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www.treatmentactiongroup.org

TB Diagnostics Pipeline: New Tools & Opportunities to Improve Access to Testing

DAVID BRANIGAN

TREATMENT ACTION GROUP

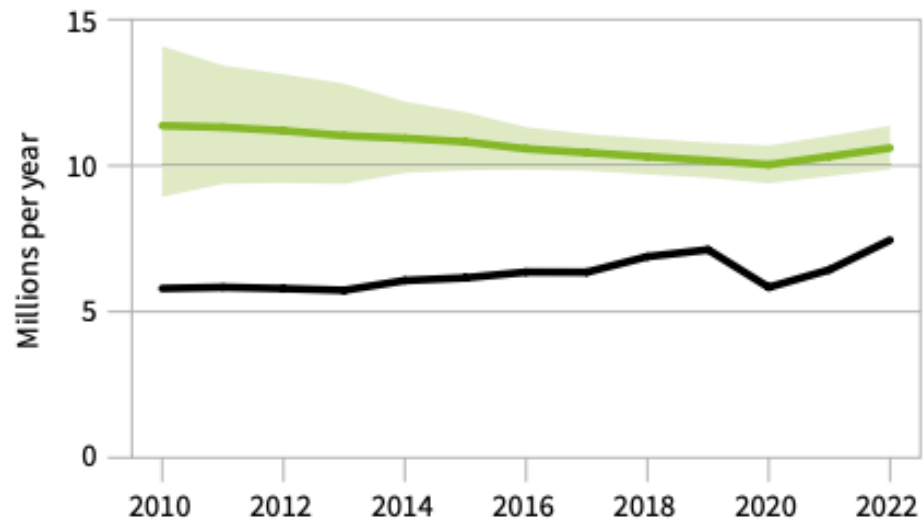
15 MAY 2024

TB DIAGNOSTIC GAPS

FIG. 21

Global trend in case notifications of people newly diagnosed with TB (black) and the estimated number of incident TB cases (green), 2010–2022

The shaded area represents the 95% uncertainty interval.



Source: WHO Global TB Report, 2023

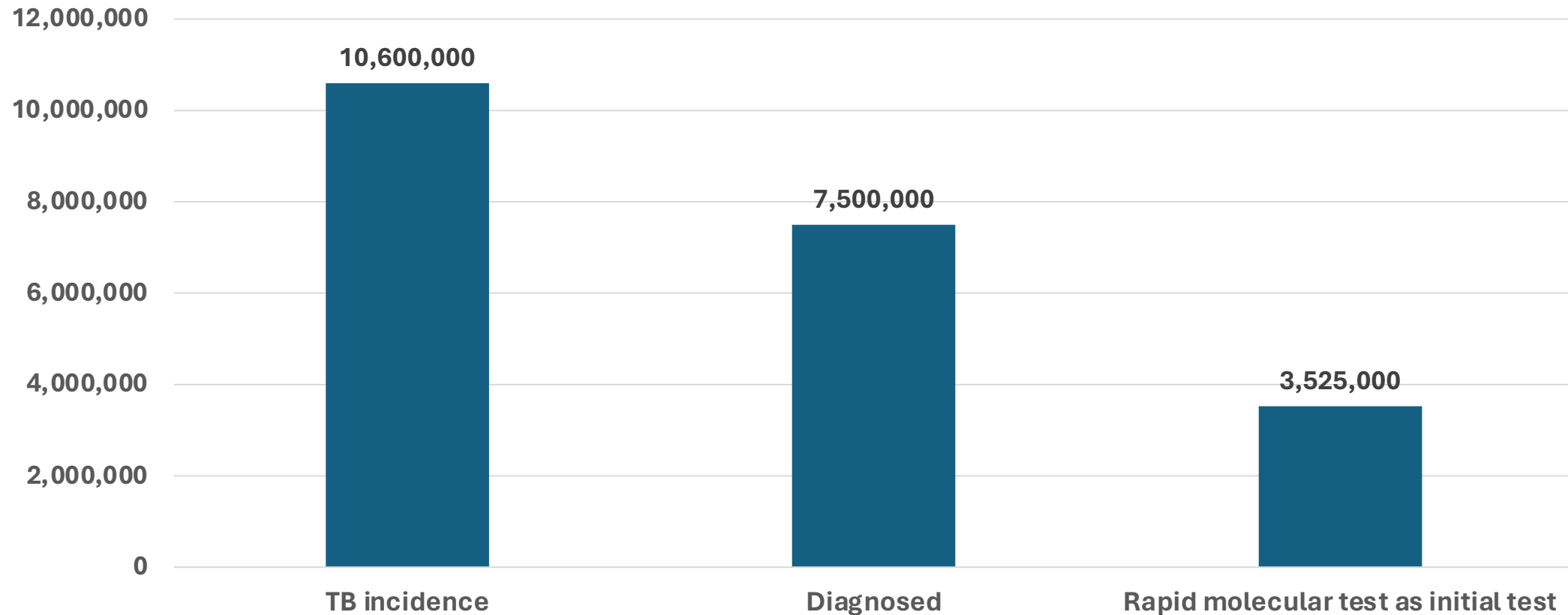
- Finding and diagnosing tuberculosis (TB), continues to be the most challenging aspect of the TB cascade of care. In 2022, up to **30% of people with TB remained undiagnosed** and untreated.
- And **just 47% of people diagnosed with TB received a rapid molecular test as the initial TB test** in accordance with WHO recommendations. Country programs continue to rely on smear microscopy.
- Of the 450,000 people estimated to have developed RR/MDR-TB in 2022, **just 43% were diagnosed and initiated DR-TB treatment.**
- Meanwhile, more than **70% of young children with TB are never diagnosed.**
- There is an urgent need to improve approaches to TB screening and diagnosis, increase access to the best available TB screening and diagnostic tools, **and invest in developing new tools needed to close testing gaps.**

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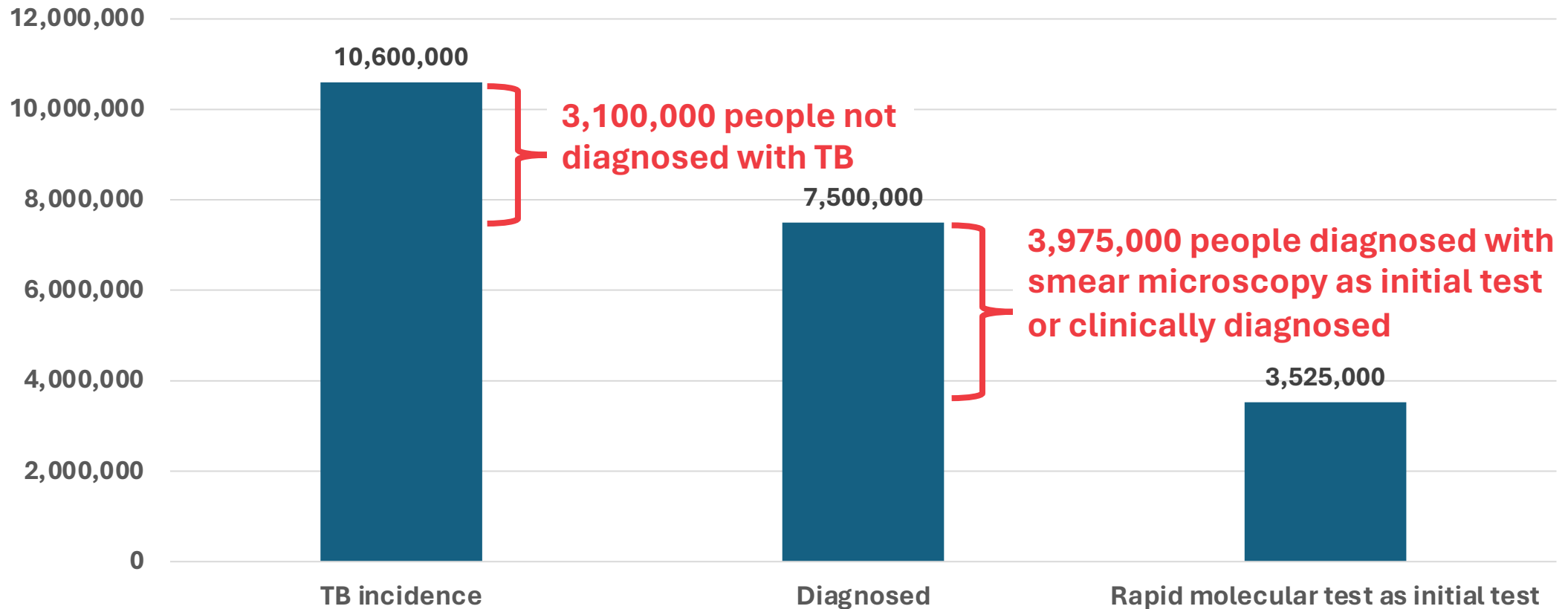
TB DIAGNOSIS IS THE WEAKEST LINK IN THE TB CASCADE OF CARE

Limited access to WHO-recommended diagnostics in 2022



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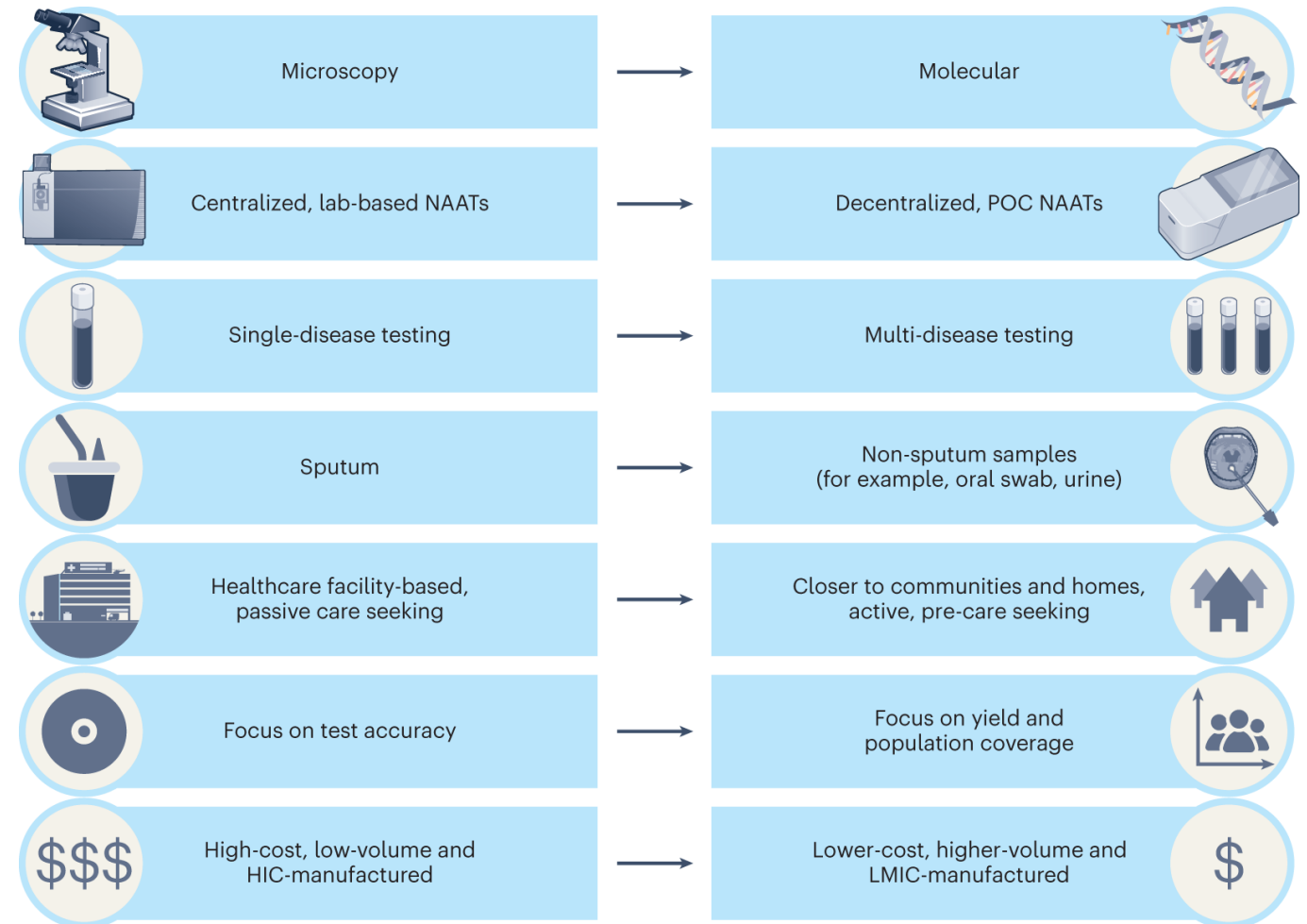


LIMITATIONS OF CURRENT TOOLS

Currently available TB diagnostic tools have limitations for access and equity:

- **Sputum-based:** not everyone can provide a sample; not appropriate for children and some people living with HIV
- **Placed at district lab or central lab levels:** NOT point-of-care tests; require sample transport resulting in delayed diagnosis and risk of loss to follow-up
- **Expensive:** high costs of tests, instruments, and service & maintenance burdening limited TB program budgets

New diagnostics are needed to address these limitations...



Source: Pai et al, Nature Microbiology, 2023
<https://www.nature.com/articles/s41564-023-01365-3>

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DIAGNOSING PEDIATRIC TB



<https://www.msfacecess.org/diagnosing-paediatric-tb-challenges-and-needs>



What needs to happen?

We need more research and development in TB diagnostics that are specifically designed for children.

Such child-adapted diagnostic tests should:

- make use of easy-to-collect samples in children, for instance through finger-prick blood tests or oral swabs;
- be highly sensitive and specific, i.e. have a high probability to correctly identify TB in children;
- be point-of-care tests, suitable for and easy to use at primary care levels by any health care worker in remote and low-resource settings, i.e. robust and independent of any lab infrastructure; and
- be affordable for low- and middle-income countries.

If a test works in children, it will work in adults, but not the other way around.

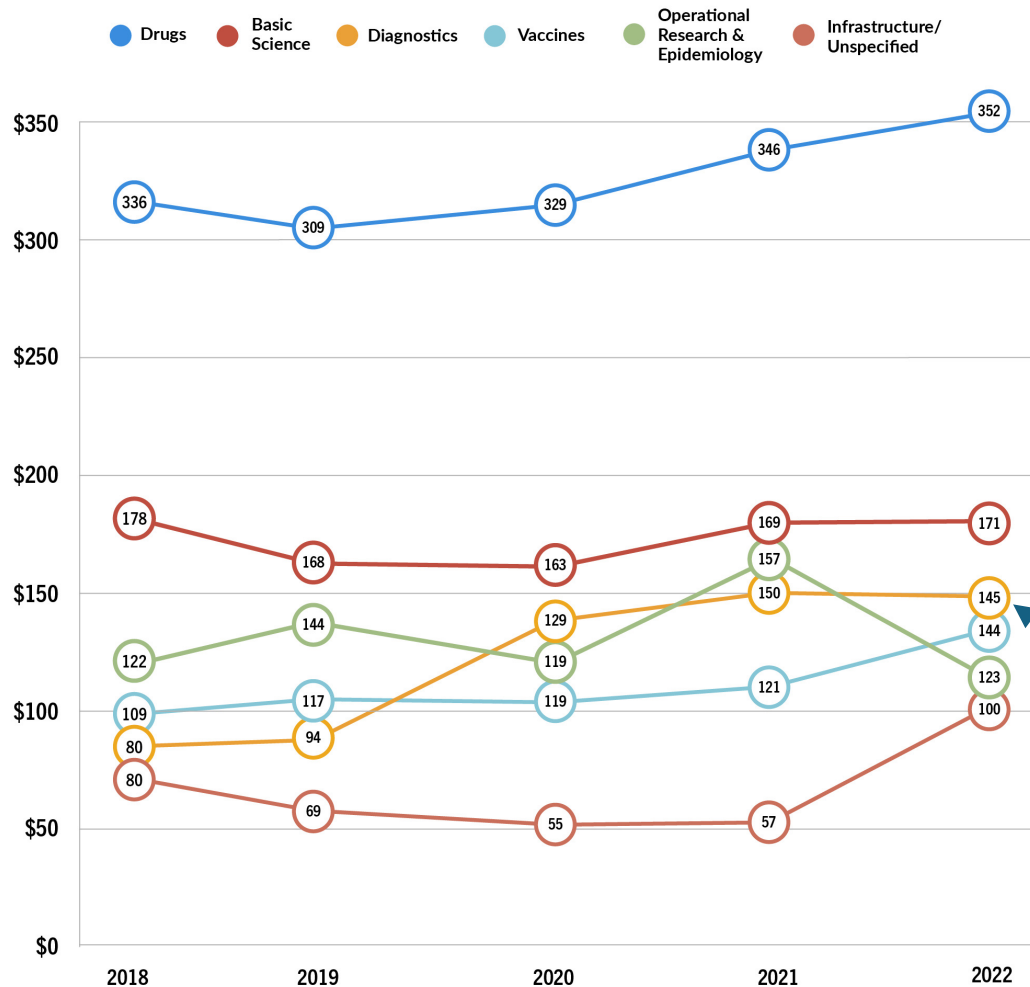
- Diagnosing TB in children is challenging, in large part because children usually have **paucibacillary TB (small amounts of TB bacteria in samples)**, which is difficult to detect using currently available tests. Meanwhile, **invasive procedures** are often required to obtain induced sputum or other samples for testing.
- Another key challenge is that there is very limited data on the diagnostic accuracy of currently available tests among children due to the focus on prioritizing adults in the development and evaluation of TB diagnostics.

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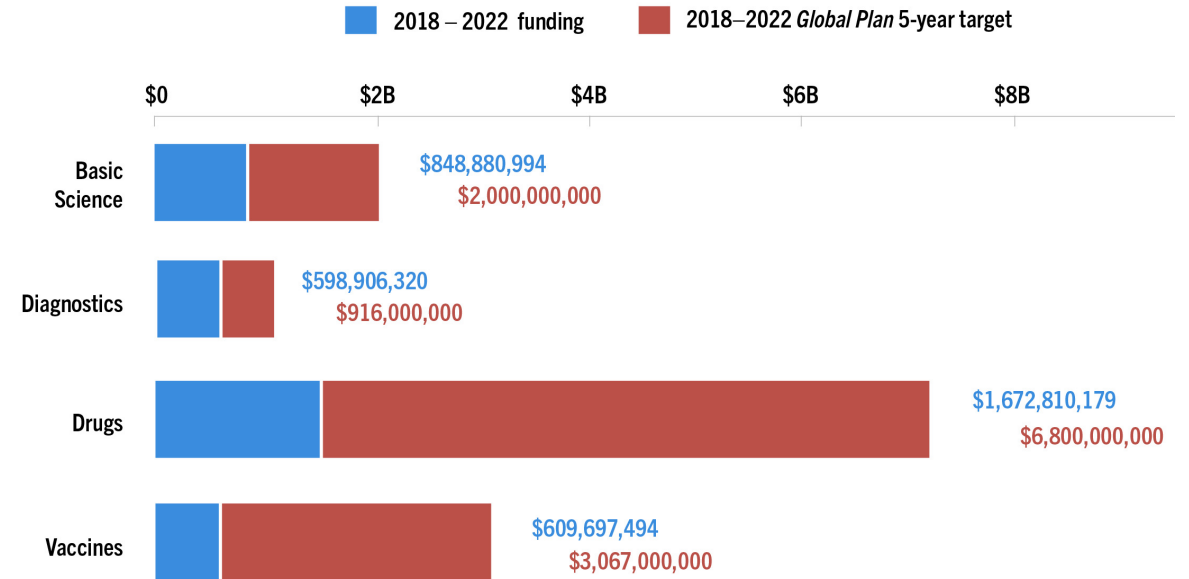
TB DIAGNOSTICS R&D FUNDING

TB R&D Funding by Research Area, 2018–2022 (in Millions)



Note: Data for years 2005–2017 not shown.

Progress toward *Global Plan* TB Research Funding Targets



Source: Tuberculosis Research Funding Trends 2005–2022: <https://www.treatmentactiongroup.org/resources/tbrd-report/tbrd-report-2023/>

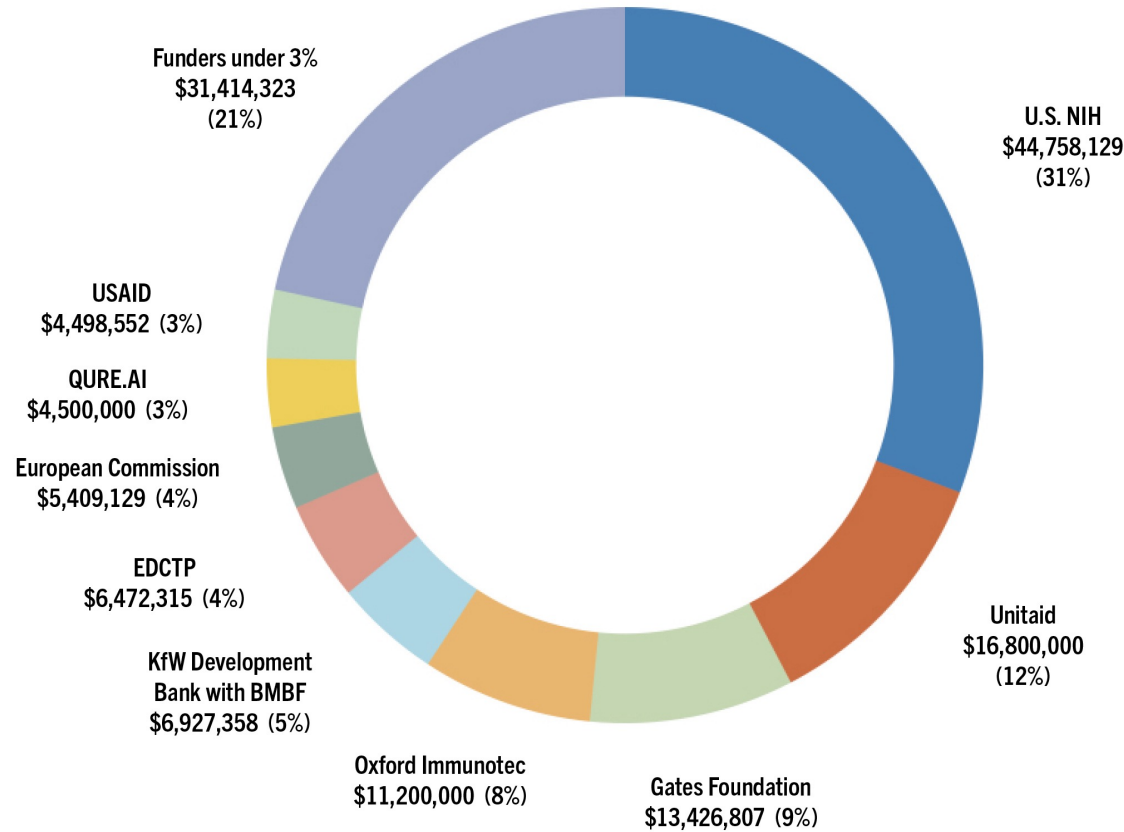
The 2023–2030 *Global Plan* sets a more ambitious funding target for TB diagnostics R&D of **\$965 million per year** — which is more than **six times larger than 2022 investment levels**.



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TB DIAGNOSTICS R&D FUNDING

Diagnostics: \$145,406,615



Other funders with investments under 3%

Company E	\$3,149,920
Australian Department of Foreign Affairs and Trade (DFAT)	\$2,605,155
German Federal Ministry of Education and Research (BMBF)	\$2,209,299
QIAGEN	\$2,127,401
U.K. Foreign, Commonwealth & Development Office (FCDO)	\$1,855,095
Molbio Diagnostics	\$1,765,236
LifeArc	\$1,678,163
Indian Council of Medical Research (ICMR)	\$1,539,248
Anhui Zhifei Longcom Biopharmaceutical Co.,Ltd.	\$1,516,396
Company Y	\$1,402,000
Wellcome	\$904,417
Global Health Innovative Technology Fund (GHIT)	\$903,243
U.K. Medical Research Council (U.K. MRC)	\$878,008
Swedish Research Council	\$639,848
RIGHT Foundation	\$600,954
Company F	\$581,576
Korea Ministry of Health and Welfare	\$546,923
Korea Ministry of SMEs and Startups	\$540,298
Japan Agency for Medical Research and Development (AMED)	\$512,338
Infervision Medical Technology	\$510,000
South Africa Department of Science and Innovation	\$462,198
India Health Fund / Tata Trusts	\$421,225
Other funders with expenditures <\$400,000	\$4,065,383

Source: Tuberculosis Research Funding Trends 2005–2022:
<https://www.treatmentactiongroup.org/resources/tbrd-report/tbrd-report-2023/>

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PUBLICLY FUNDED TB DIAGNOSTICS RESEARCH NETWORKS

FUNDERS:



RESEARCH NETWORKS:



Joint steering committee to share data and collaborate on the development of new point-of-care tests

Access conditions should be applied to all public funding of TB diagnostics R&D, to ensure affordable and equitable pricing of new diagnostics and service & maintenance agreements, and public return on public investment. Lowest sustainable pricing supports manufacturers with reasonable profit and country programs to scale up new tools to meet testing needs.

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TARGET PRODUCT PROFILES (TPPS)

WHO and FIND collaborate to develop & update Target Product Profiles (TPPs) for the diagnostic tools needed to reach and diagnose more people with TB

- TPPs define the **optimal and minimal performance and operational characteristics** for new tools and communicate these priorities to diagnostics developers.
 - **Examples of performance characteristics: sensitivity, specificity**
 - **Examples of operational characteristics: sample types, pricing of tests and instruments, turnaround time to results, infrastructure requirements, etc.**

TPP	YEAR	LINK
A test predicting progression from TB infection to active disease	2017	https://www.who.int/publications/i/item/WHO-HTM-TB-2017.18
Next-generation drug-susceptibility testing at peripheral centres	2021	https://www.who.int/publications/i/item/9789240032361
Tests for tuberculosis treatment monitoring and optimization	2023	https://www.who.int/publications/i/item/9789240081178
TB screening tests	2024 (update)	Forthcoming
TB diagnostic tests	2024 (update)	Forthcoming

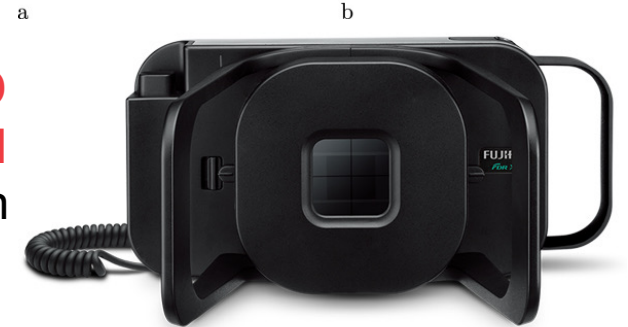
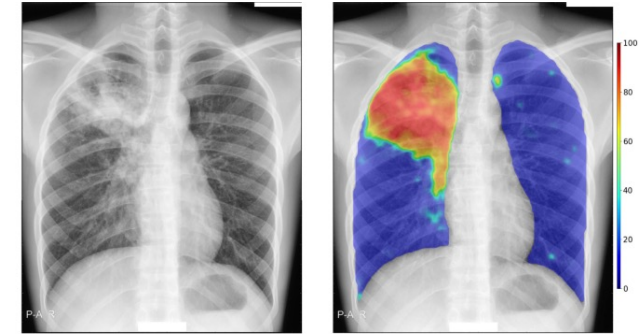
TB DIAGNOSTICS PIPELINE OVERVIEW

Type	Proof of concept / early evaluation	Analytical & clinical verification	Clinical validation	Commercially available / WHO-recommended
Screening tests			Chest X-Ray + computer aided detection (CAD)	
		Point-of-care ultrasound (POCUS)		
	Digital stethoscopes			
	Cough sound apps			
Diagnostic tests		Near-point-of-care rapid molecular tests for TB & DR-TB		
	Point-of-care rapid molecular tests for TB			
	Point-of-care urine LAM tests for TB			
			Targeted next-generation sequencing (tNGS)	
Disease progression & treatment monitoring tests	Host-response tests			
	Quantitative bacterial load tests			
TB infection tests			Next-generation skin tests	
			Point-of-care IGRAs	

SCREENING: IMAGING TOOLS

Ultraportable chest X-ray devices paired with artificial intelligence (AI) based CAD software

- Already recommended by WHO, but not yet fully scaled up for systematic screening in country programs
- To assist in detecting presumptive TB from chest X-rays (see www.ai4hlth.org for detailed information on available CAD software)
- Recommended only for people over 15 years of age; **efforts to validate CAD software for children and adolescents under 15 must be prioritized**
- The high cost of ultraportable chest X-ray devices has been a limiting factor in rolling out this effective screening intervention



Point-of-care ultrasound

- Powered by AI and paired with smartphones
- Offers a low-cost and safe imaging option for children and pregnant people in peripheral settings
- Can detect early tissue damage from pulmonary and extrapulmonary TB
- Early data shows accuracy is comparable to chest X-ray + CAD

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SCREENING: AI STETHOSCOPES & COUGH APPS

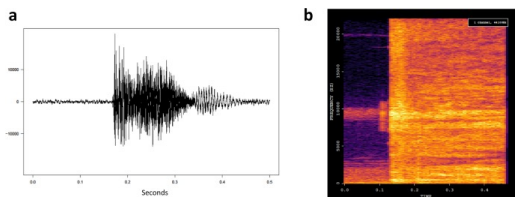
Digital stethoscopes powered by AI

- Can detect inaudible vibrations and audible lung and cough sounds
- Uses AI to map these against those of healthy lungs or other tissues to detect early damage associated with TB
- Inexpensive and can be used at the point of care to screen for TB
- Initially rolled out for COVID-19



Cough sound apps for smartphones

- Cough can be challenging to qualitatively describe, but new AI-based cough apps help make cough a more objectively quantifiable biomarker for TB
- These cough apps can be deployed in primary care and community settings and enable self-screening
- Some apps are designed to record a cough and identify the likelihood that it is associated with TB or another condition, enabling early TB screening and triage
- The downside is that by the time a person with TB is coughing, TB disease has already developed and is no longer sub-clinical



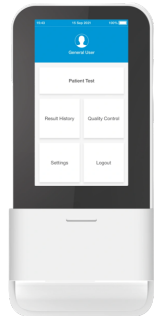
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DIAGNOSIS: POINT-OF-CARE MOLECULAR TESTS

Tongue swab-based point-of-care rapid molecular diagnostics

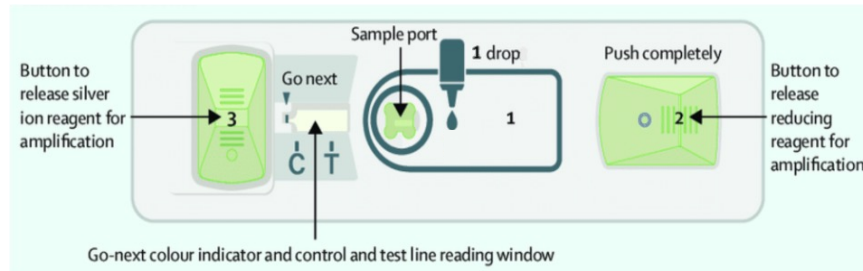
- Several companies are developing rapid molecular diagnostics for TB detection using small and fast testing instruments designed to be implemented at the point of care in community and primary care facilities, which will enable same-day testing, diagnosis, and treatment initiation.
- Tongue swab samples are easily accessible and while they are expected to be less sensitive (~ 70%) compared to sputum samples (~ 90%), since nearly everyone can easily provide a tongue swab sample, more people overall will be able to receive a diagnosis.
- These tests and instruments will help address gaps in access to testing and some are expected to be significantly less expensive compared to currently available tests. However, **the tests only detect TB and further testing using near-point-of-care molecular DST will be required to test for drug resistance.**



DIAGNOSIS: POINT-OF-CARE URINE LAM TESTS

For people living with HIV

SILVAMP TB LAM (Fujifilm)



Adapted from Broger et al, PLOS Medicine, 2020

SILVAMP TB LAM, developed by Fujifilm, amplifies detection of LAM and has been shown to be 30% more sensitive than Determine TB LAM among PLHIV (Broger et al, PLOS Medicine, 2020). **Due to manufacturing quality issues, the introduction of SILVAMP TB LAM has been delayed.**

For all people irrespective of HIV status

High-sensitivity TB LAM tests for people irrespective of HIV status are currently in development by multiple companies, including **Abbott, Boditech, Salus Discovery, SD Biosensor, Biopromic, and more.**

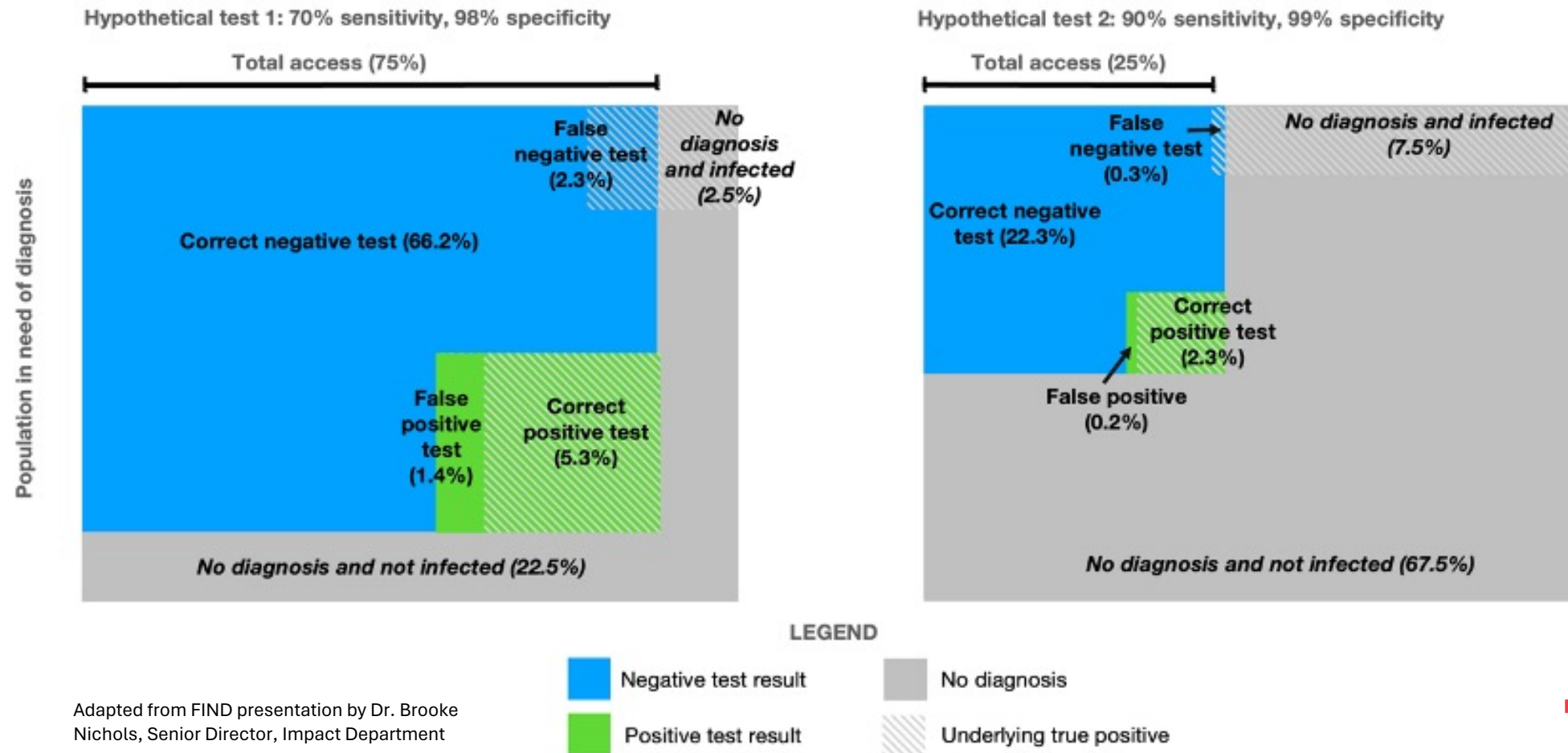
These tests offer the promise of inexpensive rapid point-of-care diagnostic testing with high diagnostic yield and a potential indication for children. Many next-generation LAM test are also paired with urine concentration and/or a digital reader.



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DIAGNOSIS: DIAGNOSTIC YIELD

It's not just about accuracy, but also about accessible sample type



Adapted from FIND presentation by Dr. Brooke Nichols, Senior Director, Impact Department

DIAGNOSIS: MOLECULAR TESTS FOR TB & DST

WHO standard

Universal access to rapid tuberculosis diagnostics



STEP 3: Being tested

Benchmark

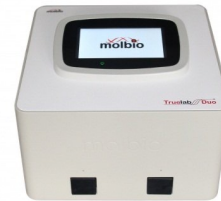
9 All patients with bacteriologically confirmed TB undergo universal drug susceptibility testing*

“Among patients with RIF-susceptible TB, testing for isoniazid and FQ resistance is increasingly important.”



Cepheid currently has a monopoly on rapid molecular DST for INH and FQ. The price of Xpert MTB/XDR is **\$14.90 per test** – too high for scaling up universal access to DST.

New companies with tests in the pipeline are entering this market:



- **Molbio** is developing tests for **INH and FQ** resistance, as well as **BDQ** resistance. Of note, Truenat can be implemented in microscopy centers, closer to the point of care than GeneXpert. Availability is expected by 2025.



- **SD Biosensor** is developing a test for TB and resistance to **RIF and INH** on the STANDARD M10 platform, similar to GeneXpert. Availability is expected by 2025.

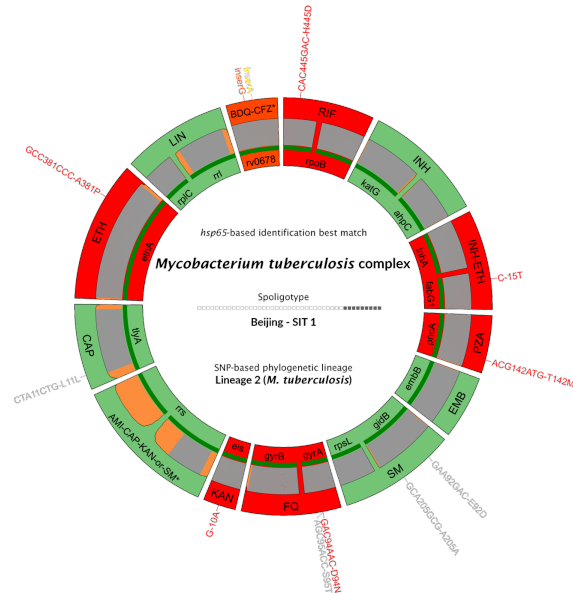
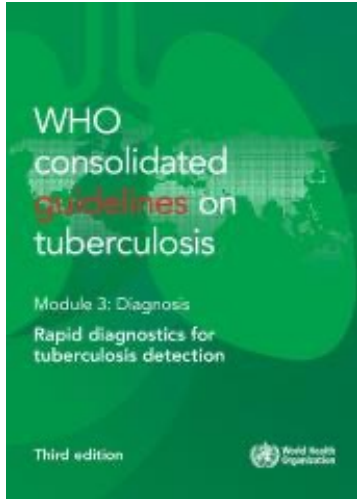


- **Bioneer** is developing a test for TB and resistance to **RIF, INH, and FQ** -- the first rapid molecular test to incorporate all of these in a single test – on the IRON qPCR platform, similar to GeneXpert. Availability is expected by 2025.

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DST: TARGETED NEXT-GENERATION SEQUENCING



“Since sensitivity for bedaquiline, linezolid and clofazimine resistance is suboptimal [using tNGS]... **Further testing of samples with a susceptible result (using culture- based phenotypic DST) would be warranted, particularly when the risk of resistance is high.**”

Bedaquiline	Phenotypic DST	Se: 67.9 (42.6–93.2)	3 (31)	Low
	Phenotypic DST	Sp: 97.0 (94.3–99.7)	4 (519)	High
Linezolid	Phenotypic DST	Se: 68.9 (38.7–99.1)	4 (31)	Low
	Phenotypic DST	Sp: 99.8 (99.6–100)	6 (1093)	High
Clofazimine	Phenotypic DST	Se: 70.4 (34.6–100)	4 (36)	Low
	Phenotypic DST	Sp: 96.3 (93.2–99.3)	6 (789)	High

For people with confirmed pulmonary TB and RR-TB, **tNGS: “may be used... rather than culture-based phenotypic drug susceptibility testing”**

Recommended tests from:

- GenoScreen
- Oxford Nanopore Technologies

“Centralized versus decentralized placement may have equity implications for access: Given the high-level specialized laboratory infrastructure, specialized human resources and technical complexity needed for targeted NGS, the technology may be suitable for placement only at centralized, reference laboratories. This may have equity access considerations.”

“Based on the empirical analysis, the cost of targeted NGS was estimated to be:

- US\$ 134 to US\$ 257 in South Africa;
- US\$ 120 to US\$ 198 in Georgia; and
- US\$ 121 to US\$ 175 in India.

These costs are dependent on patient volume, batching and negotiated cost per targeted NGS kit.”

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DISEASE PROGRESSION & TREATMENT MONITORING

Host-response tests for disease progression and treatment monitoring

- Host-response tests for disease progression and/or early TB can also be used for treatment monitoring
- They test for biomarkers in the immune system or specific gene signatures expressed by the body in response to the presence of live TB bacteria
- Currently available rapid molecular tests for TB cannot be used for treatment monitoring because they detect live and dead TB bacteria
- Cepheid's Xpert MTB-HR fingerstick blood-based host-response test is the most advanced and promising test in this class; because it is blood-based, it also shows promise to support child TB diagnosis



Bacterial load tests for treatment monitoring

- These tests quantify TB bacteria in samples and can perform in hours what mycobacterial culture takes weeks to perform
- The quantity of bacteria detected by these tests can be used to monitor the effectiveness of TB treatment, assess the potential risk of poor treatment outcomes or the need for longer treatment, and also test for cure
- TB Mycobacterial Load Assay (TB MBLA) is one prominent example of this class of tests

TB INFECTION TESTS

Next-generation TB-specific skin tests (TBST):

- These new WHO recommended TB-specific skin tests (TBST) are more specific (**less false positives**) compared to conventional tuberculin skin tests (TST), which sometimes return false positive results among people vaccinated with the Bacille Calmette-Guérin (BCG) vaccine
- They are in-vivo tests that produce results in 2-3 days, and have similar accuracy but lower costs compared to IGRAs
- These tests are not yet quality assured by WHO Prequalification (PQ) program due to a lack of a PQ pathway for in-vivo tests, which has delayed roll-out



Point-of-care interferon gamma release assays (IGRAs):

- IGRAs are generally laboratory-based blood tests for an immune response to TB antigens, and due to their high costs are not widely used in LMICs
- New IGRAs are in development that consolidate laboratory procedures into a simple lateral flow test with a digital reader, enabling implementation at the community level, costing between \$4 (SD Biosensor) and \$12 (Qiagen) per test
- However the samples require 16-24 hours for incubation so results are not available on the initial visit

REGULATORY APPROVAL PROCESS

Global

- **WHO Global TB Program Review:** WHO Global TB Program convenes Guideline Development Groups (GDGs) to develop class-based recommendations for novel classes of tests and to update existing recommendations based on the availability of new clinical performance and other data.
 - Examples of WHO-recommended test classes: rapid molecular tests for TB and RIF resistance; rapid molecular tests for INH, FQ, and second-line drug resistance; urine LAM tests for people living with HIV; targeted next-generation sequencing; line probe assays, etc.
- **WHO Prequalification (PQ):** WHO has recently starting applying PQ to TB diagnostics. Ideally, manufacturers will apply directly to PQ to review and assess quality assurance of new tests in already-recommended test classes. However, PQ is currently behind and equipped to review only two classes of TB diagnostics: (1) rapid molecular tests for TB and DST and (2) urine LAM tests for people living with HIV. In the interim until PQ gets fully up to speed, WHO Global TB Program will convene technical advisory groups to review new tests in existing classes not yet covered by PQ.
- **Global Fund Expert Review Panel for Diagnostics (ERPD):** Separate from WHO, the Global Fund has a mechanism to review new diagnostics and to provide interim approval based on available data with a requirement for WHO review or PQ within 2 years. ERPD-approved tests can be procured by the Global Fund for supported countries in lieu of WHO review/PQ.

National

- Once approved on a global level, **tests must also be approved by national regulatory authorities**, requiring manufacturers to apply for registration in each country. In some cases, national regulatory authorities may require additional in-country studies on the clinical performance of tests. To expedite national regulatory approval, WHO has developed a **collaborative procedure for accelerated registration** that harmonizes PQ and national data requirements.

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KEY THEMES: ACCESSIBILITY

Sample types

- Easily accessible samples such as tongue swabs, urine, and blood are acceptable and should be prioritized for new diagnostics development.
- These samples increase the overall number of people able to be tested and receive a diagnosis (diagnostic yield), but their diagnostic accuracy is lower than sputum.

Use cases / diagnostic placement

- A number of new diagnostics can be placed at the point of care in community and primary care settings enabling same-day testing and treatment. In these settings, should tongue swabs, urine, or sputum be used for diagnosis, given their relative accuracy?
- What about self-sampling and self-testing?
- These new point-of-care diagnostics also only test for TB and not drug resistance. So, what should follow-on DST look like in practice?
- Where should rapid molecular DST be placed to minimize sample transport delays? And can targeted next-generation sequencing be decentralized and made more accessible?
- What about disease testing integration?

KEY THEMES: EVIDENCE-BASED PRICING

Pricing of new tests should be based on evidence

- Ideally, the cost of production should be transparent and publicly available
- Pricing should be based on the cost of production plus a reasonable profit mark-up
- For small companies, a reasonable margin of profit may be larger to ensure sustainability; for established companies the margin of profit can be much lower
- Service & maintenance of testing instruments should be high quality and monitored by key performance indicators; priced transparently, affordably, and equitably; and ideally included in the price per test depending on country preferences.
- Access conditions should be applied to all public and philanthropic funding of TB diagnostics R&D (upstream)
- Access principles for multi-disease molecular diagnostics should be applied to procurement and pricing negotiations (downstream): <https://www.treatmentactiongroup.org/statement/ten-principles-for-access-to-multi-disease-molecular-diagnostics-a-global-call-to-action/>
- Time for \$5 Campaign: <https://www.msfacecess.org/time-for-5>

Cepheid's Price Gouging for Lifesaving Test

BUT
Cepheid charges
\$10 - \$20
?!?!?!?

Costs Cepheid
ONLY
\$3 - \$4.60
to produce!

This lifesaving test should NOT be 2-4x more expensive than it costs to make.

TIME FOR \$5! **CEPHEID, IT'S TIME FOR \$5!** ACCESS CAMPAIGN

The infographic features a central illustration of a Cepheid Xpert device. A green arrow points from the text 'Costs Cepheid ONLY \$3 - \$4.60 to produce!' to the device. A red arrow points from the text 'BUT Cepheid charges \$10 - \$20 ?!?!?!?' to the device. The background is dark blue with white and red text.

NEXT STEPS: DEMAND CREATION & MARKET SHAPING

Next steps:

1. Sensitize affected communities, national programs, and other stakeholders to new diagnostics nearing the end of the pipeline
2. Work with country governments to build consensus around use cases, placement, and target prices, and to update guidelines, National Strategic Plans, etc. accordingly
3. Work with donors and other global health actors to support countries + inform market shaping interventions in line with country government priorities + needs

2025?: Near-point-of-care molecular DST

- Bioneer IRON qPCR RFIA Kit, SD Biosensor STANDARD M10 MDR-TB, Molbio Truenat MTB-INH/FQ/BDQ = introducing competition with Cepheid Xpert MTB/RIF Ultra and Xpert MTB/XDR

2025-6?: Point-of-care molecular + urine-LAM tests for TB

- Tongue swab-based molecular tests from LumiraDx, Boditech, Co-Dx, Nuclein, Pluslife, Molbio, Salus Discovery, Cepheid*, and others
- Fujifilm's SILVAMP TB LAM for people living with HIV; high sensitivity LAM tests for people irrespective of HIV status from Abbott, Boditech, SD Biosensor, Salus Discovery, Biopromic, and others

* Tongue swab sample collection protocol being developed for Xpert MTB/RIF Ultra; not a new assay

THANK YOU!!

RESOURCES:

TB Diagnostics Pipeline Report 2023

https://www.treatmentactiongroup.org/wp-content/uploads/2023/11/2023_pipeline_TB_diagnostics_final.pdf

Tuberculosis Research Funding Trends 2005–2022

<https://www.treatmentactiongroup.org/resources/tbrd-report/tbrd-report-2023/>

WHO Standard: Universal Access to Rapid Tuberculosis Diagnostics

<https://www.who.int/publications/i/item/9789240071315>

Transforming Tuberculosis Diagnosis (Pai et al, Nature Microbiology, May 2023)

<https://doi.org/10.1038/s41564-023-01365-3>

MSF Access Campaign factsheet on pediatric TB diagnostics

https://www.msfacecess.org/sites/default/files/2024-01/MSFAC_Factsheet_Paediatric%20TB%20diagnostics_Final.pdf

For any additional questions on the TB diagnostics pipeline, please don't hesitate to be in touch:

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