WHO endorsement/policy the most important factor for accessing global markets? What is the timeline and cost for WHO process? How does WHO decide on which technologies to consider for policy review?
- Is there a WHO PQ process for TB diagnostics, and if so, how long will it take? What is the difference between WHO policy and WHO PQ for TB?
- What kind of evidence is required at the country level to get policy endorsements and registration? Is WHO endorsement or prequalification alone sufficient? Are country evaluations still required?

#9. PROCUREMENT AND MARKET ACCESS

How do countries procure TB diagnostics? How autonomous is their decision making? How much is it influenced/guided by WHO and/or donors?

- Who are the major buyers in developing countries (e.g. Ministries of Health (MoH), National TB Programs (NTPs), international donors)?
- What are the most important MOH concerns, and how does the MOH procure, direct procurement, and make decisions on vendors?
- What are the market access challenges and options for addressing them? Is procurement linked to regulatory approval? Will each country require an independent study of a TB diagnostic?
- What are the logistics and distribution challenges? Different for public vs. private sector, or is there a single centralized process in countries?
- What will be required by developers/suppliers to provide sales and after-sales support, as well as service and maintenance?

#10. SCALE-UP

Once a product has been validated, registered and put on the market, and once policy endorsements are obtained, what are the challenges for uptake and scale-up in high burden countries?

- Which validated tests have been successfully scaled-up, what were reasons for the success, and how long did it take to reach scale?
- How do country level policy makers make decisions on tests to scale-up?
- If some tests have not been scaled-up even after policy endorsements, why? What are the biggest barriers and how can they be overcome?
- When and how do donors fund/subsidize and support roll-out of TB diagnostics?
  - Who are the major players in funding scale-up (e.g. UNITAID/ GFATM/BMGF/ PEPFAR/USAID), and their historical role and funding mandate/priorities?
  - Since donors are already supporting the roll-out of GeneXpert, will they consider other technologies for buy-down and/or scale-up?
  - Is WHO endorsement mandatory for donor support for scale-up?
  - What are the long-term prospects after donor funding ends?
  - Are there markets that are not dependent on donor funding?

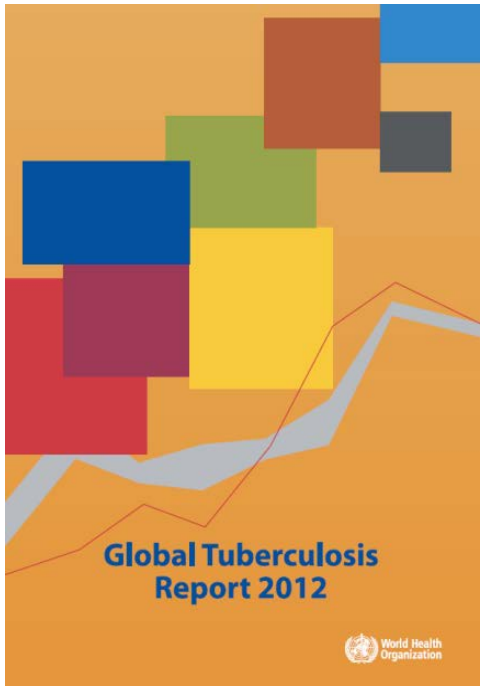
Answering these FAQs will make a big difference to test developers

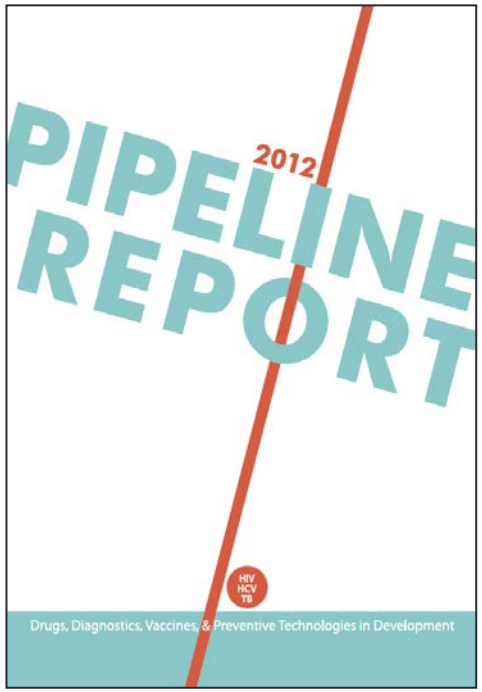
- “If we can help get this info out, more people will consider developing TB products…”
- “these questions are very good and we have had to learn the answers the hard way!”
- “great idea to put them together… when we first started with TB, we had no idea about any of this. I think it will be a tremendous help especially for the smaller companies out there who are perhaps new to the entire diagnostics…”
- “top ten FAQ is a fantastic idea! we spent much of our time trying to understand these particularly nuanced areas in shaping our business case.”
- “If we had the answers to those questions, it would have saved us lots of time…”
- “having had access to such information would have had a very positive impact on our development and it would have helped us to correctly set our internal expectations.”

Why haven’t we addressed these FAQs already??

- Well, we have answered them, in bits and pieces
  - May not be perfect or nuanced
  - May not answer all questions
  - May need to be updated/revised in light of rapidly changing landscape
- For some questions, I am not sure we know the answers!

Global TB burden and Dx landscape



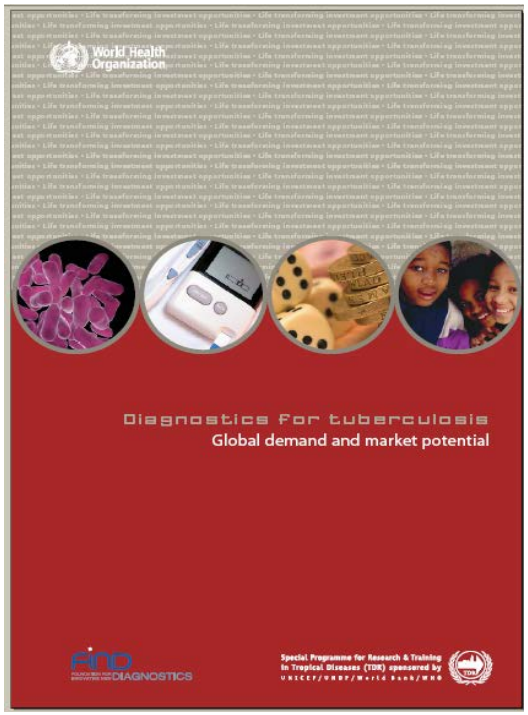


http://www.who.int/tb/publications/global_report/en/index.html

http://www.unitaid.eu/resources-2/news/974-tuberculosis-diagnostic-landscape

http://www.pipelinereport.org/toc/tb-diagnostics

Market size, potential and dynamics



FIND/TDR 2006

http://www.finddiagnostics.org/export/sites/default/resource-centre/find_documentation/pdfs/tbdi_full.pdf

http://tbevidence.org/resource-center/market-analyses/

TPPs – some exist, but which will be most impactful?

Work in progress
Supported by BMGF

APPENDICES

Table 3: Minimum specifications for a POC TB diagnostic test

Test specification	Minimum required value
Medical decision	Treatment initiation
Sensitivity - Adults *[for pulmonary TB only, regardless of HIV status]*	Pulmonary TB: - 95% for smear positive, culture positive - 60%-80% for smear negative, culture positive *[Detection of extrapulmonary TB being a preferred but not minimal requirement]*
Sensitivity - Children *[including extrapulmonary TB regardless of HIV status]*	- 80% compared to culture of any specimen and - 60% of probable TB (noting problem of lack of a gold standard)
Specificity - adults	- 95% compared to culture
Specificity - children	- 90% for culture-negative probable TB (noting problem of lack of a gold standard) - 95% compared to culture
Time to results	3 hours max. (patient must receive results the same day) [Desirable would be <15min]
Throughput	20 tests/day minimum, by 1 laboratory technician
Specimen type	Adults: urine, oral, breath, venous blood, sputum *[Desired: NON sputum-based sample type and use of finger prick instead of venous blood]* Children: urine, oral, capillary blood (finger/heel prick)
Sample preparation	- 3 steps maximum - Safe: biosafety level 1 - Ability to use approximate volumes (i.e., no need for precise pipetting) - Preparation that is not highly time sensitive
Number of samples	One sample per test
Readout	- Easy-to-read, unambiguous, simple "yes", "no", or "invalid" answer - Readable for at least 1 hour
Waste disposal	- Simple burning or sharps disposal; no glass component - Environmentally acceptable disposal
Controls	- Positive control included in test kit - Quality control simpler and easier than with sputum smear microscopy
Reagents	- All reagents in self-contained kit - Kit contains sample collection device and water (if needed)
Storage/stability required	- Shelf life of 24 months, including reagents - Stable at 30°C, and at higher temperatures for shorter time periods - Stable in high-humidity environments
Instrumentation	- If instrument needed, no maintenance required - Instrument works in tropical conditions - Acceptable replacement cost - Fits in backpack - Shock resistant
Power requirement	Can work on battery
Training	- 1 day maximum training time - Can be performed by any health worker
Cost	<US$10 per test after scale-up

POC
test (MSF/TAG/STP)*

TPP for a simple, affordable triage test for TB

Characteristic	Optimal (ideal)	Minimal
INTENDED USE		
Goal of Test	Easy to use test that captures all patients with active TB (at the expense of false positives) and can be used to identify and refer those who require further, confirmatory testing	Easy to use test that requires minimal technology and captures most patients with active pulmonary TB, and can be used to identify and refer those who require further, confirmatory testing
Drug resistance screening	None	None
Target use setting	In the community by minimally trained community health workers and untrained providers	Health post and primary care clinics
Target population	Individuals suspected to have active TB	Individuals suspected to have active, pulmonary TB
Sample type	Non-sputum samples (e.g., urine, oral mucosal transudates, saliva, blood (finger-stick))	Sputum, non-sputum sample type preferred (e.g., urine, oral mucosal transudates, saliva, blood (finger-stick))
Reference Test	Liquid culture	Liquid culture
TARGET PRICE		
Target price of consumables or test-strip (all) FOB	< 1 USD	< 4 USD
Target price of instrumentation	No instrument	< 1,000 USD
EXPECTED PERFORMANCE		
Diagnostic sensitivity	>98% for all patients	> 98% of smear-positive and >80% smear-negative patients
Diagnostic specificity	> 70%	>60%
Inter-rater agreement	>99%	>95%
Analytic sensitivity	< 10^2 cfu/ml	< 10^2 cfu/ml
Quantitation	Qualitative	Qualitative
Time-to-result	< 15min	<45 min
Maximum number of samples that can be processed per day	> 48, asynchronously	>20 tests per 8-hour day, asynchronously

POC triage test

TPP for a simple, affordable molecular TB test for use in microscopy centers and peripheral laboratories

Characteristic	Optimal (ideal)	Minimal
INTENDED USE		
Goal of Test	Diagnosis of active pulmonary TB for the purpose of treatment initiation; diagnosis of MDR TB by diagnosis of drug resistance to rifampin, isoniazid and fluoroquinolone	Diagnosis of active pulmonary TB for the purpose of treatment initiation
Drug resistance screening	Detection of rifampin, isoniazid, and fluoroquinolone resistance testing via a separate cartridge with additional consumable cost (Reflex Testing)	Rifampin drug resistance testing via a separate cartridge with additional consumable cost (Reflex Testing)
Target use setting	Health center with a peripheral laboratory (microscopy center), and where TB treatment is available	Health center with a peripheral laboratory (microscopy center), and where TB treatment is available
Target population	Individuals suspected to have active, pulmonary TB	Individuals suspected to have active, pulmonary TB
Sample type	Sputum	Sputum
Reference Test	Liquid culture	Liquid culture
TARGET PRICE		
Target price of consumables or cartridge (all) FOB	< 4 USD	< 8 USD
Target price of instrumentation	< 5,000 USD	< 10,000 USD
Time to Market	≤ 24 Months	≤ 36 Months
EXPECTED PERFORMANCE		
Diagnostic sensitivity	> 98% smear-positive and 80% smear-negative patients	95% of smear-positive and 65% smear-negative patients
Diagnostic specificity	> 99 %	>97%
Analytic sensitivity	< 10^3 cfu/ml	< 10^3 cfu/ml
Analytic specificity	No cross reactivity with other organisms including non-tuberculous mycobacteria(NTM)	No cross reactivity with other organisms including non-tuberculous mycobacteria(NTM)

Simple and affordable
molecular dx

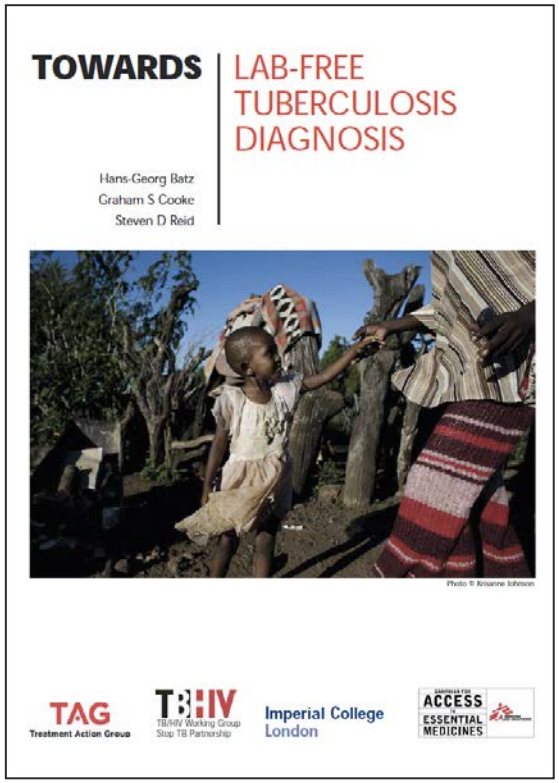
Product characteristics for high-throughput molecular TB testing

Characteristic	Optimal	Minimal
Sample type	Sputum; gastric lavage, CSF, pleural fluid, tissues	Sputum or digested decontaminated sputum
Sample Handling	Sputum – received 1-7 days of transport	Sputum - received <24 hours of transport
Throughput	>1000 Samples per 12 hour shift, asynchronously	>380 Samples per 12 hour shift, asynchronously or near equivalent
Multi-use platform	Yes	Yes
Analytic sensitivity	$\leq 10^3$ cfu/ml	$\leq 10^3$ cfu/ml
Analytic specificity	No cross reactivity with other organisms including NTMs	No cross reactivity with other organisms including NTMs
Diagnostic sensitivity	> 98% smear-positive and 70% smear-negative patients	95% of smear-positive and 60% smear-negative patients
Diagnostic specificity	> 99%	>97%
Total number of manual steps	≤2, fully automated	<10 steps
Time-to-result	≤1 shift	≤2 days
Cost of instrumentation	<100,000 USD	<500,000 USD
Cost of consumables (all) FOB	<5 USD	<15 USD
Reagent Kit stability	24m at 40°C, 70% humidity, incl. transport stress (48h at 50°C)	12m at 30°C, 70% humidity, incl. transport stress (48h at 50°C)
Operating temperature	≤45°C	≤35°C
Additional equipment required	None	Heat block, centrifuge, sample processing equipment
Biosafety	Equivalent to microscopy	BSL3 lab
Room separation	All activities in one room	Reagent prep, processing and amplification separate
Controls	Internal full-process positive control and negative controls	External controls
Drug resistance screening	Detects resistance to Rif, INH, FQ and PZA	Reflex to drug resistance on same platform with at least RIF
Electronics and software	Integrated	Separate computer required
Instrumentation	Single device	Sample prep + amp/detection
Walkaway operation and random access and STAT sampling	Yes	No
Quantitation	Semi-quantitative	Qualitative
Reagent integration	No need to pipet reagents	Pipetting sample and a buffer.
Result capturing & documentation	Printed and electronic wireless transmission capable	Electronic
Training & education needs	< 1 day, microscopy technician	<1 week, PCR technician

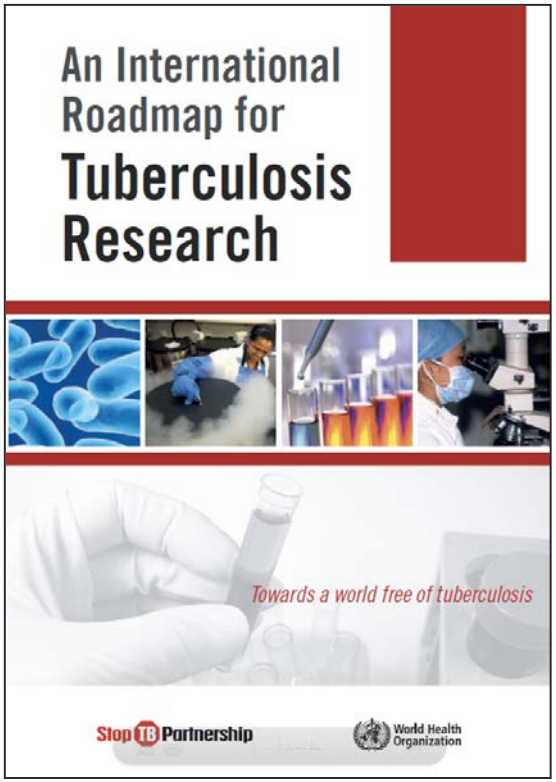
High throughput molecular dx
for centralized labs

http://tbevidence.org/resource-center/target-product-profiles/

Unmet needs and research priorities

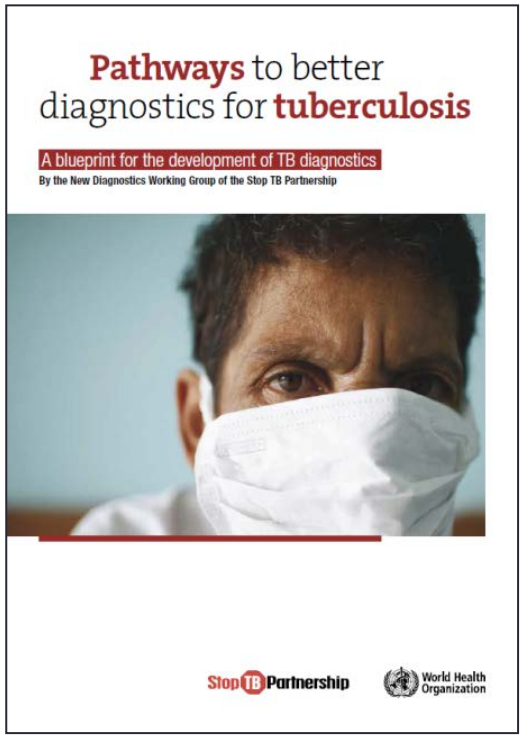


http://www.treatmentactiongroup.org/tb/publications/2011/tbpocdia



http://www.stoptb.org/global/research/

Value chain and evidence required



NDWG 2010

http://www.stoptb.org/wg/new_diagnostics/

Which New Diagnostics for Tuberculosis, and When?

Frank Cobelens,[1] Susan van den Hof,[1,2] Madhukar Pai,[3] S. Bertel Squire,[4] Andrew Ramsay,[5] and Michael E. Kimerling[6] on behalf of the Evidence for Scale-up Group

[1]Department of Global Health, Academic Medical Center; and Amsterdam Institute of Global Health and Development, Amsterdam, and [2]KNCV Tuberculosis Foundation, The Hague, Netherlands; [3]Department of Epidemiology and Biostatistics, McGill University, Montreal, Canada; [4]Clinical Research Group, Liverpool School of Tropical Medicine, United Kingdom; [5]United Nations Children's Fund/United Nations Development Programme/World Bank/World Health Organization (WHO) Special Programme for Research and Training in Tropical Diseases, WHO, Geneva, Switzerland; and [6]Bill and Melinda Gates Foundation, Seattle, Washington

J Infect Dis 2012

IVD regulation and harmonization

GHTF
1992 - 2012

Global Harmonization Task Force
Working Towards Harmonization in Medical Device Regulation

http://www.ghtf.org/

http://www.who.int/phi/publications/Increasing_Access_to_Diagnostics_Through_Technology_Transfer.pdf

http://www.nbr.org/downloads/pdfs/CHA/PHS_2012_Technology_Regulation.pdf

Post-policy scale-up challenges

Making innovations accessible to the poor through implementation research

S. B. Squire,* A. R. C. Ramsay,† S. van den Hof,‡§ K. A. Millington,* I. Langley,* G. Bello,¶ A. Kritski,# A. Detjen,** R. Thomson,* F. Cobelens,§ G. H. Mann*

IJTLD 2011

New tuberculosis technologies: challenges for retooling and scale-up

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IJTLD 2012

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PLOS | MEDICINE

Policy Forum

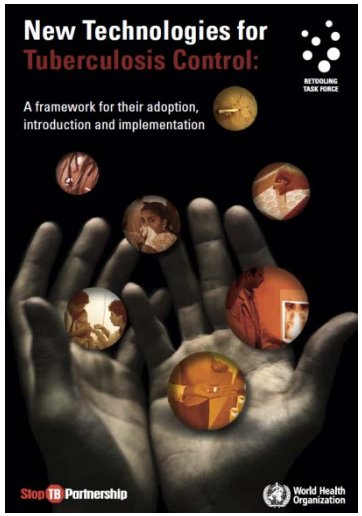
Point-of-Care Testing for Infectious Diseases: Diversity, Complexity, and Barriers in Low- And Middle-Income Countries

Nitika Pant Pai[1], Caroline Vadnais[2], Claudia Denkinger[2,3], Nora Engel[4], Madhukar Pai[2,5]*

Stop TB Partnership

INTRODUCING NEW APPROACHES AND TOOLS FOR ENHANCED TB CONTROL (INAT) SUBGROUP

http://www.stoptb.org/wg/dots_expansion/inat.asp



What we need

- More cohesive, credible, up-to-date answers to these FAQs, in the post-GeneXpert phase
  - Answers must include input from all key stakeholders
  - Work by diverse groups need to be integrated
- Compiled in one place for any test developer to freely access
- More importantly, we need a ‘honest broker’ agency/team to:
  - help answer more nuanced questions
  - technical assistance with product development and validation
  - make the connections that test developers want

Thank you!

- To the NDWG for this opportunity
- To all companies, test developers and colleagues who provided input
- Additional comments are welcome!

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Disclosure

- No financial/industry conflicts
- I have co-chaired the NDWG in the past
- I currently serve as a consultant to the Bill & Melinda Gates Foundation (but my talk reflects my personal views)
- I receive grant support from the Bill & Melinda Gates Foundation, CIHR & Grand Challenges Canada