The landscape of TB diagnostics in India and barriers to innovation

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TB control in India

• Scale up of DOTS in India is one of the greatest public health accomplishments in our generation
• Yet undiagnosed and poorly managed TB continues to fuel the epidemic such that India continues to have the highest number of TB cases.
• Recognizing these challenges, the GoI has set an ambitious goal of providing universal access to quality diagnosis and treatment for all TB patients in the country.
• Innovative technology and innovative delivery systems that engage both public and private sectors are essential for reaching this goal.
  – Improved TB diagnosis and new technologies are therefore critical

India

• Strong and growing economy
• Globally competitive
• Increasing purchasing power
• Megamarket for almost every product or service
• Ability to dramatically reduce cost structure increase access (e.g. generic drugs and low-cost vaccines)
• Strong science and R&D skill base for innovations (e.g. innovations in IT, biotech, telecom)
• Huge economies of scale in R&D and manufacturing
• Strong and thriving private sector
• Potential for public-private partnerships
• International donor support (BMGF, GFATM, UNITAID, USAID, DFID, Wellcome Trust, etc.)
• There are several successful examples and precedents

Success story with drugs: ART

Rapid action in India for low cost flu vaccines, drugs and diagnostics

China, Brazil, and India: Crashing the gates of the top ten IVD markets

A look at the recent past, the present, and the near-term future of these emerging markets.
Indian IVD market

- Exact size is unknown (estimates vary a lot)
- But everyone agrees that it is a growing market (~20% annual)
- Everyone agrees that market is highly fragmented/segmented
  - Diagnostic companies: MNCs, Indian manufacturers, distributors (traders), intermediaries
  - Public vs. private
  - Urban vs. rural
  - Types of tests: Biochemistry, hematology, pathology, microbiology, etc.
  - Labs: large, medium, small
- Cost-conscious and highly competitive

Indian TB diagnostics market

- About 2 million active TB cases are reported each year
- Conservatively, about 10 million TB suspects need testing for TB every year; ~1 million need MDR screening
- In addition, testing for latent TB (e.g. TST, QFT), and extra-pulmonary TB will increase numbers that would need TB testing
- Exactly $5 value of expenditure on TB diagnostics not known
- Indian-made tests have a large potential export market
- About 60 – 70% of testing is likely to happen in the private sector
- TB tests on the Indian market:
  - Liver microscopy (mostly direct FL, undertaken in private sector)
  - Chest X-rays (looking for active TB)
  - Sputum culture (mostly in medical labs and medical schools)
  - Liquid culture (e.g. BACTEC, MGIT,ifle, etc.) (offered in select lab networks)
  - Molecular NADs for active TB (mostly in fever clinics/bloodhore on IHC, mostly private sector)
  - New diagnostics (previously introduced in MYS: also entering private lab market)
  - TST (used mostly in children)
  - QFT/GAM (used in India being used for active TB)
  - Serological antibody-based tests (very widely used in private sector)

Important points to note early

- No new drugs from India
- Probably no new vaccines
- Very few new diagnostics (see later)

- India is strong in generics, but weak in R&D

Indian IVD market

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Indian diagnostics market is miniscule in comparison to pharma

Pharma is ~10 billion $

Diagnostics <5% of pharma size

Pharmas not interested in diagnostics

Those who tried, mostly gave up

Biotechs are mostly into drugs, biologics and vaccines

But things are changing...

"Moving beyond less sophisticated, outsourced services like telephone call centers, India has been advancing up the business value chain, particularly in low and medium diagnostics. Now it is showing a flair for manufacturing, particularly in goods demanding high skill production and superior prices..."
Quality remains a big concern

Indian IVD companies

- ~50 or so, but not including small distributors
- Only a handful of these are manufacturers
- All major MNCs have India offices:
  - Roche, Abbott, Bio-Rad, bioMerieux, Inverness, BD, Beckman Coulter, Siemens,
  - ThermoFisher/Qualigens, Quidgen
- Mostly act as distributors (very little local manufacturing; hardly any local R&D)
- Major Indian manufacturers (strong in generic rapid tests and ELISA):
  - Tulip Group, Goa
  - Span Diagnostics, Surat
  - J Mitra, Delhi
  - Transasia, Mumbai
  - Himedia Labs, Mumbai
- Smaller/boutique/start-up companies:
  - ReaMetrix, Xcyton, bigtec labs, etc.
  - Some of these are trying innovations and are keen on R&D

Labs in India

- Widely varying numbers (20,000 – 60,000!)
  - Depends on how one defines a “lab”
  - Very few large labs
  - Most labs in cities/towns
- Only 100+ have some sort of accreditation/certification (ISO, NABL, CAP)
  - Anyone can start a lab in India
  - Hardly any data on quality of lab services
  - Several anecdotes suggest poor quality assurance
  - Hardly any attempt at EQA
  - Certification based on documentation and processes, not on validity/reliability of tests offered

- Key question: if quality cannot be assured, how will it impact scale-up of new TB technologies??

REGULATORY ENVIRONMENT

Accredited / certified labs in India

<table>
<thead>
<tr>
<th>Accreditation</th>
<th>Number</th>
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<tbody>
<tr>
<td>NABL</td>
<td>~500</td>
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<tr>
<td>ISO</td>
<td>~400</td>
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<tr>
<td>NABH</td>
<td>~300</td>
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<tr>
<td>CAP</td>
<td>&lt; 100</td>
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Total no. of labs – estimated ~60,000

John Kenneth, SIRI
Regulatory environment

- Fuzzy and not transparent for diagnostics
- Diagnostics are hardly mentioned in the Indian Drugs & Cosmetics Act
- No clear documentation of what exactly is needed by DCGI
  - Sometimes, DCGI regulates diagnostics like they regulate drugs
- Importing is usually straightforward
  - No clarity on acceptable test performance
- Manufacturing is a state-level issue (takes longer and requires site inspection)
- No system for withdrawing bad tests
- TB is classified as a "non-critical" test and therefore poorly regulated
  - No attempt to revisit the critical/non-critical list (which was put together when HIV emerged, e.g. blood bank screening)

- Key question: how can regulation of TB diagnostics be improved??

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SUBOPTIMAL DIAGNOSTICS

TB serology in India

- TB serology (mostly ELISA) is very widely used in the private sector
- Market for serology exceeds microbiological methods in almost all the labs
- Irrational testing practices are widespread
- All major service labs offer serology
  - Most widely used test is ANDA (France)
  - Brings in big revenue
  - >1.5 million tests done every year
  - >$15 million may be spent on serologies in India every year

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Serological Testing for Active Tuberculosis in India is More Costly and Less Effective than Sputum Smear Microscopy

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Dowdely D et al. Under review...
Hypothetical “Study Population”

- 1.5 million TB suspects
  - Conservative estimate of annual volume of serologic tests in India (sensitivity analysis on 3 mil)
- 1 in 7 actually have TB
  - Estimate from FIND, comparable to other studies
- Among TB patients, 53% are “highly infectious”
  - Would be diagnosed with 2 sputum smears in an ideal lab
- 5% HIV prevalence
- ANDA (from updated meta-analysis [Steingart K et al. PLoS Med 2007]):
  - Sensitivity = 76% highly infectious
  - Sensitivity = 59% less infectious
  - Specificity = 87%
  - Loss to Follow-Up = 15%
  - Cost = $20

Summary of findings

- If used instead of sputum microscopy, serology would result in an estimated 14,000 more TB diagnoses and 121,000 false-positive diagnoses.
- However, by detecting more-infectious cases, smear would avert an estimated 102,000 more DALYs and 32,000 more secondary cases than serology, at approximately one-fourth the incremental cost ($11.9 million vs. $47.5 million).
- Addition of culture to sputum smear would avert 130,000 incremental DALYs at a cost of $255 per DALY averted.
- Relative to smear plus culture, molecular testing would avert 37,000 additional DALYs at $209 per DALY averted.
- Serology was more costly and less effective than smear microscopy in all sensitivity analyses.

2010: negative policy from WHO

- Commercial serological tests provide inconsistent and imprecise estimates of sensitivity and specificity. There is no evidence that existing commercial serological assays improve patient-important outcomes.
- Overall data quality was graded as very low and the Expert Group strongly recommended that these tests not be used for the diagnosis of pulmonary and extra-pulmonary TB.
Other statements

• International Standards for TB Care discourages use of TB serology

• IAP has discouraged TB serologies

• RNTCP is planning a consensus statement against these tests

• IAMM is planning a position statement

How can we roll-out new tests if bad tests 'eat up' the diagnostic space, and prevent us from using good tests?

VALUE CHAIN FOR IVD DIAGNOSTICS IN INDIA

First need to understand the value chain for diagnostics in India:

STATUS QUO: 3 VALUE CHAIN MODEL, WITH MODEL #1 DOMINATING

WHERE WE WANT TO GO: MODEL #2 AND #3 DOMINATING

Model 1: Imports

Model 2: Domers

Model 3: Innovators

Model 1: Imports

Model 2: Domers

Model 3: Innovators

Model 1: Imports

Model 2: Domers

Model 3: Innovators
Will need a strong internally initiated and supported effort for innovations.

**Model 2: Generics**

- Lack of TB drugs to copy (only enter-ventured)
- Concerns about IP (patient phenotypes)
- Concerns that market might not be profitable enough
- Lack of funds for development (even if it is needed)
- Rare cases where funding is available, take time and generic start chews
- Perception that DDI is not a private industry friendly
- "Might not work in India" is matched with "low quality"
- Generic diagnostics need to be initiated urgently

**Barrier**

- Success and experience to generate drugs and vaccines in hospitals
- Generic diagnostics are already being made
- When missing output for a year, but quality is low in India
- Can be done with limited funds by major players
- Lack of quality control in industry
- Until recently, IP was not an issue (tender, wrong checking)
- Even now, perception that IP is not a problem, unless patented

**Enabler**

- Trying to get TB skin (not TB drugs)
- Efforts to develop TB skin in parallel
- Enabling technologies and equipment
- Funding from various sources
- Setting up of quality control laboratories

**To move from Model #1 to #2**

**Model 3: Innovations**

- Industry not strong in R&D (weak to strong in leading and generic)
- Academics do not understand product development (patent and publishing)
- Academics are not research partnerships, acquisition, sales
- Poor R&D culture
- Time consuming and expensive to manufacture
- Difficult regulatory environment
- Lack of industry interest (few market worth the effort)
- Banks, venture capitalists (soft money) and are not in academia
- Industry funds access to science, very small
- Licence not in exchange (e.g., any term is OK)
- Most of the innovation research is not supported from outside India
- Necessity assessment from philanthropic foundations, politicians or soldiers

**Enabler**

- Strong engineering necessary, financing needed
- Increasing funding via BSE, DST, BRP, etc.
- Special initiatives for science
d- SBIR, etc.
- Strong academic initiatives motivated TB
- Clinical studies can be quickly done and rapidly completed
- Emerging cell and gene-based technologies to quantify R&D
- Start companies, including emerging technologies
- Success in TB lined up multiple
- Non-conventional players engaged (engineers, chemists, banks)

**But can innovations happen without external push/resources?**

- There are good examples of:
  - "outsourced" innovations and "off-shored" R&D (e.g., John F. Welch Technology Centre, Bangalore; AstraZeneca’s Bangalore Research Institute)
  - But they have been externally initiated/supported
  - Will need a strong internally initiated and supported effort for diagnostic innovations

"We found terrific scientific, engineering and administration talent in India that India serves almost every business at GE" - Jack Welch, General Electric Co
<table>
<thead>
<tr>
<th>More resources are now available in India and this might help with innovations</th>
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<tbody>
<tr>
<td>• DBT grants</td>
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<td>• Technology Development Board</td>
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<td>• CSIR/DST</td>
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<td>• GOI partnerships with Wellcome Trust, etc</td>
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<td>• Grand Challenges Explorations (GCE)</td>
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<td>• Grand Challenges Canada</td>
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<td>• X Prize Foundation</td>
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<td>• Philanthropic groups</td>
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<table>
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<tr>
<th>Key questions for our group discussion</th>
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<tbody>
<tr>
<td>• How can we change diagnostic behaviors and replace bad tests with good technologies?</td>
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<tr>
<td>• How can we ensure quality in lab testing to support roll-out of new technologies?</td>
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<tr>
<td>• Despite the high TB burden, why is India yet to produce innovative TB products (diagnostics, drugs or vaccines)?</td>
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<tr>
<td>• What are the most important barriers for innovation?</td>
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<tr>
<td>• Should India stick to its strengths and focus only on generics?</td>
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<td>• Why is the Indian industry not interested in TB (despite the market)?</td>
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<td>• Why are academia-industry partnerships so weak in India?</td>
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<tr>
<td>• What are the sources of funding for TB innovations?</td>
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<td>— How can we convince GOI, Indian industry, VC and philanthropists to support TB innovations?</td>
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<td>— Has the grant model worked?</td>
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<td>— Will a prize model work in India?</td>
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<td>• How can successes in sectors such as IT be replicated in health technologies?</td>
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