GH LABS NAATOS PRODUCT FEASIBILITY ASSESSMENT

DELIVERABLE: VOICE OF THE CUSTOMER ANALYSIS

DATE: 1 DECEMBER 2023
PRESENTED BY: MARKET ACCESS AFRICA

Market Access Africa is pleased to submit this report to GH Labs for market research and information gathering supporting the product development and commercialization of NAATOS.

Executive Summary

Introduction | Our goal was to outline key developmental milestones and market entry strategies for NAATOS

As a non-profit corporation fully funded by Gates Ventures (the private office of Bill Gates) Entity, Global Health Labs, Inc (GH Labs) innovates to reduce health disparities, especially in low- and middle-income countries to develop health technology solutions for the people who need them most.

GH Labs engaged Market Access Africa to support field & client intelligence gathering to inform critical development milestones for the NAATOS TB Molecular lateral flow device.

The output of this work include the development of opportunity summaries, market access and regulatory insights.

MAA conducted the analyses described above focusing on systematically conducting a landscape deep-dive in 4 target countries and providing GHL with thematic focussed and market-specific(where relevant) insights.

Methodology | The voice of the customer (VOC) analysis explored key thematic priorities for a successful launch in the public and private sector of 4 target countries

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Approach

	Areas assessed	How we obtained data	Output
Market Landscape	• Diagnostics landscape • Stakeholder mapping • Patient Pathways	• Desk research: literature reviews and data extraction	• Market insights report findings and insights from KIIs*
Policy Considerations & Regulatory Pathways	• Mapping product lifecycle process • Clinical validation pathway • Regulatory Framework	• Key Informant Interviews (KIIs) with public and private sector stakeholders	• Product insights report*
Product Insights	• Customer Feedback on market requirements vs specification including product value proposition, use case and menu options**	• Key Informant Interviews (KIIs) with public and private sector stakeholders	• Voice of the customer feedback on the product captured across thematic areas and countries
Deployment Considerations	• Market deployment and development of opportunity summary		• Product Deployment Summary

Market Requirements & Product Specification for TB diagnostics

GH+Labs

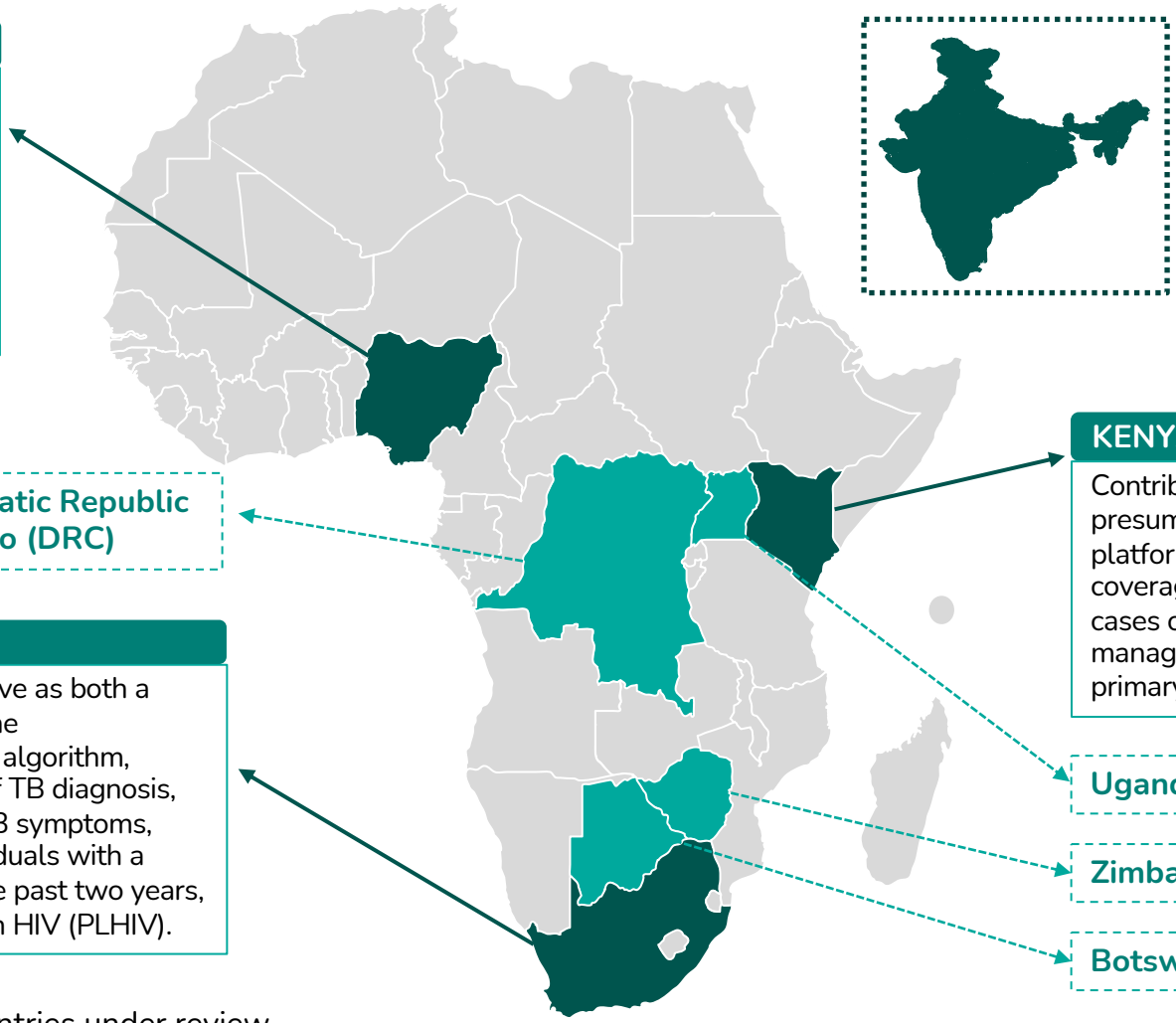
* Market insights report **combines** findings and recommendations with product insights and executive summaries

Country Feedback | Based on their needs and TB testing algorithms, countries saw different opportunities for NAATOS adoption

COUNTRIES UNDER STUDY

NIGERIA

NAATOS to serve as both a triage test and a screening tool which will improve testing at L1 facilities; where today there's limited testing being done at L1. Patient samples are collected and sent to more to L2 & L3 for diagnosis using the existing TB Dx. These Dx require storage, temperature , and power infrastructure amongst other things.



INDIA

Potential to support India's ambitious plans for intensified case finding using molecular testing: presumptive TB testing targets have been increased from ~1700 per 100,000 population to ~3000 per 100,000, to an overall target of 42 million TB tests per year.

KENYA

Contributors highlighted the critical need for presumptive cases to be tested with a molecular platform as a first test. There is significantly low coverage at lower-level facilities resulting in 40% of cases of being missed in the TB diagnosis and management cascade. NAATOS can become the primary TB diagnostic tool at L1 and L2 facilities.

Democratic Republic of Congo (DRC)

Uganda

Zimbabwe

Botswana

SOUTH AFRICA

NAATOS presents an opportunity to serve as both a triage test and a screening tool within the Targeted Universal Test & Treat (TUTT) algorithm, enhancing the efficiency and accuracy of TB diagnosis, across a spectrum of clients including TB symptoms, close contacts of recent TB cases, individuals with a history of completed TB treatment in the past two years, and newly diagnosed People Living with HIV (PLHIV).

xx Spotlight countries

xx Other countries under review

Product Specification | Stakeholders provided feedback on key considerations for NAATOS adoption (1/8)

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Thematic Area 1 | Usability and Test Performance

Market Requirements	Current NAATOS Specifications	Notes on Stakeholders' Desired Specifications	Country Specific Insights
Invalid rate	• NAATOS device-related failure for product feasibility must achieve a failure rate of <35%	• Current guidelines specify an error rate of <5% of total tests for the platforms in use and this is a key consideration for adoption	• Many of the KIIs across the 8 markets pointed to the current national guidelines with an error rate of <5% of total tests for the platforms in use, highlighting this metric as a gate-keeper to market entry
Walk away operation	• NAATOS V1 requires only two to three user interactions before walking away and returning to record the result (excluding sample prep)	• User-friendly testing process • Integration of sample preparation and testing phases into a streamlined system • Consolidation of sample preparation module and heat module - the user shouldn't have to do anything else after adding the swab to the sample preparation tube	• **IN**: Getting prototypes testing into the hands of end users as early as possible at L1/L2 facilities the system across users (nurses or paraprofessionals) in the clinical pathway
Time to result	• NAATOS V1 must produce a result within <60 min (including sample prep time)	• While some stakeholders anticipate that time to result for NAATOS will be within 1 hour or less compared to the existing platforms, others view NAATOS as a rapid test with expectation of rapid results • Ideal: 15-minute test • Minimal: 60-minute test • If the test results take longer, there is a risk that the clients might leave and not return for the treatment • Clients will be at the clinic for 1.5 – 2 hours at a minimum, waiting in queues, but a nurse may only have 15 minutes with the client	• **NG**: Patients from resource-poor settings typically travel miles to get to testing sites, a fast TAT can ensure that treatment starts same day reducing the possibility of patients abandoning the treatment (loss to follow up-LTFU)

Product Specification | Stakeholders provided feedback on key considerations for NAATOS adoption (2/8)

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Thematic Area 2 | Transport & Storage Conditions

Market Requirements	Current NAATOS Specifications	Notes on Stakeholders' Desired Specifications	Country Specific Insights
Transportation	• NAATOS V1 must not require cold chain storage during shipment or storage	• Transportation under refrigeration is available from privately contracted companies (sometimes at added cost) • Ambient temperature conditions for storage and transportation without refrigeration are preferred • There is an increase in MoH's demand for test kit delivery directly to Level 1 facilities	• **KY:** Transportation of kits is the responsibility of Kenya Medical Supplies Agency (KEMSA) and cold chain is costly and more complex to support • **IN**: Shipping is no longer costly to most parts of the country, but other logistic planning continues to be poor
Shelf life	• NAATOS V1 must have a shelf life of >12 months • (Corporate presentation: shelf life of >18 months from the date of manufacturing)	• The quantities to be procured are dependent on forecasting and quantification done by the TB Program • Ideal: 18 months and. acceptable: 12 months • Current procurement for test kits can be 2-3 times per year in a number of markets • Cost of shipping is costly to rural areas, so frequency of shipping is low hence longer shelf life is preferred	• **KY**: The product should be 75% of the shelf life at the time of delivery or in-country or at the warehouse.
Storage conditions	NAATOS V1 must be stored at 0 °C to 40 °C and 90% humidity	• The temperatures are usually between 22-25 °C in the country and very rarely exceed 45°C • Majority of facilities with extreme temperature conditions have refrigerators for storage of reagents • Fridges for reagent storage can be a problem in the smaller L1 facilities, and scheduled power outages in larger facilities pose a risk	• **ZA**: Humidity levels can be high in places like Durban where its frequently 90-95% humidity
Quality Control of Operation conditions	NAATOS V1 must operate at: • Temperature: +15 °C to +35 °C • Humidity: 25% to 80% relative humidity	• Some regions especially the Northern part of Kenya usually experience higher temperature 27-30°C • Fridges for reagent storage can be a problem in the smaller L1 facilities, and scheduled power outages in larger facilities pose a risk	• **KY**: Some regions especially the Northern part of country usually experience higher temperatures 27-30°C and rarely go below 14 °C

Product Specification | Stakeholders provided feedback on key considerations for NAATOS adoption (3/8)

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Thematic Area 3 | **Integrated Service Delivery**

Market Requirements	Current NAATOS Specifications	Notes on Stakeholders' Desired Specifications	Country Specific Insights
Multiuse platform	• NAATOS V1 must be designed as a multi target disease platform (TB, STI, etc.)	• Multi disease testing is currently in place since the advent of COVID-19 particular for GeneXpert incorporating HIV, TB and cervical cancer • This feature is a key advantage for NAATOS	• **KY**: Multi-disease testing is currently in place since the advent of COVID-19. Already using GeneXpert in some counties (for HIV, TB and HPV) • **NG**: Value in addressing prevalent health concerns beyond the primary focus (e.g., bacterial STIs, HIV viral load, and drug resistance detection) . • Stakeholders shared that a multi-disease platform would be most welcome and also private sector practitioners preferred multi-disease platforms. • **IN**: Value in addressing prevalent health concerns beyond the primary focus (e.g., Resistance testing, vector-borne diseases like malaria, dengue, chikungunya and other health threats)
Consideration for Special Populations	• Not defined by GHL	• Stakeholders highlighted the need for clarity on the benefit of NAATOS for paediatric or children population (also consider children <2 years) as these represent a "hard to sample population" • TB suspects unable to produce sputum • PLHIV where TB-LAM is missing TB +ve • Close contacts, people on TB Rx in past 2 years	• **ZA:** With TuTT pilots underway, opportunity for presumptive TB patients in rural areas, PLHIV where TB-LAM is missing, Communities without Laboratories or storage facilities, children and high burden facilities

Product Specification | Stakeholders provided feedback on key considerations for NAATOS adoption (4/8)

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Thematic Area 4	Market Access (Manufacturing Considerations & Costs)

Market Requirements	Current NAATOS Specifications	Notes on Stakeholders' Desired Specifications	Country summary
Quality control	• Not defined by GHL	• Batch to batch testing is key to ensure that there are no problems with the kit and for NAATOS these can be provided to facilitate this process • Training and sensitization should be provided to build competency from staff carrying out these tests. • The company should consider providing EQA material, that will be a plus.	• **ZA**: Existing TB program is working with SmartSpot to manufacture panels for their EQA
Manufacturing	• NAATOS V1 must be manufactured at scale and with device fabrication and assembly process that is compatible with high-volume automation	• Key is to ensure a steady supply of the test kits at facilities to avoid shortages • Scale is important alongside local manufacturing partners to be developed. This is driven by Africa CDC and the Africa Collaborative Initiative	• **IN**: Scale is important alongside local manufacturing partners to be developed (Buy India)
Product price	NAATOS V1 must have a price of no more than $5 USD per test – At full production (10MM units/year) – At initial release, 3x full production (1MM units/year) – At pilot production, 10x full production (50k units/year)	• Stakeholders are hopeful that NAATOS will be an affordable test.. • The current inclusive cost for a molecular test is about $14 . • It is expected that NAATOS will be $5 $2 $3, available at the lower facilities.	• **ZA**: Whilst the public health program is still paying >$5/Mol Dx, respondents express a desire for a low-cost test (with suggested price points ranging from $2 to $5) for a PoC – which would justify not having a DST and potentially reflexing further downstream

Product Specification | Stakeholders provided feedback on key considerations for NAATOS adoption (5/8)

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Thematic Area 5 | Technical Performance

Market Requirements	Current NAATOS Specifications	Notes on Stakeholders' Desired Specifications	Country summary
Sample preparation steps	• The sample prep module must achieve target sample lysis (percent recovered)	• Stakeholders engaged technical laboratory TB testing highlighted challenges in sample Prep in the existing platform • Clarity in the timing for sample lysis	• **ZA:** Stakeholders were interested to know how they would label samples individually when running four samples at the same time. • **KY:** Stakeholders engaged technical laboratory TB testing highlighted challenges in sample Prep in the existing platform. Asked for clarity in the timing for sample lysis
Sample volume	• The sample prep module must deliver the appropriate sample volume • (Corporate presentation: 150 - 200µL)	• Some samples require more reagents for example some are more viscous than others. • The elute can be stored for subsequent/repeat testing without having to ask the patient to produce another sample. The sample is also used to perform Rif testing.	• **ZA**: No pipette measurement should be required, however, the ± 6 drops needs to be clarified – what happens if its 5 drops or 7 drops? • **NG**: Stakeholders were comfortable with following the package insert instructions on volume to be used.
Sample volume measurement	• The sample prep module must not require training to successfully and repeatably dispense target volume on the user interface within a reasonable tolerance	• There should be no manual steps or need for additional accessories	• **IN**: 'If there is a way, we could use the whole sample from the patient and then in the lab we can have elutes that concentrate the sample increasing the chances of detection'' • **NG**: Stakeholders were comfortable with following the package insert instructions on volume to be used.

Product Specification | Stakeholders provided feedback on key considerations for NAATOS adoption (6/8)

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Thematic Area 5 | **Technical Performance**

Market Requirements	Current NAATOS Specifications	Notes on Stakeholders' Desired Specifications	Country summary
Instrument design / amplicon contamination	• NAATOS V1 must prevent the escape of amplification products and not contaminate the testing area	• ''The way the sample is being collected, this is a swab and there is a high chance of missing this bacillus if the patient has a low bacillary load''.	• **KY**: Stakeholders were fine with the sample preparation model/design • **ZA**: Concern with the other DNA collected in the mouth – what are the targets of the assay?
Data display	• NAATOS V1 must have a visual read out of the test result that can intuitively be interpreted	• Stakeholders indicated that the positive results from NAATOS can be classified further as either high, medium or low such that we can have a band for high medium or low. • This will help us in terms of grading and to be able to know whether we are diagnosing the cases early or late. • It may be fully quantitative, but it can be semi quantitative.	• **ZA**: There were concerns about SoC LFAs having a 2-line read-out while NAATOS LFA had a 3-line readout during training with different cadres of health professionals
Field Testing and Real-world Performance	• Not defined by GHL	• Stakeholders expect that that NAATOs devices will be stable under the testing conditions and various environments	• **ZA**: Stakeholders are interested in how the test performs in diverse real-world settings beyond controlled laboratory environments. The conditions across the country are incredibly diverse; infrastructure, skills, environment etc

Product Specification | Stakeholders provided feedback on key considerations for NAATOS adoption (7/8)

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Thematic Area 6 | Product Design (Usability & Safety)

Market Requirements	Current NAATOS Specifications	Notes on Stakeholders' Desired Specifications	Country summary
Power module	• The power module must support the required daily throughput	The power module for NAATOS is a key advantage embraced by all stakeholders • Power outages have become infrequent and no longer present a major challenge in most high-burden settings, but the battery module would allow the test to be used in point of care settings (like active case finding in community)	• **KY**: Majority of L1 & L2 facilities have power challenges. In some regions power supply can be interrupted for up to 24 hours • **ZA**: With the on-going load-shedding having a same day TAT is perceived as beneficial
Sample preparation module design	• Random access not possible? • Can insert 1 to 4 samples at a time for extraction.	• Stakeholders expressed concern about expiry of reagents. Some of the sample preparation packs that come with the reagents expire before some of the reagents are used. • Part of the kits sometimes have different expiry dates and hence you cannot proceed with normal testing.	• **ZA**: Has GHL considered pathogen enrichment (concentration) step could improve sensitivity vs direct measurement/ testing a little volume of extracted swab solution
Safety	• NAATOS V1 must not pose a burn risk to the user during normal operation	• The feedback highlighted current concerns about safety with particular interest in waste generation for GTC (guanidine thiocynate) • Do the reagents have GTC?	• **ZA**: Users should not be able to remove the tube from the sample prep module earlier than the required incubation period for (I) optimal lysis and prevention of burning
Data Management	• The need for connectivity to LIMS or HIS to match standard of care	• For devices that do not have a connectivity module, the traditional way of capturing data from lab registers is done by the lab technician. • Captured in a paper-based system; transcribed onto an LIS/HIS at a district or regional level feeding up into national level reporting	• **ZA:** Result needs to be captured or read automatically as soon as test is complete to ensure traceability • Tracking and tracing more effective when connectivity is added to a LF test. • Though todays SoC for TB LAM is manual, this is not ideal and should be improved upon

Product Specification | Stakeholders provided feedback on key considerations for NAATOS adoption (8/8)

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Thematic Area 7 | Sample and Performance Characteristics

Market Requirements	Current NAATOS Specifications	Notes on Stakeholders' Desired Specifications	Country summary
Sensitivity	• NAATOS V1 must have a clinical sensitivity ≥ 80%	• Sensitivity >80% needed for acceptance • Stakeholders emphasized the need for higher or sensitivity comparable to the existing platforms • Evidence on whether the test has been compared to any other that is currently being used in the country to determine if it is worthy of engaging in TB testing. • Sensitivity for other interest groups/patient populations would be essential	• **ZA**: While Sensitivity is a priority, awareness of other Mol POC, e.g. MolBio, with lower sensitivity but considered "good enough" for adoption • **NG**: As a miniumum should meet or exceed the accuracy of existing methods
Specificity	• NAATOS V1 must have a clinical specificity ≥ 98%	• Specificity is a key consideration for the regulatory clearance for NAATOS • Specific level not specified	• **ZA**: A high specificity (above 95%) is considered essential
Sample Type	• NAATOS V1 will utilize a dorsal tongue swab sample	• Non sputum samples will benefit groups such pediatric and PLHIV who have difficulty producing sputum	• **ZA:** Focusing on sputum alone might lead to an inferior test • Potential benefits non-sputum sample collection methods
Treatment monitoring capability	• NAATOS V1 will not provide drug sensitivity	• ''I request that NAATOS should have an additional lateral flow such that when you have found a positive you can proceed to check for Rif resistance or any of the first line drugs that we use for Tuberculosis''. • ''If it is not able to perform resistance pattern testing, then we can have it as an initial diagnosis just like we have microscopy and those who turn positive to go through other machines	• **ZA**: "The absence of resistance in a new test might be seen as a disadvantage especially as the country scale up 3 new testing platforms each with DST included and potentially positioning of NAATOS into algorithm for settings where *Xpert cannot go*."

1 Introduction

2 Product Specifications

3 **Recommendations**

Recommendations | Early engagement and considerations across the value chain (1/2)

Consideration	Recommendation
1 **Stakeholder & Local Partner Engagement**	• Identify key stakeholders, such as the TB Technical working group (TWG) and guideline committees and engage them early in the process. Understand their needs and expectations. Understand their needs and expectations. Drive advocacy through the identified groups to create awareness and generate support for the new diagnostic tool.
2 **Training: Planning, Implementation Considerations**	• Plan comprehensive training sessions to ensure that laboratory staff and clinicians understand the benefits of the tool. Implement on-site training sessions. Emphasize the benefits of the test being quick, with easy steps and components. Leverage previous experiences, e.g. roll-out of TB LAM in South Africa, for best practice on-site training for PoC technologies
3 **Workflow: site assessment, challenges, design**	• Conduct a thorough assessment of the existing clinic workflow. Understand where the instrument will be located and co-located within the clinic setting. Consider the physical placement, such as having one unit per clinic or one unit per consulting room. Determining which staff cadre is responsible for conducting the test and collecting samples. Consider the experience with other diagnostic tools, such as TB urine LAM and Single Cartridge Xpert, to inform strategies for overcoming potential barriers.
4 **Channel considerations: Community level introduction, national strategies**	• Highlight the potential integration of the new diagnostic tool into Primary Health Care services. Address concerns of clinicians about workload by emphasizing the benefits of point-of-care diagnosis. Showcase the learnings from successful precedents, such as the TB LAM test and MolBio. In some markets, explore beyond facility level adoption e.g. mobile health units
5 **Clinical evidence: Data generation, proof of concept, key populations (e.g. children), EPTB**	• Critical to generate and publish evidence (global as well as local) in a wide range of publications and make the evidence accessible to decision-makers in both private and public sectors. Many stakeholders spoke to the challenges experienced with pediatric patients & PLHIV who are often unable to produce sputum. Considering expansion of use-case for clients with EPTB continues to pose a major diagnostic challenge in key markets for which there are no clear and forthcoming solutions

Recommendations | Early engagement and considerations across the value chain (2/2)

Consideration	Recommendation
6 Environmental Considerations: Biosafety & Waste Disposal	• Training and support for safe disposal of samples and consumables is not provided adequately in existing molecular systems. Consider early how to manage liquid vs solid waste with clear guidance on GTC handling (if required) and limit waste/explore recyclable
7 Data Management: Connectivity & Reporting	• Easy connectivity in TB management system is currently missing in most lab systems, and a new test with seamless LIMS connectivity would be a welcome solution. Where PoC/LFA exists today, manual transcription leaves room for errors and delays in national reporting database.
8 After Sales Considerations: Procurement cycles, On-site support, maintenance, in-country local presence	• Understand and prepare for potential bottlenecks in procurement and supply chain related to test components and batteries; these challenges have contributed to the less-than-optimal uptake of existing molecular tests today. Labs have been experiencing significant struggles related to equipment breakdowns and poor maintenance support with existing installed molecular diagnostics – so appropriate strategies on downtime is critical
9 Continuous Improvement: building feedback loops, adaptation and iteration	• Establish mechanisms for continuous monitoring and feedback. Gather insights from users regarding the usefulness and impact of the diagnostic tool. Address specific concerns, such as workflow challenges and the need for sample collection from patients who struggle to produce sputum. Based on feedback and real-world usage, be prepared to adapt the training and implementation process iteratively. Overcome challenges related to specificity, sensitivity thresholds, and any barriers identified during the initial stages
10 Change Management Considerations: Resistance, Competition, Crowded Market	• Consider change management strategies to address resistance. Clearly communicate the benefits of new diagnostic tool, involve staff in decision-making processes, and create a culture that embraces innovation and improvement. For example, GeneXpert, despite challenges, is accepted as the standard of care in both public and private sectors in some markets leading to resistance to adopt Truenat. Further, there may be other point of care molecular tests (including saliva-based tests) under various stages of development whose launch may coincide with NAATOS

India

Diagnostic Landscape (Public) | TB testing under the National TB Elimination (NTEP) program continues to be dominated by microscopy but molecular testing is increasing

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Key messages

1 Public sector facilities provide about 50% of all TB testing; molecular testing is largely centralized

Implications for NAATOS

- TB Testing is provided via a multi-tiered system of lab facilities **~23,000 district microscopy centers and ~5000 molecular testing/NAAT labs**
- Despite NTEP's intent to move molecular tests upstream and to replace microscopy as a first line test, microscopy increased from 8.2 million to 13.9 million tests over 2021-2022; in the same period, **molecular testing (Xpert + Truenat) increased from 3.6 million to 5.8 million tests**

2 Challenges with existing molecular diagnostics contribute to delayed and missed diagnosis

- **Stock-outs** of cartridges (Xpert) and chips (Truenat) due to procurement and supply chain failures are frequent
- Limited availability of skilled workforce, sample transportation challenges and poor equipment maintenance also contribute to frequent **underutilization of molecular diagnostic facilities**

3 NAATOS has a role to play in NTEP's vision to increase decentralized testing

- NTEP's priorities for 2023-24 are include **intensified case finding and decentralisation of rapid molecular diagnostics** to ensure optimal utilisation of NAAT facilities
- NAATOS presents an opportunity to serve as a screening tool as well as a diagnostic test especially in **hard-to-reach areas** where NAAT facilities are not present or underutilized

Diagnostic Landscape (Private) | Private sector contributes to 50-60% of TB testing and is an important potential entry point for NAATOS

Key messages	Implications for NAATOS
1 The Indian private sector is a key contributor to TB testing	• About 70% of all health expenditure in India is paid out of pocket (OOPs); about 60% of all people with symptoms of TB first seek care in the private sector • Private sector contributed to ~30% of overall notified TB case notifications in 2023 (i.e., over 700,000 cases out of 2.4 million cases), representing a large market base; • About 25% of annual TB budget is earmarked for private sector engagement aimed at improving the quality of services at as well notification from the private sector. Innovative partnership models like IPAQT, JEET and PPSAs have significantly expanded TB testing in private sector
2 The private sector is complex in structure and moderately regulated	• The actual number of private laboratories in India is unknown, and is estimated to be between 40,000 and 100,000; this includes at least 3 types of facilities: standalone labs or collection centers, private hospitals with attached labs and large reference labs • Most labs do not have an MD professional – some have medical lab tech diploma holders, other are self-taught lab techs; certifications are required but not enforced
3 Diagnostics can be used in the private sector before being approved by NTEP	• Unlike the public sector labs, private labs can (and do) use non-approved tests; there is a widespread use inappropriate samples and off-label use of serological tests • Private labs can use a test as long it is registered with Central Drugs Standard Control Organisation (CDSCO) and approved for import, which can take place before NTEP approval (for example: Xpert was used in the private sector 2 years before it was adopted by NTEP)

Diagnostic Landscape | Workflows at public and private clinics (L0/L1) are similar and point to challenges related to access, sample collection and turnaround times

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Patient arrives at the clinic

- Person with symptoms arrives at clinic (first point of contact):
  - Public: PHC, HWC
  - Private: GP, Informal provider, chemist

Vital Room

- Registration and vitals assessment carried out by non-medical staff (can be a wide range of cadres - nurse, TBHV, STS, Asha worker)

Triage

- Examination by medical officer; chest X-ray frequently carried out as part of symptom screening

TB symptom management

- Patient is assessed for TB clinically
- Presumptive cases given a sputum cup, with options for sputum collection at home or at the clinic
- Majority of facilities have designated sample collection points

YES

- *Access challenges: distance to clinic, transport costs, long queues at clinic (not a significant challenge in rural facilities), cost of care (in private sector)*
- *Social challenges: stigma, lack of awareness*

- *Staff shortages at all levels of cadres*
- *Some studies show delays range from 18 to 31 days between presentation and screening*

Sample collection

- Sample collected (mostly by non-medical staff)
- Sputum samples commonly obtained from presumptive cases
- Other sample types are usually collected for EPTB
- Stool for children has also been implemented

- *Many people with symptoms not able to produce sample*
- *Sample transport can/does lead to sample losses and degradation*

- *WHO-approved rapid diagnostics (WRDs) not available at L0/L1 centers*
- *Long turnaround times, which in turn lead to high losses to follow up and delayed treatment initiation*
- *Some studies show delays range from 13 to 30 days between screening and diagnosis*

TB Management

- If positive, initiate Drug Sensitive TB Rx
- If RIF resistant initiated Drug Resistant TB Rx
- If neg, investigate further

Diagnosis and results

- Testing carried out at L2/L3 facilities
- Results received by patient (via SMS/WhatsApp) and by provider

Sample processing and shipment

- Packaged and sent for testing to L2 facilities (for molecular testing)
- Sample packaging is performed by clinical personnel in facilities without onsite laboratory

xx Diagnostic gaps

Time

Patient presentation

Initial Screening and sample collection

Diagnosis

Patient treatment and management

PHC: Primary Health Clinic; **GP**: General Practitioner; **HWC**: Health and Wellness Center; **TBHV**: TB Health Visitor; **STS**: Senior Treatment Supervisor

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Diagnostic Landscape | There are a few key "high-influence entities" which play important roles in the diagnostic landscape (1/2)

Entity	Key points	Implications for NAATOS
1 NTEP – CTD and MoHFW	• Overall supervision of all TB activities in India. Main decision maker for introduction of new diagnostics.	• Must begin dialogue early with this critical decision-maker on several areas – GH labs as a company, introduction to NAATOS, its optimal placement in primary care and community settings, feasibility studies, and potential to improve quality of testing in private sector
2 Donors (Global Fund, USAID and World Bank)	• The MoHFW has availed a USD 400 million International Bank for Reconstruction and Development (IBRD) loan from World Bank which is 30% of the total program cost; the Global Fund has allocated USD 280 million for TB which is split between NTEP, and implementation partners (CHAI, FIND, the Union and Plan India)	• Expected to remain as significant donors and influencers of India's NTEP strategy; must engage at an early stage and build a base of support
3 WHO India Office	• Technical support to NTEP (at the level of center and state) in multiple TB-focused activities, including tendering, procurement, supply and LIMS	• Likely to lead/be included in the Technical Expert Committee, to review NAATOS application for adoption; must engage at an early stage and build a base of support
4 BMGF India Office	• Funding and technical support to various central and state level implementation projects and capacity building initiatives, especially in private sector engagements; also supporting projects under implementation agencies like CHAI and PATH	• Expected to remain as significant donors and influencers of India's NTEP strategy; BMGF connection with GH labs can be a point in favour as long as the test is not viewed as a "foreign test"

Diagnostic Landscape | There are a few key "high-influence entities" which play important roles in the diagnostic landscape (2/2)

Entity	Key points	Implications for NAATOS
5 ICMR institutes (NIRT, NITRD and others)	• The Indian Council for Medical Research (ICMR) is the lead agency for clinical trials and operational research for new drugs and diagnostics. Its partner institutes include (1) the National Institute for Research in Tuberculosis (NIRT) in Chennai which is also one of India's eight national reference labs (NRLs) and a WHO designated Supranational Reference Laboratory (SNRL) • for the South-east Asia Region, and (2) the National Institute for Tuberculosis and Respiratory Diseases (NITRD) in New Delhi which is one of the eight NRLs and a Center of Excellence with Global Laboratory Initiative (GLI)	• Networking priority to build awareness of the NAATOS platform, to build a plan for research/feasibility studies and to craft a plan for introduction of the test as a POC test in future algorithms
6 Private sector (Networked Dx labs and Private-Hospital-Associated labs)	• Provide TB diagnostic services to 50-60% of all TB patients in the private sector; the large chains have their own procurement and supply chain mechanisms and have significant buyer power	• Significant market player which can be an early adopter; consider engaging with 2-3 large chain and placing NAATOS platforms in satellite labs or sample collection locations
7 Implementation partners (CHAI, PATH, FIND)	• Implementation of various TB-focused public private partnership projects. CHAI manages the Initiative for Promotion of Affordable and Quality TB tests (IPAQT) which was designed to expand private sector usage of WRDs and to align private labs with NTEP goals. FIND is a technical support partner to NTEP in tendering, procurement and LIMS.	• Potential partners for engagement with private sector labs, and for building alignment with NTEP; potential partners for pilot studies that can provide additional evidence for efficacy of NAATOS in field settings
8 India Health Fund (IHF)	• Recognised and respected by NTEP as a key supporter of innovative testing platforms; strong understanding of Indian health systems	• Networking priority (already done) to build inroads into NTEP and to identify + initiate other relevant local partnerships

India

Product Value Proposition | Stakeholders recognized several positive attributes of NAATOS that makes it an attractive option for adoption

Key takeaway

NAATOS presents an opportunity to support India's ambitious plans for intensified case finding using molecular testing: presumptive TB testing targets have been increased from ~1700 per 100,000 population to ~3000 per 100,000, i.e., an overall target of 42 million TB tests per year

As part of the end TB strategy, NTEP has declared priority actions which include: (1) Systematic active case finding campaigns in communities and within health facilities, and (2) Further decentralisation of rapid molecular diagnostics. NAATOS has the potential to contribute to both actions by offering a user-friendly, reliable test which can be used in a decentralised manner

NAATOS attributes which received the greatest recognition

Performance	• Stakeholders express a strong interest in the 60 min turnaround time which can materially impact the high loss to follow up between sample collection and test results • Public and private stakeholders shared that sensitivity rates of 70-80% would be enable the test to be placed as a preferred first line test in NTEP's decentralised molecular testing strategy
Ease of sampling and user-friendly operations	• The test is viewed as easy to understand, train for and implement. Some stakeholders expressed concern about the lack of resistance testing being barrier and limiting test usage to a screening tool • Most stakeholders believe that the test could aid in task-shifting because it could be used by all cadre levels after a training of 1-2 days
Applicability in hard-to-reach settings	• NAATOs can aid the GoI strategy of wide-spread case-finding campaigns in areas hitherto not reached due to access challenges • Existing molecular technologies (especially Xpert) have limited potential to be decentralised due to complex operational requirement and cost
Private sector labs need an alternative to Xpert	• There is a recognized need to challenge the Xpert monopoly due to challenges related to poor equipment maintenance, cartridge shortages and lack of portability • Truenat has not been taken up by the private sector; possible reasons include limited marketing efforts contributing to lower level of trust

Product Specification | Stakeholders provided feedback on key considerations for NAATOS adoption (1/3)

Market Requirements	Current NAATOS Specifications	Notes on Stakeholders' Desired Specifications	Steps to Close Gap
Invalid rate	• NAATOS device-related failure for product feasibility must achieve a failure rate of <35%	• Invalid rates should ideally be <5%	• Costs of replacing failed modules/consumables will need to be factored into total cost
Walk away operation	• NAATOS V1 requires only two to three user interactions before walking away and returning to record the result (excluding sample prep)	• User-friendly testing process • Integration of sample preparation and testing phases into a streamlined system • Consolidation of sample preparation module and heat module - the user shouldn't have to do anything else after adding the swab to the sample preparation tube	• Prototypes testing into the hands of end users as early as possible • Usability & acceptability studies are key • Consider the clinic facilities the system will be in • Consider the users are nurses or paraprofessionals
Time to result	• NAATOS V1 must produce a result within <60 min (including sample prep time)	• A 60-min turnaround time is deemed acceptable for Indian settings	• Feasibility and ease-of-use studies to demonstrate 60-min turnaround time to be carried out in local settings • Strong implementation and algorithm guidance to support earlier testing in the patient workflow, ensuring that test & treatment can take place in same visit
Transportation	• NAATOS V1 must not require cold chain storage during shipment or storage	• Maintaining cold chain in transport continues to be a challenge although there have been improvements in recent years due to increased vaccination drives • Transportation without refrigeration would be ideal	• N/A
Shelf life	• NAATOS V1 must have a shelf life of >12 months • (Corporate presentation: shelf life of >18 months from the date of manufacturing)	• Ideal: 24 months • Acceptable: 18 months • Shipping is no longer costly to most parts of the country, but other logistic planning continues to be poor; kit procurement would ideally be done 1-2 times a year	• N/A

Product Specification | Stakeholders provided feedback on key considerations for NAATOS adoption (2/3)

Market Requirements	Current NAATOS Specifications	Notes on Stakeholders' Desired Specifications	Steps to Close Gap
Storage conditions	• NAATOS V1 must be stored at 0 °C to 40 °C and 90% humidity	• Temperatures can range from -10°C to + +50°C; humidity levels can be as high as 90% in some regions • Power outages have become infrequent and no longer present a challenge, but refrigeration (for reagent storage) may not be available in many L0-L1 facilities	• Data to determine how long kits can be stored in temperature and humidity extremes without refrigeration
Quality Control of Operation conditions	NAATOS V1 must operate at: – Temperature: +15 °C to +35 °C – Humidity: 25% to 80% relative humidity	• Temperatures can range from -10°C to + +50°C; humidity levels can be as high as 90% in some regions • Power outages have become infrequent and no longer present a challenge, but refrigeration (for reagent storage) may not be available in many L0-L1 facilities	• Data to determine performance in temperature and humidity extremes
Multiuse platform	• NAATOS V1 must be designed as a multi target disease platform (TB, STI, etc.)	• Value in addressing prevalent health concerns beyond the primary focus (e.g., Resistance testing, vector-borne diseases like malaria, dengue, chikungunya and other health threats)	• Adoption decision more attractive by providing a comprehensive solution to diverse healthcare needs, matching the patient journey
Manufacturing	• NAATOS V1 must be manufactured at scale and with device fabrication and assembly process that is compatible with high-volume automation	• "Make in India" policy encourages manufacture within country • In 2023, Cepheid set up a local manufacturing base for India-made TB diagnostics.	• Explore partnerships with local manufacturing partners which already have pre-existing relationships of trust with CTD and states
Product price	NAATOS V1 must have a price of no more than $5 USD per test – At full production (10MM units/year) – At initial release, 3x full production (1MM units/year) – At pilot production, 10x full production (50k units/year)	• Respondents express a desire for a low-cost test (with suggested price points ranging from $2 to $5)	• Definition of an "affordable" or "cost-effective" TB test goes beyond the test's individual price • Consider broader economic factors • Consider overall test cost, feasibility • Consider cost of community deployment • Overall cost-effectiveness involves considering the entire testing algorithm and implementation factors

Product Specification | Stakeholders provided feedback on key considerations for NAATOS adoption (3/3)

Market Requirements	Current NAATOS Specifications	Notes on Stakeholders' Desired Specifications	Steps to Close Gap
Sample preparation steps	• The sample prep module must achieve target sample lysis (percent recovered)	• There should be no manual sample purification	• N/A
Power module	• The power module must support the required daily throughput	• Power outages have become infrequent and no longer present a major challenge in most high-burden settings, but the battery module would allow the test to be used in point of care settings (like active case finding in community)	• N/A
Field Testing and Real-world Performance	• Not defined by GHL	• Stakeholders are interested in how the test performs in diverse real-world settings beyond controlled laboratory environments	• Identify local partners early and initiate local performance studies
Consideration for Special Populations	• Not defined by GHL	• The effectiveness of the test in special populations, such as those unable to produce sputum, is important • Many stakeholders expressed a hope that the test could be used in pediatric populations	• Whenever possible, test the tool with paediatric populations
Quality control	• Not defined by GHL	Internal control accounting for any processing errors: – Sample application to strip reporting of results External control accounting for any processing errors: – Swab-based to account for processing errors – Sample prep to results	• N/A

1. Diagnostic landscape
2. Stakeholder feedback
3. **Policy considerations**
4. Deployment considerations

Policy Considerations | Critical policy enablers highlighted by stakeholders for a new TB NAAT test

1

Performance and Affordability

- Stakeholders highlight the importance of the lateral flow assay providing results within an hour, being available and effective at field level sites, affordable (less than USD 5 was recommended), and easy to use. Additionally, there's an emphasis on the test having high sensitivity and specificity rates. Such a test could be ideally placed at public L0/L1 centers like PHCs and HWCs, and also at private clinics.

2

Alignment with National Guidelines and Approval Processes

- Public sector facilities can only adopt a new test after it is approved by the NTEP and included in a revised algorithm. Private sector facilities can use the test sooner – after CDSCO approvals and import clearances. For both sectors, global approvals would be helpful but not essential; India's "Make in India" policy implies that approval and uptake are easier for products manufactured within country.

3

Considerations for Implementation and Patient Flow Integration

- There was a lack of clarity/conviction among stakeholders around the test placement - whether it should be used for screening, triage or as a diagnostic tests for treatment initiation; it is essential to build further evidence on feasibility, i.e., how the new test fits into the current testing algorithm, required skillset of personnel. Other suggestions included drug sensitivity testing, testing turnaround times in actual settings and evaluation of the test for paediatric populations.

1. Diagnostic landscape
2. Stakeholder feedback
3. Policy considerations
4. **Deployment considerations**

Policy Considerations | All diagnostic products need to be registered with CDSCO as a first step; the process of NTEP adoption can be started simultaneously

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Process of registration with central licensing authority (CLA): CDSCO

Registration with a global body	• The product is registered with a global regulatory body, such as the FDA
Application to CDSCO	• Appoint Local Agent: A local authorized agent is selected, from a list of approved bodies • The agent registers the product on the CDSCO's online portal, and applies for permission to perform evaluation studies in India
Test license and performance studies	• Apply for special license to import small quantities for evaluation • Carry out performance studies at government institute (usually one of the ICMR institutes) • Inspection of the manufacturing facility may be required
Manufacturing/ Import License granted	• Based on results of performance evaluation, CDSCO grants an Import License/Manufacturing License, post which the product can be imported/ manufactured and sold in country

Process of adoption by NTEP

Application and invitation to TEC	• The manufacturer submits an application to the Central TB Division (CTD) which is the MoH department in charge of the NTEP • The CTD invites the Technical Expert Committee (TEC) - which includes representatives from ICMR, FIND, WHO India, private sector and others - to review the application. • The TEC considers the application and develops plans for health technology assessment (HTA) including studies to be performed; appoints government institutes/sites for studies
Performance studies	• ICMR institutes carry out performance Studies to establish the performance of the product under TEC's guidance; even if such studies have been done in other settings, the TEC may require them to repeated in India specific settings, especially rural and semi-urban sites
Feasibility and other studies	• Usability and acceptability studies are conducted in the intended use settings, to establish feasibility for scale-up, and user-friendliness; the TEC may request additional evaluations like cost-effectiveness and/or clinical utility
Adoption and inclusion into algorithms guidelines	• The TEC reviews the results of the studies and provide a go/no-go decision to CTD and MoH, which take a final decision and provide guidance around how guidelines and algorithms need to be adapted to include the new test

Each of these pathways can take 3 months to 1 year; private labs can use a test as soon as it is approved by CDSCO, which can take place before NTEP approval

Deployment Considerations | Interviewees made several suggestions for smooth product adoption of NAATOS (1/2)

1 **Early application to CDSCO**

Identify the key stakeholders, such as the TB Technical working group and guideline committees and engage them early in the process. Understand their needs and expectations

2 **Identification of local partners**

Drive advocacy through the identified groups (slide 6) to create awareness and generate support for the new diagnostic tool; pan comprehensive training sessions to ensure that laboratory staff and clinicians understand benefits of the tool

3 **Proof of concept**

It is imperative to generate and publish evidence (global as well as local) in a wide range of publications, and to make the evidence accessible to decision-makers in both private and public sectors

4 **Evidence with pediatric samples**

Many stakeholders expressed the hope that the new lateral flow test would solve the challenges experienced with pediatric patients who are often unable to produce sputum

5 **Prepare for Procurement and Supply Chain Challenges**

Understand and prepare for potential bottlenecks in procurement and supply chain related to test components and batteries; these challenges have contributed to the less-than-optimal uptake of existing molecular tests

Deployment Considerations | Interviewees made several recommendations for smooth product adoption of NAATOS (2/2)

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6 **Prepare for resistance and competition/crowding**

GeneXpert, despite challenges, is accepted as the standard of care in both public and private sectors; the latter has especially been resistant to adopt Truenat. Further, there may be other point of care molecular tests (including saliva-based tests) under various stages of development which may overwhelm decisionmakers. It would be worthwhile to build plans to address resistance and to build confidence in the new tool through clear communication of the benefits

7 **Maintenance support**

Lab managers have been experiencing significant struggles related to equipment breakdowns and poor maintenance support with existing installed molecular diagnostics

8 **Explore potential for extra-pulmonary TB (EPTB)**

About 40% of TB cases in India are EPTB and pose a major diagnostic challenge for which there are no clear and forthcoming solutions

9 **Bio-safety and disposal**

Training and support for safe disposal of samples and consumables is not provided adequately in existing molecular systems

10 **Data connectivity**

Easy connectivity to Ni-Kshay, India's web-based (and recently, mobile application-based) TB management system is currently missing in most lab systems, and a new test with seamless LIMS connectivity would be a welcome entry

Kenya

Diagnostic Landscape | The health system in Kenya operates under a decentralized government comprising of National and County Health Units

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Key Messages	Implications for NAATOS
1 TB diagnosis and management services are supervised by the National TB Program	• The **National Government** works in liaison with counties and **allocates resources** to support the functions of the devolved government including healthcare • There are **47 county administrative units** each responsible for health services within their jurisdiction • The **entry point for engagement** would be the **National TB Programme** which provides guidance on TB services in the country. It sits under the Ministry of Health's Department of Preventive and Promotive Services
2 The country has embraced new WHO approved molecular platforms for TB Dx	• Diagnostic instruments include GeneXpert (215), Truenat (37), TB LAM lateral flow assay, TB LAMP (26), digital chest X-ray, LPA, culture & drug susceptibility testing and LED and ZN microscopy • **Truenat and Xpert are mainly used for diagnosis of TB** and Rif-resistance detection • **Integrated use of the platforms** has already commenced, mainly shared with HIV and Cancer Programs
3 NAATOS holds promise to address significant gaps in the Dx cascade	• There is a **gap in access to molecular diagnostic services** at lower-level facilities (L1 & L2). These facilities are majorly dependent on conventional microscopy • Samples are collected from L1 & L2 facilities and transported for molecular testing at higher level facilities • TB diagnosis is **dependent on the efficiency of the available sample referral system** • **Availability of commodities is a major challenge** to TB testing in the country, particularly with regards to the supply of GeneXpert cartridges

Diagnostic Landscape | There is a major gap in accessing diagnosis at initial point of care seeking (up to 45%)

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Patient arrives at the clinic

- Goes to the queueing system
- Patient details and records are captured electronically
- A unique number is issued used for tracking patient's progress

Vital Room

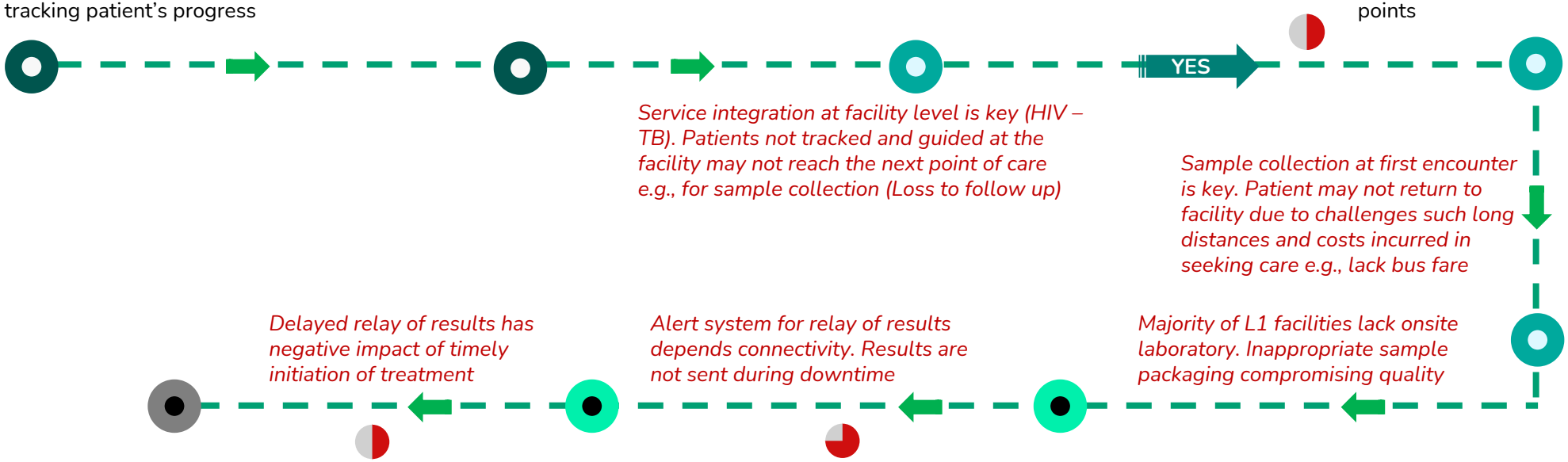
- Patient moves to Vital room for recording of vitals and creation of patient record

Triage

- Cough monitors segregate patients with cough as an IPC measure
- Majority of facilities are implementing facility level active case finding (ASF)

TB symptom management

- Patient is assessed for TB clinically
- Presumptive cases given a sputum cup, with options for sputum collection at home or at the clinic
- Majority of facilities have designated sample collection points



Sample collection

- Sputum samples commonly obtained from presumptive cases
- Other sample types are usually collected for EPTB
- Stool for children has also been implemented

TB Management

- If positive, initiate Drug Sensitive TB Rx
- If RIF resistant initiated Drug Resistant TB Rx
- If neg, investigate further

Diagnosis and results

- The expected TAT for facilities with onsite testing platforms is 24 hours
- Truenat and Xpert are linked to an alert system that relays results to clinicians by SMS before hard copies are delivered
- Microscopy is performed as initial test for TB in facilities without a mWRD

Sample processing and shipment

- Samples collected at peripheral facilities are shipped by riders to referral sites
- Sample packaging is performed by clinical personnel in facilities without onsite laboratory

xx Diagnostic gaps

Time

Patient presentation

Initial Screening and sample collection

Diagnosis

Patient treatment and management

GH+Labs

Diagnostic Landscape | Patients referred to higher-level facilities often do not make it there

Key challenges and proposed solutions for clinical workflow improvement

	Patient-related financial challenges	Staffing and personnel challenges at L1 & L2	Patient loss to follow-up from peripheral facilities	Waiting time at peripheral facilities
Challenge				
Proposed solutions	• Establish access to a POC molecular testing at lower-level facilities • This will reduce congestion at referral facilities	• There is need to increase the number and enhance retention of healthcare workers at peripheral facilities • Currently a clinician or a nurse is responsible for clinical services and general administrative services in the facility	• Build capacity for testing at L1 & L2 facilities • Increase the ratio of HCWs to patients	• The opening and closing times for facilities also affect services and clinical work • Most peripheral facilities start their clinical services late which affects the quality of service and waiting times for patients • There is need for enhanced administrative oversight for these facilities to ensure efficiency

> ***Patients generally have challenges (financial) such as lack of means for transport or bus fare and when they hear that they are being referred to a higher facility, they will lose hope***

> ***Out of the 90% of presumptive cases that are referred for TB testing at other facilities only 30% reach those facilities***

Product Value Proposition | Kenyan stakeholders see the advent of NAATOS as an opportunity to bridge the gap between clinical screening and laboratory diagnosis

Key takeaway

Contributors highlighted the critical need for presumptive cases to be tested with a molecular platform as a first test. There is significantly low coverage at lower-level facilities resulting in 40% of cases of being missed in the TB diagnosis and management cascade. NAATOS can become the primary TB diagnostic tool at L1 and L2 facilities.

Diagnostic gaps	Implications for NAATOS
Low coverage of TB diagnostic tools at lower-level facilities	• Stakeholders highlighted low coverage and a gap in access to molecular tests (access to a molecular tests is slightly above 50%) • They see NAATOS as an initial screening tool that can be used in conjunction with existing diagnostic platforms that can subsequently test for Rif-resistance
Delays in the TB Dx cascade	• In the interviews, there was concern about delays in transportation of specimens from lower-level facilities to referral sites as it contributes to longer turnaround times and delayed initiation of treatment for diagnosed cases • NAATOS is expected to bridge this gap and testing can be performed at first encounter with the patient
Shortage of testing commodities	• Commodity shortages experienced in the country are a major concern to all stakeholders • The greatest interruption in TB diagnostic services is due to the shortage of GeneXpert cartridges. TB is primarily tested through GeneXpert machines, which are mainly placed in L4, L5 and L6 facilities • The stakeholders expect NAATOS to be consistently available once introduced into the market
Reliance on Microscopy as a POC tool	• Stakeholders expressed the need for a molecular test to be deployed at lower-level facilities to increase case detection. The low sensitivity of microscopy means a significant number of cases are missed
Staffing constraints	• Stakeholders mentioned the challenge of personnel turnover at lower-level facilities, negatively impacting TB testing services • The Government is currently strengthening community health services through a team of community health promoters • NAATOS needs to be user-friendly and require minimal training in order to be used by community health workers

> ***"We still do not have a POC test, and we have been relying on microscopy which is not sensitive. If we can have a molecular rapid diagnostic test that can be used as a point of care, then this can actually help to bridge the gap that exists in that particular aspect"***

Product Specification | Stakeholders provided feedback on key considerations for NAATOS adoption (1/5)

Market Requirements	Current NAATOS Specifications	Notes on Stakeholders' Desired Specifications	Steps to Close Gap
Invalid rate	• NAATOS device-related failure for product feasibility must achieve a failure rate of <35%	• Current guidelines specify an error rate of <5% of total tests for the platforms in use and this is a key consideration for adoption	• Innovative approaches should be put in place to ensure stability of the device under varying conditions • These should target both manufacturing as well as implementation level
Walk away operation	• NAATOS V1 requires only two to three user interactions before walking away and returning to record the result (excluding sample prep)	• The feature of sample collection via swab is beneficial • Stakeholders expect further clarity on sample preparation procedures and reagent s involved and timing	• Once the platform is introduced user experience feedback should be sought to address any concerns • This is key for both pre analytical and analytical steps.
Time to result	• NAATOS V1 must produce a result within <60 min (including sample prep time)	• Stakeholders anticipate that time to result for NAATOS will be within 1 hour or less compared to the existing platforms • Stakeholders view NAATOS as a rapid test with expectation of rapid results	• Training of other non-laboratory cadres such as community health promoters to perform and interpret test accurately will be key • Post market follow up should be done to address challenges arsing on the workflow to enhance efficiency
Transportation	• NAATOS V1 must not require cold chain storage during shipment or storage	• Transportation of kits is the responsibility of Kenya Medical Supplies Agency • Transportation under refrigeration is available from privately contracted companies	• The packaging design should be able to withstand conditions and difficult terrains during transportation
Shelf life	• NAATOS V1 must have a shelf life of >12 months • (Corporate presentation: shelf life of >18 months from the date of manufacturing)	• The product should be 75% of the shelf life at the time of delivery in Kenya or in-country or at the warehouse • The quantities to be procured are dependent on forecasting and quantification done by the TB Program	• Liaison with the Program and Kenya Medical Supplies Agency is Key during procurement cycles

Product Specification | Stakeholders provided feedback on key considerations for NAATOS adoption (2/5)

Market Requirements	Current NAATOS Specifications	Notes on Stakeholders' Desired Specifications	Steps to Close Gap
Storage conditions	• NAATOS V1 must be stored at 0 °C to 40 °C and 90% humidity	• The temperatures are usually between 22-25 °C in the country • Majority of facilities with extreme temperature conditions have refrigerators for storage of reagents	• The aspect of storage of reagents should be discussed with the TB Program and other stakeholders during the adoption processes for readiness of facilities
Quality Control of Operation conditions	NAATOS V1 must operate at: – Temperature: +15 °C to +35 °C – Humidity: 25% to 80% relative humidity	• Some regions especially the Northern part of Kenya usually experience higher temperature 27-30°C • Rarely temperatures go below 14 °C	
Multiuse platform	• NAATOS V1 must be designed as a multi target disease platform (TB, STI, etc.)	• Multi disease testing is currently in place since the advent of COVID-19 particular for GeneXpert incorporating HIV, TB and cervical cancer • This feature is a key advantage for NAATOS	• GH Labs should strive to incorporate a wide range of diseases to be tested on NAATOS testing platform • Operational aspects should be discussed with implementing partners to maximise the benefit
Manufacturing	• NAATOS V1 must be manufactured at scale and with device fabrication and assembly process that is compatible with high-volume automation	• Key is to ensure a steady supply of the test kits at facilities to avoid shortages • The government is also encouraging and is advocating for local manufacturing of essential products	• Demand estimation for the commodity should be done to ensure commensurate manufacturing that will satisfy the need
Product price	NAATOS V1 must have a price of no more than $5 USD per test – At full production (10MM units/year) – At initial release, 3x full production (1MM units/year) – At pilot production, 10x full production (50k units/year)	• Stakeholders are hopeful that NAATOS will be an affordable test • The current inclusive cost for a molecular test is about $14 • It is expected that NAATOS will be $5 $2 $3, available at the lower facilities	• The cost of NAATOs should optimized considering all aspects including other costs incurred in the procurement , shipment and clearing costs that have impact on the cost per test

Product Specification | Stakeholders provided feedback on key considerations for NAATOS adoption (3/5)

Market Requirements	Current NAATOS Specifications	Notes on Stakeholders' Desired Specifications	Steps to Close Gap
Sample preparation steps	• The sample prep module must achieve target sample lysis (percent recovered)	• Stakeholders engaged technical laboratory TB testing highlighted challenges in sample Prep in the existing platform • Clarity in the timing for sample lysis	• Consideration for provision of sufficient sample prep reagents is key
Sample volume	• The sample prep module must deliver the appropriate sample volume • (Corporate presentation: 150 - 200µL)	• Some samples require more reagents for example some are more viscous than others • The elute can be stored for subsequent/repeat testing without having to ask the patient to produce another sample. The sample is also used to perform Rif testing	.
Sample volume measurement	• The sample prep module must not require training to successfully and repeatably dispense target volume on the user interface within a reasonable tolerance	*"If there is a way we could use the whole sample from the patient and then in the lab we can have elutes that concentrate the sample increasing the chances of detection"*	• An option for concentration of the sample can increase the chances of detection
Instrument design / amplicon contamination	• NAATOS V1 must prevent the escape of amplification products and not contaminate the testing area	*"The way the sample is being collected, this is a swab and there is a high chance of missing this bacillus if the patient has a low bacillary load"*	• Training and competency testing for technical personnel is key to minimize contamination
Data display	• NAATOS V1 must have a visual read out of the test result that can intuitively be interpreted	• Stakeholders indicated that the positive results form NAATOS can be classified further as either high, medium or low such that we can have a band for high medium or low • This will help us in terms of grading and to be able to know whether we are diagnosing the cases early or late • It may be fully quantitative but it can be semi quantitative	• Stakeholders expressed the need for a connectivity option for NAATOS to support data sharing
Safety	• NAATOS V1 must not pose a burn risk to the user during normal operation	• The feedback highlighted current concerns about safety with particular interest in waste generation for GTC. • Do the reagents have GTC?	

Product Specification | Stakeholders provided feedback on key considerations for NAATOS adoption (4/5)

Market Requirements	Current NAATOS Specifications	Notes on Stakeholders' Desired Specifications	Steps to Close Gap
Power module	• The power module must support the required daily throughput	• Majority of L1 & L2 facilities have power challenges • In some regions power supply can be interrupted for up to 24 hours • The power module for NAATOS is a key advantage embraced by all stakeholders	• Ensure stability of power modules supplied with NAATOS devices
Field Testing and Real-world Performance	• *Not defined by GH Labs*	• Stakeholders expect that that NAATOs devices will be stable under the testing conditions and various environments	
Consideration for Special Populations	• *Not defined by GH Labs*	• Stakeholders highlighted the need for clarity on the benefit of NAATOS for paediatric or children population	
Quality control	• *Not defined by GH Labs*	• Batch to batch testing is key to ensure that there are no problems with the kit and for NAATOS these can be provided to facilitate this process • Training and sensitization should be provided to build competency from staff carrying out these tests • The company should consider providing EQA material, that will be a plus	• For NAATOS consider a system in for internal controls
Sample preparation module design	• Random access a possibility • Can insert 1 to 4 samples at a time for extraction	• Stakeholders expressed concern about expiry of reagents. Some of the sample preparation packs that come with the reagents expire before some of the reagents are used • Part of the kits sometimes have different expiry dates and hence you cannot proceed with normal testing	• As much as possible sample packs should have fairly uniform expiry periods

Product Specification | Stakeholders provided feedback on key considerations for NAATOS adoption (5/5)

Market Requirements	Current NAATOS Specifications	Notes on Stakeholders' Desired Specifications	Steps to Close Gap
Sensitivity	• NAATOS V1 must have a clinical sensitivity ≥ 80%	• Sensitivity >80% needed for acceptance • Stakeholders emphasized the need for higher or sensitivity comparable to the existing platforms • Evidence on whether the test has been compared to any other that is currently being used in the country to determine if it is worthy of engaging in TB testing • Sensitivity for other interest groups/patient populations would be essential	• Support and encourage local evaluation studies to generate evidence and country level performance data
Specificity	• NAATOS V1 must have a clinical specificity ≥ 98%	• Specificity is a key consideration for the regulatory clearance for NAATOS • Specific level not specified	• N/A
Data Management	• *Not defined by GH Labs*	• For devices that do not have a connectivity module, the traditional way of capturing data from lab registers is done by the lab technician	• Consider integration of a connectivity option for NAATOS
Sample Type	• NAATOS V1 will utilize a dorsal tongue swab sample	• Non sputum samples will benefit groups such paediatric and PLHIV who have difficulty producing sputum	• N/A
Treatment monitoring capability	• NAATOS V1 will not provide drug sensitivity	*"I request that NAATOS should have an additional lateral flow such that when you have found a positive you can proceed to check for Rif resistance or any of the first line drugs that we use for Tuberculosis"* *"If it is not able to perform resistance pattern testing, then we can have it as an initial diagnosis just like we have microscopy and those who turn positive to go through other machines"*	• Stakeholders expressed the desire for NAATOS to detect Rif-resistance • However they suggested that NAATOS can be used for initial screening with follow-up testing on other platforms for Rif-resistance

1. Diagnostic Landscape
2. Stakeholder Feedback
3. **Policy Considerations**
4. Deployment Considerations

Policy Considerations | A process map emerged from the stakeholder feedback on the process for new TB diagnostic integration in the testing algorithm in Kenya (1/2)

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1

Verification of approval status for the new platform

- First of all, the TB Program will confirm that the testing platform is approved internationally by bodies such as the FDA or WHO before proceeding.

2

Engagement with local regulatory bodies

- The company will engage local regulatory bodies to initiate the registration processes for the product in the country. The key players in this include the Pharmacy and Poisons Board and Kenya Medical Laboratory and Technologists Board.
- These entities will verify the documentations related to the device and **carry out local validation/performance evaluation** supported by the company.

3

Discussion by the Diagnostic Committee of Experts (COE)

- Once approved by the regulatory bodies, at the program level, the **diagnostic committee of experts, a (COE)** is convened to discuss the next steps for introduction of the new platform. The committee will consider the recommendations of the regulatory bodies and other material including the sensitivity specificity and all these parameters.

4

Resource mobilization to support implementation

- The TB program takes the lead in mobilizing for resources to support the adoption process.
- At this stage the Program plans for procurement of kits and devices.
- Further the Program involves other key players including the **health sector working group** comprising of stakeholders who can then support this endeavour of resources mainly the USAID, Global Fund, and the Ministry of Health.

Policy Considerations | A process map emerged from the stakeholder feedback on the process for new TB diagnostic integration in the testing algorithm in Kenya (2/2)

5

Formal adoption of the testing platform by the Ministry of Health

- After the COE has synthesized the issue of adoption, the Kenya Coordination Mechanism becomes involved, with oversight led by the Permanent Secretary of the Ministry of Health for the adoption process.
- Once it has been adopted the next step is implementation.

6

Implementation

- Once the platform is recommended for adoption, the TB Program initiates the process for revision of tools to incorporate the new platform.
- **Facility mapping** for early implementation and scale up is conducted.

7

Procurement and installation

- Once the planning processes have been finalized, procurement of devices and kits is initiated.
- After procurement, other activities, such as placement installation and capacity building take place.
- Data collection is done at initial stages using the revised tools.

8

Data review and policy changes

- Once the implementation process is complete, the Program reviews the data, identifying and resolving issues that emerge with ongoing implementation.

> *"Is there any change? Is there a better timeline? Are we getting more cases? Therefore, the flow continues in terms of cycles"*

Policy Considerations | The main barriers to adoption highlight a need to involve all stakeholders in the introduction of a new diagnostic tool in order to maximize uptake

Barrier	Implication	Private sector considerations
1 Failure to engage regulatory bodies	• Initiating the marketing process without obtaining explicit authorization from the legal authorities in the country presents a significant challenge • The bodies need to carry out initial verification and validation for the new devices, and that may take time	• The private sector in Kenya is guided by the National guidelines disseminated by the TB program
2 Lack of engagement with other stakeholders	• All key stakeholders should be involved in the process of introducing the new diagnostic platform • When all stakeholders are not involved e.g., funders, resources may not be available to support rollouts to procure kits in the subsequent procurement cycle	• Private sector labs can be engaged the Public Private Mix initiative implemented by the NTP in Kenya
3 Inadequate capacity building	• The absence of effective capacity-building strategies poses a challenge when establishing a diagnostic capacity network that involves facility mapping for referrals • The implication is that the test does not pick up if you don't involve people in that area	• There is need to involve Private sector hospital personnel in rollout processes
4 Supply chain problems	• Early planning is needed to ensure timely and steady supply of commodities	• Private sector entities are not entirely dependent on the mainstream supply chain serving public facilities

> ***"If you don't fix your supply chain when rolling out these tools, it becomes a challenge also, you can have money, but your supply chain is weak or has a gap or you didn't identify then you are landing into that problem"***

1. Diagnostic landscape
2. Stakeholder feedback
3. Policy considerations
4. **Deployment considerations**

Deployment Considerations | Stakeholder feedback on further considerations for adoption and implementation of NAATOS in Kenya (1/2)

1 Clear plan/approach for data capture

- Stakeholders suggest the need for a clear plan or guidance for capturing data to align with the established Country data flow pattern

2 Maintenance and servicing plan

- There is need to establish a clear plan for servicing and maintenance or replacement of parts for damaged or malfunctioning devices
- Consider training personnel with higher level knowledge about the device to facilitate trouble shooting procedures at facility level

3 Device accessories

- Provide clear guidance on site-level requirements and device accessories needed for testing

4 Waste disposal and environmental impact

- The impact of reagents and device components in the environment is a key consideration
- Provide guidance on the type of waste generated and appropriate disposal methods

5 Capacity building

- Capacity building for utilization of the new platform is essential and this is usually achieved through manufacturer's training i.e., onsite and offsite training or through Trainer of Trainers (TOTs) approach
- Training sessions must incorporate practical sessions and competency testing, crucial for ensuring optimal testing at the facility level

Deployment Considerations | Stakeholder feedback on further considerations for adoption and implementation of NAATOS in Kenya (2/2)

6

Packaging requirements

- Packaging requirements for the kits should align with the guidance established by the Pharmacy and Poisons Board in Kenya usually required for all products

7

General stakeholder perception

- Stakeholders expressed the need for a molecular test for TB at the community level facilities

> ***"This will be a game changer for those cases that are missed from peripheral to referral facilities. We have a lot of cases where a patient has undergone 3 to 4 times but still turned negative but when a molecular is done it turns positive for TB"***

Nigeria

1. **Diagnostic landscape**
2. Stakeholder feedback
3. Policy considerations
4. Deployment considerations

Diagnostic Landscape | The National Tuberculosis & Leprosy Control Program (NTBLCP) coordinates Nigeria's TB prevention and control

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Key messages

1 **The public sector processes the largest proportion of TB diagnostics in Nigeria through the (NTBLCP) network of Laboratories across the country**

2 **95% of GX machines, TB LAMP & Truenat are in secondary and tertiary facilities, most level 1 facilities (PHCs) rely primarily on sputum smear microscopy or require sample transportation for TB diagnosis**

3 **There is consistent low TB case detection in Nigeria despite huge investments in expansion of both diagnosis and treatment services across the country**

Implications for NAATOS

- The provision of TB services is predominantly focused on the public sector, with limited insight into TB diagnosis practices within the vast majority of private-sector providers who are not currently engaged by the NTP. However, recent discussions have emerged regarding potential partnerships with the private sector through the PPM.
- NAATOS can partner with NTBLCP to strengthen private sector role in TB disease control.
- NAATOS is considered timely for decentralizing TB diagnostics to the patients in both sectors.

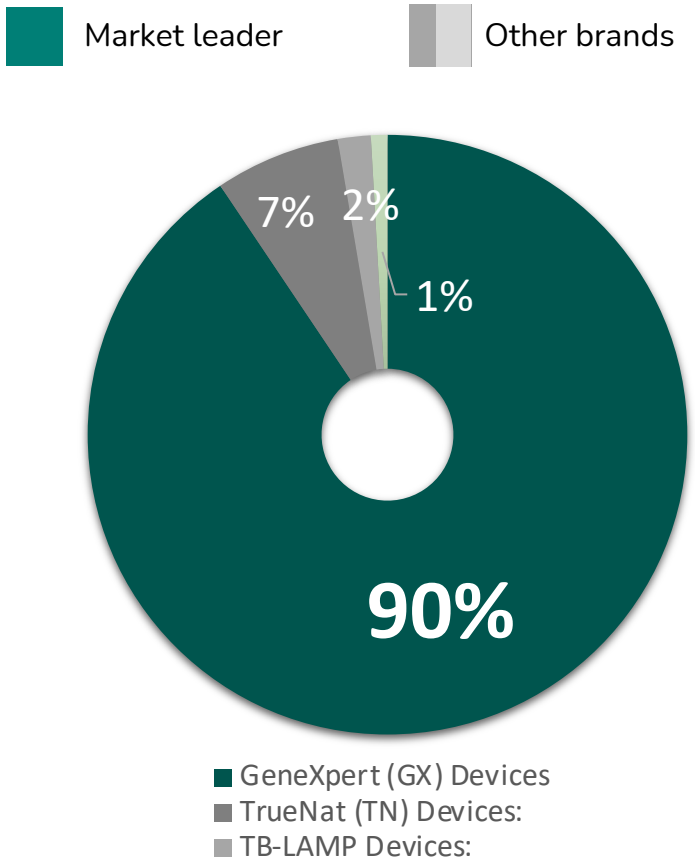
- Stakeholders shared how patients either have to travel a long distance to get tested or samples need to be transported to Labs with Gene Expert testing capacity when TB testing referral occurs. Decentralizing testing is imperative to improve TB diagnostics in remote and resource poor settings.
- Lack of infrastructure and trained personnel at L1 facilities has had a huge impact on TB testing emphasizing the need to adopt a POC test which can provide a result while patient is in clinic and needs minimal specialization.
- NAATOS as a POC device will be a welcome solution to L1 TB testing and should target unmet needs at L1 facilities.

> ***"It's wise to target L1 facilities, because that's where the most opportunity is and I would be more than happy to discuss with my executive director on piloting this in the country, if we get to that point."***

- Active case-finding interventions have been initiated to tackle the issue of low case detection, with the TB Case Detection Rate estimated to be very low, at around 30%.
- Stakeholders have expressed that a point-of-care (POC) device capable of screening from house to house would be highly beneficial for these interventions.
- NAATOS presents an opportunity to function as both a triage test and a screening tool within the current TB testing algorithm, thereby enhancing the efficiency and accuracy of TB diagnosis.

Diagnostic Landscape | The NTBLCP is eager to try new and improved technologies and platforms as a way to bridge gaps in diagnostic capacity

NTLBCP breakdown of TB devices by manufacturers (% of total)



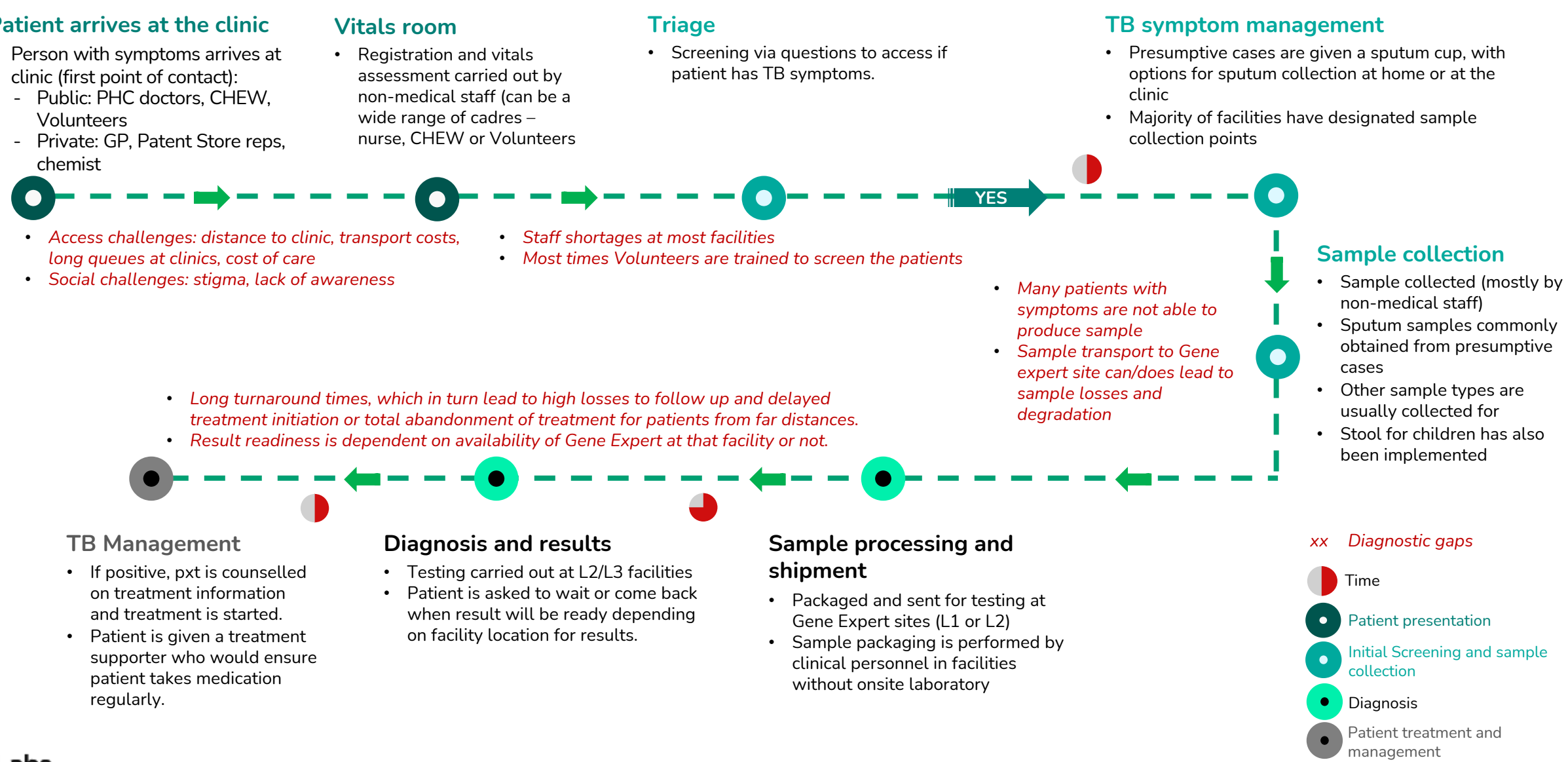
- The **GeneXpert serves as the primary TB diagnostic tool**, with 510 devices deployed across the TB network of labs.
- In line with the **NTBLCP's commitment to exploring new technologies**, in addition to the Gene Expert devices, they have introduced the Truenat system,and TB Lam.
- Although GeneXpert is designated as the mainstay of TB diagnosis in Nigeria, **only 54% of notified cases** in 2020 were diagnosed using GeneXpert due to **capacity constraints**. TB LAM is recommended for TB diagnosis in AHD and for severely-ill PLHIV.
- Clients have expressed **openness to new nucleic acid amplification test (NAAT) suppliers**, provided they can deliver comparable or superior quality to Cepheid.

> ***"The NTP is flexible with introducing new TB diagnostic tools as long as it helps bridge the gaps in the program."***

Diagnostic Landscape | There is a growing concern about the inequitable distribution of TB diagnostic services across sectors and levels of care in Nigeria

Trend and shifts	Description
1 Expansion of TB testing Algorithm	• There is a significant interest in testing platforms to tackle issues in the current systems, such as access gaps, low case identification, limited capacity, and infrastructure challenges. The NTBLCP demonstrates flexibility and eagerness to experiment with and adopt approved platforms as a strategy to address diagnostic gaps. • The exploration of opportunities to transition from passive to active case finding in primary healthcare (PHC) and community settings is underway.
2 Diversification of Dx Platforms	• The different new platforms offer advantages and supports diversification of the NTP diagnostic network which is one of the goals of the program. • The program recognizes that bridging gaps would need to go beyond just increasing the number of machines but must create a diversified and optimized laboratory network capable of leveraging the strengths of various tools to comprehensively meet the diagnostic needs of the population.
3 Growing need to explore Private sector potential	• While the country boasts a significant private sector for TB commodities, the market's size remains largely unknown outside of the Public-Private Mix (PPM) program. Notably, 66-92% of patients with respiratory symptoms and fever initially seek care in private settings. • Nigeria has a dynamic and expanding PPM Program, with participation surging from 627 clinical facilities in 2015 to 4,038 in 2020. Additionally, more than 23,600 non-clinical private providers, including labs and pharmacies, are actively engaged. • The specimen's easy workflow and the presence of a rechargeable battery make it a promising TB diagnostic tool, particularly for the private sector.

Diagnostic Landscape | The typical clinical workflow as outlined by stakeholders highlights diagnostic gaps



Diagnostic Landscape | Some challenges identified by stakeholders in the current workflow indicate a need for testing at the initial point of care (POC)

Challenges and proposed solutions for clinical workflow improvement

	Challenge	Proposed solutions
	Missed TB screening opportunities	• Explore community-based approaches for point-of-care testing to identify TB cases earlier • Reducing reliance on symptom screening questionnaire • Implement testing earlier in the patient flow at the clinic to optimize and reduce waiting times
	Challenges obtaining quality sputum and sample transportation	• Focusing on non-sputum sample types • Improve efficiency of sample referral network • Establish access to point of care molecular testing at lower-level facilities like NAATOS
	Extended TAT for results leading to loss in follow-up	• Implementation of testing at point-of-care in a way that ensures treatment is possible at same visit • Implement connectivity solutions with NAATOS for efficient data management systems • Increase administrative oversight for these facilities to ensure efficiency
	Human Resource & Infrastructure Limitation	• Increase number per facility and capacity building of volunteers and community Health workers • Focus on improving infrastructure limitations such as power, storage and testing capacity of most facilities for better outcomes

> *If there is a nucleic amplification point of care test, it will go a long way to improve our clinical workflow.*

> *The one problem in the level 1 and 2 facilities is human resources. With adequate manpower services would be provided better.*

1. Diagnostic landscape
2. **Stakeholder feedback**
3. Policy considerations
4. Deployment considerations

Product Value Proposition | Stakeholders have highlighted numerous favorable qualities of NAATOS, making it a compelling choice for adoption

Key takeaway

NAATOS offers the potential to function as both a preliminary assessment and a screening instrument, enhancing testing capabilities at L1 facilities where there is minimal current testing. Presently, patient samples from L1 facilities are transferred to more sophisticated settings (L2 & L3) for diagnosis with existing TB diagnostic tools, largely due to their requirements for specific storage, temperature, and power infrastructure, among other factors.

Stakeholder feedback on NAATOS value proposition

Affordable Solutions	• Stakeholders expressed a strong interest in an affordable, and easy-to-use diagnostic solutions. • The country relies heavily on external support (USAID, Global Fund) for TB diagnosis and management, with current funding falling short for ample commodity procurement. • NAATOS being a POCT is viewed as a significant innovation in the TB program.
Favourable view of NAATOS for L1 Facilities	• The perception is that NAATOS will bridge major gaps in the TB diagnostic landscape by affording testing at L1 facilities. • Patient samples are collected and sent to more advanced settings(L2 & L3) for diagnosis using the existing TB diagnostic tools as most of them require some storage, temperature and power infrastructure amongst other things.
Challenging Traditional Testing Approaches	• There's a clear necessity to move beyond conventional testing methods and adopt more proactive approaches. The importance of rapidly deploying NAATOS as a mobile DNA-based diagnostic tool connected to care is underscored. • This transition is seen as a community-focused strategy to disrupt transmission, tackling the unrealistic timelines linked with traditional testing models.
Impact on TB Contact Tracing Programs	• The single fact that the NAATOS device can easily be moved to resource limited setting is another game changer for contact tracing, reducing logistical challenges in storing and moving samples collected at L1 facilities. • Stakeholders expressed a strong interest in the device stating that it could also be used in congregate settings such as schools, prisons and other key populations.

Product Specification | Stakeholders provided feedback on key considerations for NAATOS adoption (1/5)

Market Requirements	Current NAATOS Specifications	Notes on Stakeholders' Desired Specifications	Steps to Close Gap
Invalid rate	• NAATOS device-related failure for product feasibility must achieve a failure rate of <35%	• Current guidelines specify an error rate of <5% of total tests for the platforms in use and this is a key consideration for adoption	• Innovative approaches should be put in place to ensure stability of the device under varying conditions • These should target both manufacturing as well as implementation level
Walk away operation	• NAATOS V1 requires only two to three user interactions before walking away and returning to record the result (excluding sample prep)	• User-friendly testing process • Integration of sample preparation and testing phases into a streamlined system • The point of care element will help avoid sample mismatch.	• Prototypes testing into the hands of end users as early as possible • Usability & acceptability studies are key • Consider the clinic facilities the system will be in • Consider the users are nurses or paraprofessionals
Time to result	• NAATOS V1 must produce a result within <60 min (including sample prep time)	• Ideal: 30-minute test • Minimal: 60-minute test • If the test results take longer, there is a risk that the patients might leave and not return for the treatment • Patients from resource poor settings typically travel miles to get to testing sites, a fast TAT can ensure that treatment starts same day reducing the possibility of patients abandoning the treatment.	• Strong implementation and algorithm guidance to support earlier testing in the patient's clinic journey, ensuring that test & treatment takes place in same visit • Modular concerns may be overcome through feasibility and ease-of-use studies • Start test as soon as the clients arrive at the clinic
Transportation	• NAATOS V1 must not require cold chain storage during shipment or storage	• Ambient temperature conditions • Mobility of device is a major advantage that would be considered • The device will negate the need for specimen transportation as it is a point of care device	• Build in portable carry bags into the packaging
Shelf life	• NAATOS V1 must have a shelf life of >12 months • (Corporate presentation: shelf life of >18 months from the date of manufacturing)	• Ideal: 24 months • Acceptable: 18 months • NTBLCP operates a quarterly resupply exercise. • Cost of shipping is costly to rural areas, so frequency of shipping is low	• Factor in delay time at the ports and time to deliver to remote locations when designing shelf life

Product Specification | Stakeholders provided feedback on key considerations for NAATOS adoption (2/5)

Market Requirements	Current NAATOS Specifications	Notes on Stakeholders' Desired Specifications	Steps to Close Gap
Storage conditions	• NAATOS V1 must be stored at 0 °C to 40 °C and 90% humidity	• Temperature ideally should be within 2-25 degrees Celsius but being able to stay up to 40 degrees is a major win for NAATOS • Humidity levels can be high in Northern Nigeria and the specifications seem perfect for Nigeria • Fridges for reagent storage can be a problem in the smaller L1 facilities, in fact they barely have any storage capacity in most of them	• Data to determine how long kits can go beyond 40°C
Operating environment, temperature and humidity level	NAATOS V1 must operate at: – Temperature: +15 °C to +35 °C – Humidity: 25% to 80% relative humidity	• Stakeholders were pretty impressed with operating temperature and wondered if operating temperature could be as high as 50 degrees • Humidity levels can be high in most states in Northern Nigeria.	• Look at design to ensure that WHO TPP minimal standards can be met
Multiuse platform	• NAATOS V1 must be designed as a multi target disease platform (TB, STI, etc.)	• Value in addressing prevalent health concerns beyond the primary focus (e.g., bacterial STIs, HIV viral load, and drug resistance detection) • Stakeholders shared that a multi-disease platform would be most welcome and that private sector practitioners had a preference for multi-disease platforms.	• Adoption decision more attractive by providing a comprehensive solution to diverse healthcare needs, matching the patient journey
Manufacturing	• NAATOS V1 must be manufactured at scale and with device fabrication and assembly process that is compatible with high-volume automation	• Scale is important alongside local manufacturing partners to be developed • Driven by Africa CDC and the Africa Collaborative Initiative	• Look at possible kit assembly solutions within Africa to support the initiative.
Product price	NAATOS V1 must have a price of no more than $5 USD per test – At full production (10MM units/year) – At initial release, 3x full production (1MM units/year) – At pilot production, 10x full production (50k units/year)	• Respondents express a desire for a low-cost test (with suggested price points ranging from $2 to $5) • The TB program is free to patients but the cost of other factors like sample transportation add the cost of the program so it is important to consider all such cost when pricing but hopefully, transportation would not be a part of the pricing cost for NAATOS seeing as it is a point of care device.	• Definition of an "affordable" or "cost-effective" TB test goes beyond the test's individual price • Consider broader economic factors • Consider overall test cost, feasibility • Consider cost of community deployment • Overall cost-effectiveness involves considering the entire testing algorithm and implementation factors

Product Specification | Stakeholders provided feedback on key considerations for NAATOS adoption (3/5)

Market Requirements	Current NAATOS Specifications	Notes on Stakeholders' Desired Specifications	Steps to Close Gap
Sample preparation steps	• The sample prep module must achieve target sample lysis (percent recovered)	• There should be no manual sample purification • Most stakeholders were fine with the sample preparation model we shared with them. • Stakeholders were interested to know how they would label samples individually when running four samples at the same time.	• Build in means to label sample preparation tubes when working with all 4 samples at a time.
Sample volume	• The sample prep module must deliver the appropriate sample volume • (Corporate presentation: 150 - 200µL)	• Stakeholders were comfortable with following the package insert instructions on volume to be used.	• N/A
Sample volume measurement	• The sample prep module must not require training to successfully and repeatably dispense target volume on the user interface within a reasonable tolerance	• Stakeholders were comfortable with following the package insert instructions on volume to be used.	N/A
Instrument design / amplicon contamination	• NAATOS V1 must prevent the escape of amplification products and not contaminate the testing area	• Stakeholders were comfortable with the sample preparation model	N/A
Data display	• NAATOS V1 must have a visual read out of the test result that can intuitively be interpreted	• Stakeholders felt really assured based on the dual control line for result read-out. • Connectivity of results will also be critical to support result report & meet the standards of data centralization	We need to produce ways for result connectivity
Safety	• NAATOS V1 must not pose a burn risk to the user during normal operation	Users should not be able to remove the tube from the sample prep module earlier than the required incubation period for: – Optimal lysis – Prevention of burning	N/A

Product Specification | Stakeholders provided feedback on key considerations for NAATOS adoption (4/5)

Market Requirements	Current NAATOS Specifications	Notes on Stakeholders' Desired Specifications	Steps to Close Gap
Power module	• The power module must support the required daily throughput	• Most facilities have power challenges and this would really help • Ensure continuous operation with rechargeable batteries. Full charge should ideally support 8 hours operation time.	• N/A
Field Testing and Real-world Performance	• *Not defined by GHL*	• Stakeholders showed huge interests in NAATOS as a point of care device that would be ideal for Case Finding, contact tracing, testing in congregate settings such as schools, resource limited settings.	• Set up pilot programs to show the potential .
Consideration for Special Populations	• *Not defined by GHL*	• Presumptive TB patients in rural areas • PLHIV where TB-LAM is missing • Communities without Laboratories or storage facilities. • Children • High Burden facilities	• Generate performance data with these population groups vs. current standard of care, i.e. Xpert Ultra all populations & TB-LAM for PLHIV
Quality control	• *Not defined by GHL*	• Batch to batch testing is key to ensure that there are no problems with the kit and for NAATOS these can be provided to facilitate this process • Training and sensitization should be provided to build competency from staff carrying out these tests. • The company should consider providing EQA material, that will be a plus.	• N/A
Sample preparation module design	Confirm with GHL: – Random access not possible? – Can insert 1 to 4 samples at a time for extraction.	• Concern raised regarding four places for the sample prep tube in the device because the natural tendency for people is to wait until they have sufficient samples for an entire run • Risks of undermining key value proposition • WHO TPP: multiple samples should be able to be tested at the same time; random access should be possible	• Prototype usability & behaviour studies to help shape training material, overcomes batching tendencies and maximise utilisation of random-access features

Product Specification | Stakeholders provided feedback on key considerations for NAATOS adoption (5/5)

Market Requirements	Current NAATOS Specifications	Notes on Stakeholders' Desired Specifications	Steps to Close Gap
Sensitivity	• NAATOS V1 must have a clinical sensitivity ≥ 80%	Varying responses from interviews • Sensitivity is a major priority for the TB programme • Should meet or exceed the accuracy of existing methods • Major requirement for every single stakeholder we engaged	• Support & encourage local evaluation studies to generate evidence and country level performance data.
Specificity	• NAATOS V1 must have a clinical specificity ≥ 98%	• A high specificity (≥ 95%) is considered essential • Was also a major requirement from stakeholders as a pre-requisite to be considered in the program.	• N/A
Data Management	• Confirm with GHL: • Is connectivity available?	• Currently, only the Gene Expert has a data system called the Aspect Report and the program is trying to see if they can leverage it for the other TB diagnostic tools. • Currently, they manually collate information using registers and use WhatsApp to send results. PHC-LGA-STATE-NATIONAL	*Explore with GHL*
Sample Type	• NAATOS V1 will utilize a dorsal tongue swab sample	• Stakeholders were excited about the specimen sample type for the NAATOS device as they historically experience issues with sputum specimen production with some patients and this is a very welcome development. • However, there was concern that after a simple tongue swab, if the patient was positive , the patient would still need to produce a sputum sample to ascertain TB resistance.	• N/A
Treatment monitoring capability	• NAATOS V1 will not provide drug sensitivity	• As much as stakeholders appreciated the technique, the limitation in identifying the TB strain was a big concern. However, they felt positioning NAATOS as a point of care/field testing device had advantages that outweighed the former.	• Positioning of NAATOS into algorithm for settings where Xpert cannot go. Triage, community screening settings, and clinic level screening

1. Diagnostic landscape
2. Stakeholder feedback
3. **Policy considerations**
4. Deployment considerations

Policy Considerations | Stakeholders have emphasized critical policy enablers for the implementation of a new TB NAAT test

1

Performance and Affordability

- Stakeholders have repeatedly emphasized the critical need for the nucleic acid lateral flow assay to deliver results in under an hour. They stress the importance of the test being easily accessible and located near patients, cost-effective, and user-friendly. Moreover, there is a strong focus on ensuring that the test possesses high sensitivity and fully aligns with the World Health Organization's Target Product Profiles (TPPs), meeting global health standards.

2

Alignment with Guidelines and Feasibility

- Adhering to NTLBCP guidelines is key for public sector market access, as they are a top priority and known for strict operations. Additionally, it's important to consider how the new test fits into existing testing methods, manage changes in sputum collection and drug sensitivity, and improve usability.

> ***It is essential to have the buy-in of the national TB program. It is advisable to start with them before discussing with anyone else.***

3

Considerations for Implementation and Patient Flow Integration

Stakeholders have emphasized the significance of assessing how the new test will impact work processes, particularly in busy environments. Key considerations for implementing the test include:

- Evaluate the impact of the test on workflow in busy settings.
- Determine the responsible party for administering the test.
- Ensure the test is user-friendly for all staff.
- Integrate the test into patient care routines efficiently.
- Prevent patients from leaving before treatment.
- Seamlessly incorporate the test into the existing testing process.
- Consider the special needs of specific groups, such as young children.

Policy Considerations | To attain NTP endorsement for the adoption of a new diagnostic tool, certain steps need to be followed

Policy process step	TB
1 National policy endorsement	• WHO GDG endorsement is a precondition for adoption by the NTP. No additional local field studies are required for policy endorsement.
2 Technical Review by NTP	• Technical Review: NTP-led workshop to present evidence for test adoption. Local clinical and lab validation studies are not required if similar studies have been conducted in other countries. • During meeting, an implementation roadmap will be developed which is then sent to the Minister of Health recommending national adoption of the device. • Once approval is granted, the country can begin to implement the roadmap.
3 Product Registration	• Diagnostic devices introduced by the NTBLCP for public sector use do not require a formal registration process with the NAFDAC or MLSCN, except when sales in private sector is envisioned then registration and validation with the Medical Laboratory Science Council of Nigeria (MLSCN) is a must. • NTBLCP and partners (NGOs, PPM facilities etc.) may apply for a special approval and import authorization for Dx devices without having to undergo the usual registration process.
4 Policy/toolkit revision and country planning	• National algorithms and toolkits are updated (e.g., SOP, guidelines, training manual). The program also defines role/placement of device in the broader network. • Implementation roadmaps and updated tools integrated into existing program implementation systems. Activities include quantification and supply planning, budget planning, procurement via GDF, integration into systems (e.g., connectivity, maintenance, warehousing, QA).
5 Phased Implementation	• Phase 1 implementation: Controlled implementation in select sites is required to produce local data that guides the national rollout. Often supported by partners, pilots create buy-in and awareness. Specific study elements determined by NTBLCP/technical partners. Pilots may last 3-6 months. • National roll-out: Findings of pilot shared with stakeholders; revisions (if applicable) are made to roadmap, national diagnostic plan, positioning, guidelines, algorithm or tools before rollout begins.

Policy Adoption | Stakeholders are crucial for new diagnostic tool adoption, providing technical and financial support

Stakeholders	Why are they important?
National Tuberculosis and Leprosy Control Program (NTBLCP)	Critical decision-maker and gate-keeper
Global Fund	Provides majority of TB funding and significant amount of HIV funding in country ($26M for TB and 15% of total HIV budget in 2020)
US Government (PEPFAR, USAID, CDC, DOD)	Major funder (PEPFAR funds 67% of the total HIV budget. Also, the USAID TB budget for Nigeria was $13M in 2020)
CHAI	Supporting implementation and laboratory strengthening for Advanced HIV Disease
FIND	Key player in supporting uptake and appropriate use of diagnostics to achieve health impact at global level. Limited in-country engagement in Nigeria
WHO and Global TB Program	Key TB policy decisions such as whether to adopt new Dx tools, which algorithms to implement, etc., are very heavily influenced by what WHO dictates at a global level. WHO Nigeria provides technical assistance and support for national policy updates
Institute of Human Virology Nigeria (IHVN)	Co-Principal Recipient (PR) of one of Nigeria's GF TB Grant, works closely with NTBLCP on TB programme management, & involved in decision making for budgeting and expenditure
KNCV	Key Opinion Leader, has been instrumental in Nigeria's adoption and use of new diagnostic tools including GeneXpert, TB-LAM and Truenat. They are also the in-country partner for Cepheid
National Agency for Food & Drug Administration and Control (NAFDAC)	National Regulatory Agency responsible for registration of novel diagnostic devices or granting approval for registration waivers
Stop TB Partnership Nigeria	A multi-stakeholder partnership drawn from the public, civil society and private sectors committed to ending TB in Nigeria. Hosts the annual National TB conference

1. Diagnostic landscape
2. Stakeholder feedback
3. Policy considerations
4. **Deployment considerations**

Deployment Considerations | Recommendations and best practices for streamlined product adoption

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1 **Key Stakeholder Engagement**

Identify the key stakeholders, especially the NTBLCP and guideline committees as well as other major players in the Nigerian TB space and engage them early in the process. Understand their needs and expectations.

2 **Provide Key Research Studies**

Stakeholders shared the importance of providing research papers speaking or comparing NAATOS with the current diagnostic platforms.

3 **Cost Analysis**

Stakeholders also shared that it would be good to have a cost analysis, in order to understand how expensive it would be to roll out such a test.

4 **Finding Strong Local Partners**

It is imperative that NAATOS gets a good local partner and distributor to promote advocacy among key groups and raise awareness and garner backing. Organize thorough training programs to guarantee that laboratory personnel and clinicians are well-informed about the tool's advantages.

> ***It is essential to have the buy-in of the national TB program. It is advisable to start with them before discussing with anyone else. It is important to standardize the number of sites that would be using the device. It would also be essential to involve the TB program Q&A officers in each state, as they focus primarily on TB diagnostics.***

South Africa

1. **Diagnostic landscape**
2. Stakeholder feedback
3. Policy considerations
4. Deployment considerations

Diagnostic Landscape | The majority of TB testing is provided through a network of NHLS-run labs and limited POC testing with TB-LAM

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Key messages

1 The public sector is the main provider of TB testing, with testing centralized around NHLS labs

Implications for NAATOS

- **Public sector processes largest proportion of TB diagnostics (>90%)** and testing in private sector is limited. **Majority of the TB testing is centralized** around 223 NHLS labs servicing 4710 health facilities. TB-LAM testing is performed at Point of Care (POC) for PLHIV.
- **NAATOS is considered timely** for decentralizing TB diagnostics closer to the patient.

2 The current diagnostic algorithm and design is fraught with challenges that lead to delays and loss to follow up

- Stakeholders shared how patients can be sent away with a sputum bottle for early morning collection and referred to more centralized TB clinics for treatment. **Decentralizing testing is critical to overcome loss to follow up (LTFU)**.
- The current focus on symptom screening and therefore **late-stage disease detection raises concerns about missing earlier infections**. Introducing **TB screening tools at an earlier stage is imperative** for preventing the spread of TB in communities.
- **Power outages** may impact testing timelines off-site **emphasizing the need to adopt a POC test** which can provide a result while patient is in clinic.

3 NAATOS has a role to play within the current algorithm

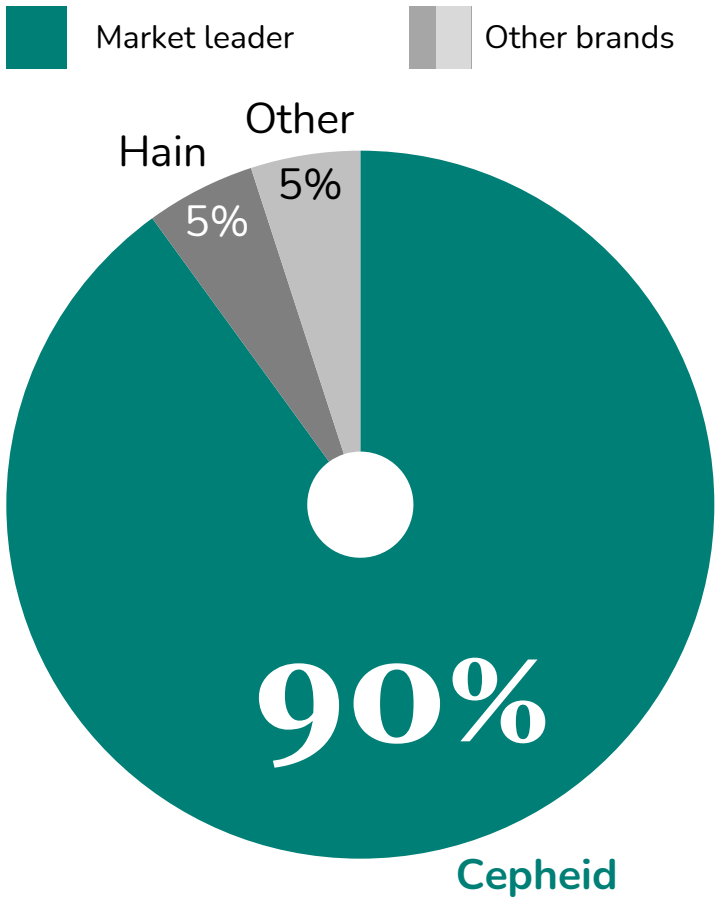
- There is a migration towards the **Targeted Universal Test & Treat (TUTT) algorithm** as it has resulted in a **17% net increase in diagnosed TB cases** per clinic per month.
- NAATOS presents an opportunity to serve as **both a triage test and a screening tool** within the Targeted Universal Test & Treat (TUTT) algorithm, enhancing the efficiency and accuracy of TB diagnosis.

Diagnostic Landscape | The shift to new technologies is driven by several emerging trends

Trend and shifts	Description
1 Dominance of GeneXpert 	• GeneXpert Ultra is the initial test for TB. It replaced the old, much slower method of diagnosing TB using microscopy around a decade ago. • The new GeneXpert XDR-TB tests, which can detect resistance to isoniazid, the fluoroquinolones, ethionamide, and some injectable medicines is being rolled out, but on a limited basis.
2 New Technologies 	• Becton Dickinson (BDMAX) Medium volume labs and Roche High volume labs are in the process of being implemented in the country and will replace GeneXpert. • Becton Dickinson (BDMAX) Medium volume labs will replace the GX 16, and Roche High volume labs will replace GX 80. • Digital X-rays with AI capabilities are in use in 12 high burden districts and are supported by the Global Fund. • XDR cartridge has been introduced for DR-TB patients and it has replaced LPA 1st and 2nd. In addition to RIF, INH resistance can also be tested for simultaneously.
3 Product Shortages 	• During the height of the C-19 pandemic, there were global shortage of Xpert cartridges by Cepheid and MGIT by BD. To manage this supply shortage, samples were re-directed to key higher volumes sites to ensure continuity of testing. • Foreign exchange fluctuations were some of the financial implications to multi-national companies which also contributed to accessing diagnostics often resulting in supply chain lapses.
4 Pricing 	• 80% of the national TB program is funded through Treasury. There are no costs to patients in public sector. – GeneXpert ULTRA ± $14 – GenXpert XDR ± $26 – Microscopy ±$4

Diagnostic Landscape | The era of the Cepheid monopoly is reaching a turning point, presenting an opportunity for new market entrants

NHLS breakdown of TB test by manufacturers, % of total



Important considerations

- TB testing is provided in the public sector through NHLS, and it is mostly a centralized system. NHLS has **223 TB diagnostic labs serving 4,710 health facilities**.
- The GeneXpert is the primary device used in for TB testing with a total of 325 analysers available (based on 2019 data). While private sector TB testing is limited, GeneXpert remains the dominant platform even in private sector.
- **On-going supply constraints** have severely damaged the Cepheid brand and market confidence. **Assay performance issues** as well as **polyresistant TB** further highlight limitations of Cepheid.
- Clients have indicated that they are **open to new NAAT suppliers** as long as they can provide the same/higher quality compared to Cepheid.
- Until now Cepheid has won 100% of all the tender from NHLS public tender. Last year, Cepheid won the low, BD won the medium throughput testing sites, while **Roche won the high throughput sites**.
- **TB LAM introduced in 1030 sites across 9 provinces**.

> We need to be testing regardless of symptoms. We are struggling to find people with TB to link them and retain them in care. To deal with TB we need to be looking at how many did we miss, [and] what if we had found them, and treat[ed] them. We need to find them all.

Source: Market research

Diagnostic Landscape | Screening gaps lead to misdiagnosis, with nurses attributing symptoms to conditions like a common cold

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Patient arrival at clinic
- Goes through queueing system
- Proceeds to reception for file collection and creation

Vital Room
- Patient moves to Vital room for recording of vitals and creation of patient record

Triage
- Assess whether patient has TB symptoms through 5 symptom questionnaire
- TUTT for PLHIV, close contacts, previous Rx in 2 years

TB symptom management
- Patients with TB symptoms given a sputum cup, with options for sputum collection at home or at the clinic

YES

Missed opportunity for patients to be screened TB, leading to no treatment initiation and onward community transmission

Challenges with sputum collection in key populations

Sample collection
- Different samples types collected (PPD skin test for children under 5, Sputum for GeneXpert, Gastric lavage, etc.)

<5% Clinics have on-site TB laboratories. Risk of sample degradation during transport

Sample submission and diagnosis
- Samples collected. Can be rejected post-receipt at the discretion of NHLS

Delays often observed from the time sample collection to reporting patient results. This results in loss to follow up

Diagnosis and results
- NHLS TB results available within 72 hours of sample collection
- SMS from NHLS to clinic with TB result

Long lead time from when doctor receives results to when patient is initiated on treatment

TB Management
- If positive, initiate Drug Sensitive TB Rx
- If RIF resistant initiated Drug Resistant TB Rx
- If neg, investigate further

xx Diagnostic gaps

Time

Patient presentation

Initial Screening and sample collection

Diagnosis

Patient treatment and management

GH+Labs

Diagnostic Landscape | Time to initiation onto TB treatment hinders proper follow-up, emphasizing the need for improved diagnostic strategies

Challenges and proposed solutions for Clinical Workflow Improvement

	Missed TB screening opportunities	Poor quality sputum collection and sample transportation	Delays resulting in loss to follow-up	Long lead time between results and treatment
Challenge				
Proposed solutions	• Explore community-based approaches for point-of-care testing to identify TB cases earlier • Reducing reliance on symptom screening questionnaire • Implement testing earlier in the patient flow at the clinic to optimize and reduce waiting times	• Focusing on non-sputum sample types • There's a need for integrated services into HIV clinics and general primary health clinics which should then include next-to-patient diagnostics and treatment	• Implementation of testing at point-of-care in a way that ensures treatment is possible at same visit. • Implement connectivity solutions with NAATOS for efficient data management systems	• The busy clinic workflow needs mechanisms to track and ensure follow-up activities, including confirmatory testing or immediate initiation of TB treatment, are conducted efficiently

1. Diagnostic landscape
2. **Stakeholder feedback**
3. Policy considerations
4. Deployment considerations

Product Value Proposition | Stakeholders expressed several positive attributes of NAATOS that makes it an attractive option for adoption

Key takeaway

NAATOS presents an opportunity to serve as both a triage test and a screening tool within the Targeted Universal Test & Treat (TUTT) algorithm, enhancing the efficiency and accuracy of TB diagnosis.

In alignment with South Africa's move towards TUTT, specimen collection for TB testing targets various groups, including those with TB symptoms, close contacts of recent TB cases, individuals with a history of completed TB treatment in the past two years, and newly diagnosed People Living with HIV (PLHIV), irrespective of symptoms.

Stakeholder feedback on NAATOS value proposition

Patient-Centric and Affordable Solutions	• Stakeholders express a strong interest in patient-centric, affordable, and easy-to-use diagnostic solutions. • The envisaged Nucleic Acid Lateral Flow Test for TB aligns with this vision, providing a closer-to-patient, cost-effective, and user-friendly option that could significantly benefit the community in terms of decentralized and democratised accessibility as well as time efficiency.
Positive Perception of NAATOS at L1 Facilities	• The feedback underscores a positive perception of Nucleic Acid Lateral Flow Tests (NAATOS) at L1 facilities. Stakeholders view them as well-understood, easy to introduce, and straightforward in implementation. • The familiarity and feasibility of lateral flow tests, coupled with their adaptability to clinic workflows, contribute to the optimistic outlook on NAATOS adoption.
Challenging Traditional Testing Approaches	• There is a recognized need to challenge traditional testing approaches and embrace more proactive strategies. The urgency of implementing NAATOS as a portable DNA-based diagnostic tool, linked to care, is emphasized. • This shift is positioned as a community-oriented approach to interrupting transmission, addressing the impractical timelines associated with conventional testing paradigms.
Integration into TUTT Algorithm and Generalist Clinical Care	• Stakeholders envision NAATOS as a triage test and screening tool within the Targeted Universal Test & Treat (TUTT) algorithm. • Beyond TB clinics, the test is seen as adaptable to routine generalist clinical care, offering scenarios like routine tongue swabs upon clinic entry, thereby capturing more TB clients lost through low-sensitivity of the 5-symptom screening method. The flexibility of integration, especially with HIV care, is emphasized, aligning with the need for solutions beyond traditional TB algorithms.
Impact on TB Contact Testing Programs	• By simplifying sample collection, particularly among high-risk groups and household contacts, NAATOS is viewed as a potential game-changer in increasing TB diagnoses. This aligns with the broader goal of enhancing community-based testing and improving outcomes within high-risk communities.

Product Specification | Stakeholders provided feedback on key considerations for NAATOS adoption (1/5)

Market Requirements	Current NAATOS Specifications	Notes on Stakeholders' Desired Specifications	Steps to Close Gap
Invalid rate	• NAATOS device-related failure for product feasibility must achieve a failure rate of <35%	• Invalid rates of <15% more palatable early on in launch, but should ideally be <2%	• Cost of replacing failed cartridges will need to be factored into total cost benefit
Walk away operation	• NAATOS V1 requires only two to three user interactions before walking away and returning to record the result (excluding sample prep)	• User-friendly testing process • Integration of sample preparation and testing phases into a streamlined system • Consolidation of sample preparation module and heat module - the user shouldn't have to do anything else after adding the swab to the sample preparation tube	• Prototypes testing into the hands of end users as early as possible • Usability & acceptability studies are key • Consider the clinic facilities the system will be in • Consider the users are nurses or paraprofessionals
Time to result	• NAATOS V1 must produce a result within <60 min (including sample prep time)	• Ideal: 15-minute test • Minimal: 60-minute test • If the test results take longer, there is a risk that the clients might leave and not return for the treatment • .Clients will be at the clinic for 1.5 – 2 hours at a minimum, waiting in queues, but a nurse may only have 15 minutes with the client	• Strong implementation and algorithm guidance to support earlier testing in the patient's clinic journey, ensuring that test & treatment takes place in same visit • Modular concerns may be overcome through feasibility and ease-of-use studies • Start test as soon as the clients arrive at the clinic
Transportation	• NAATOS V1 must not require cold chain storage during shipment or storage	• Ambient temperature conditions • Transportation without refrigeration • There is an increase in MoH's demand for test kit delivery directly to Level 1 facilities	• N/A
Shelf life	• NAATOS V1 must have a shelf life of >12 months • (Corporate presentation: shelf life of >18 months from the date of manufacturing)	• Ideal: 18 months • Acceptable: 12 months • Procurement patterns test kits can be 2-3 times per year • Cost of shipping is costly to rural areas, so frequency of shipping is low	• N/A

Product Specification | Stakeholders provided feedback on key considerations for NAATOS adoption (2/5)

Market Requirements	Current NAATOS Specifications	Notes on Stakeholders' Desired Specifications	Steps to Close Gap
Storage conditions	• NAATOS V1 must be stored at 0 °C to 40 °C and 90% humidity	• Temperatures rarely exceed 45°C • Humidity levels can be high in places like Durban • Fridges for reagent storage can be a problem in the smaller L1 facilities, and scheduled power outages in larger facilities pose a risk	• Data to determine how long kits can go beyond 40°C
Operating environment, temperature and humidity level	NAATOS V1 must operate at: – Temperature: +15 °C to +35 °C – Humidity: 25% to 80% relative humidity	• Temperatures rarely exceed 45°C, and winter mornings can be as low as 4°C within the clinics • Humidity levels can be high in places like Durban • Fridges for reagent storage can be a problem in the smaller L1 facilities, and scheduled power outages in larger facilities pose a risk	• Look at design to ensure that WHO TPP minimal standards can be met
Multiuse platform	• NAATOS V1 must be designed as a multi target disease platform (TB, STI, etc.)	• Value in addressing prevalent health concerns beyond the primary focus (e.g., bacterial STIs, HIV viral load, and drug resistance detection)	• Adoption decision more attractive by providing a comprehensive solution to diverse healthcare needs, matching the patient journey
Manufacturing	• NAATOS V1 must be manufactured at scale and with device fabrication and assembly process that is compatible with high-volume automation	• Scale is important alongside local manufacturing partners to be developed • Driven by Africa CDC and the Africa Collaborative Initiative	• Look at possible kit assembly solutions within Africa to support the initiative.
Product price	NAATOS V1 must have a price of no more than $5 USD per test – At full production (10MM units/year) – At initial release, 3x full production (1MM units/year) – At pilot production, 10x full production (50k units/year)	• Respondents express a desire for a low-cost test (with suggested price points ranging from $2 to $5)	• Definition of an "affordable" or "cost-effective" TB test goes beyond the test's individual price • Consider broader economic factors • Consider overall test cost, feasibility • Consider cost of community deployment • Overall cost-effectiveness involves considering the entire testing algorithm and implementation factors

Product Specification | Stakeholders provided feedback on key considerations for NAATOS adoption (3/5)

Market Requirements	Current NAATOS Specifications	Notes on Stakeholders' Desired Specifications	Steps to Close Gap
Sample preparation steps	• The sample prep module must achieve target sample lysis (percent recovered)	• There should be no manual sample purification	• Pathogen enrichment (concentration) step could improve sensitivity vs direct measurement/ testing a little volume of extracted swab solution
Sample volume	• The sample prep module must deliver the appropriate sample volume • (Corporate presentation: 150 - 200µL)	• Pathogen enrichment (concentration) step could improve sensitivity vs direct measurement/ testing a little volume of extracted swab solution • No measurement should be required	• Add all the sample or add 1-2 calibrated drops from buffer tube
Sample volume measurement	• The sample prep module must not require training to successfully and repeatably dispense target volume on the user interface within a reasonable tolerance	• No pipette measurement should be required	N/A
Instrument design / amplicon contamination	• NAATOS V1 must prevent the escape of amplification products and not contaminate the testing area	• Prevention of amplicon contamination should be possible by trained users of the test with all equipment provided in kit so that the strips are safe to discard in general	N/A
Data display	• NAATOS V1 must have a visual read out of the test result that can intuitively be interpreted	• Concern for interpreting results and three-line readout interpretation • Connectivity of results will also be critical to support result report & meet the standards of data centralization	• Assess absolute necessity for 2 control lines? If required, then conduct usability studies to ensure requirements for instructions and training mitigate this risk
Safety	• NAATOS V1 must not pose a burn risk to the user during normal operation	Users should not be able to remove the tube from the sample prep module earlier than the required incubation period for: – Optimal lysis – Prevention of burning	N/A

Product Specification | Stakeholders provided feedback on key considerations for NAATOS adoption (4/5)

Market Requirements	Current NAATOS Specifications	Notes on Stakeholders' Desired Specifications	Steps to Close Gap
Power module	• The power module must support the required daily throughput	• Unstable power supplies • Ensure continuous operation with rechargeable batteries. Full charge should support 8 hours operation time.	N/A
Field Testing and Real-world Performance	• *Not defined by GHL*	• Stakeholders are interested in how the test performs in diverse real-world settings beyond controlled laboratory environments	• Set up pre-clinical field testing with prototypes as early as possible
Consideration for Special Populations	• *Not defined by GHL*	• TB suspects unable to produce sputum • PLHIV where TB-LAM is missing TB +ve • Close contacts, people on TB Rx in past 2 years • Children	• Generate performance data with these population groups vs. current standard of care, i.e. Xpert Ultra all populations & TB-LAM for PLHIV
Quality control	• *Not defined by GHL*	Internal control accounting for any processing errors: – Sample application to strip reporting of results External control accounting for any processing errors: – Swab-based to account for processing errors – Sample prep to results	• Early engagement with Smartspot to help develop swab-based control materials
Sample preparation module design	Confirm with GHL: – Random access not possible? – Can insert 1 to 4 samples at a time for extraction.	• Consider benefit of single vs. multi-sample prep capability of module - should be random access • Tendency for patient to leave before the test is complete • Concern raised regarding four places for the sample prep tube in the device because the natural tendency for people is to wait until they have sufficient samples for an entire run • Risks of undermining key value proposition • WHO TPP: Multiple samples should be able to be tested at the same time; random access should be possible	• Prototype usability & behaviour studies to help shape training material, overcomes batching tendencies and maximise utilisation of random-access features

Product Specification | Stakeholders provided feedback on key considerations for NAATOS adoption (5/5)

Market Requirements	Current NAATOS Specifications	Notes on Stakeholders' Desired Specifications	Steps to Close Gap
Sensitivity	• NAATOS V1 must have a clinical sensitivity ≥ 80%	Varying responses from interviews – Sensitivity is a priority – Awareness of other evaluations, like MolBio, with lower sensitivity but considered "good enough." – Should meet or exceed the accuracy of existing methods – Willingness to accept slightly lower sensitivity (high 70s to mid-80s percent) if the specificity remains high – The importance of diagnostic yield and access is emphasized, even with potential decrements in sensitivity – Some stakeholders appreciate a balance between sensitivity and reaching people with no access to diagnostics today	• Data generation demonstrating impact and cost benefit of lower sensitivity assay • Focusing on diagnostic yield and access when an assay is feasible for community implementation
Specificity	• NAATOS V1 must have a clinical specificity ≥ 98%	• A high specificity (above 95%) is considered essential	• N/A
Data Management	• Confirm with GHL: • Is connectivity available?	• Result needs to be captured or read automatically as soon as test is complete • Tracking and tracing more effective when connectivity is added to a LF test	*Explore with GHL*
Sample Type	• NAATOS V1 will utilize a dorsal tongue swab sample	• Focusing on sputum alone might lead to an inferior test • Potential benefits non-sputum sample collection methods	• N/A
Treatment monitoring capability	• NAATOS V1 will not provide drug sensitivity	• The absence of resistance in a new test might be seen as a disadvantage	• Positioning of NAATOS into algorithm for settings where Xpert cannot go. Triage, community screening settings, and clinic level screening

1. Diagnostic landscape
2. Stakeholder feedback
3. **Policy considerations**
4. Deployment considerations

Policy Considerations | Critical policy enablers highlighted by stakeholders for a new TB NAAT test

1

Performance and Affordability

- Stakeholders consistently highlight the importance of the nucleic acid lateral flow assay providing results within an hour, being closer to the patient, affordable, and easy to use. Additionally, there's an emphasis on the test having good sensitivity and meeting the WHO Target Product Profiles (TPPs).

2

Alignment with Guidelines and Feasibility

- Adherence to National Department of Health (NDoH) guidelines is considered crucial for public sector market access. Moreover, feasibility factors, including how the new test fits into the current testing algorithm, addressing change management challenges with regards to sputum collection, drug sensitivity, and enhancing usability, are highlighted.

3

Considerations for Implementation and Patient Flow Integration

- Stakeholders express the need to evaluate the impact on workflow, particularly in high-volume settings.* Implementation considerations include determining who will run the test, ensuring ease of use by various personnel, and addressing timing issues within the patient flow. Factors such as preventing patients from leaving before receiving treatment and integrating the test seamlessly into the testing algorithm and patient flow are considered essential. Additionally, insights from stakeholders underscore the importance of considering the unique needs of specific populations, such as young children, in the implementation strategy.

Policy Considerations | TB products generally have a well-defined but time-consuming policy pathway before it can be adopted and procured by NDOH

Policy process step	TB	Private sector considerations
1 National policy endorsement	• WHO GDG endorsement is not a prerequisite for NTP adoption[1]. However, early engagement with national TB TWG critical • Once test is registered with SAHPRA[4], the national TB TWG reviews the strength of the evidence and makes recommendations to the NTP and partners on which, the NTP and NHLS will draft guidelines.	• Private sector follow national guidelines and South African Clinicians Society Guidelines
2 Clinical evaluation	• In-country clinical evaluation will need to be conducted by NHLS[2] before it will be adopted by NTP • HE2RO conducts cost effective study to assess cost of new intervention vs impact, as part of the evidence to be considered by the WHO TWG and NTP	• Private sector labs and facilities may conduct their own independent lab evaluation
3 Local studies and country planning	• Additional field studies/implementation pilots may be requested to investigate operational, acceptability and feasibility questions. Decision made by NDOH. • NDoH TB Testing & Treatment Guidelines updated/developed and launched	• Private sector facilities and labs often start with small scale pilot introduction before committing to larger volumes • Private sector laboratories prioritise assay sensitivity and then price to swing adoptions
4 Adoption, toolkit, phased implementation	• Roll out of new diagnostic tools is handled by NHLS[2] and implementing partners (e.g. CHAI), with support from the national TB reference lab and the NTP.[5] • NTP together with its Technical Advisory Group, Guideline Review Committee and partners will develop, review and update the toolkit • Results from the field studies will support larger roll out	• Adoption driven by reimbursement requirements by Medical Schemes

1. Digital chest X-ray (CXR) and Alere LF-LAM were adopted before WHO GDG endorsement | 2. National Health Laboratory Services | 3. Health Technology Assessment | 4. South African Health Products Regulatory Authority | 5. National Priority Program (NPP)

1. Diagnostic landscape
2. Stakeholder feedback
3. Policy considerations
4. **Deployment considerations**

Deployment Considerations | Interviewees highlighted specific challenges that may influence embracing the adoption of NAATOS by implementers and clinic staff

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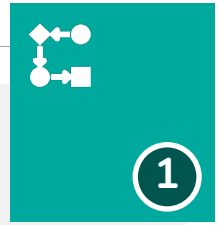
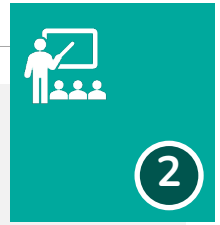


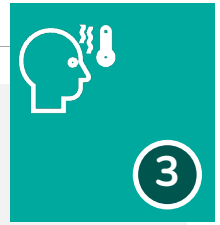
Workflow Integration

The feedback highlights concerns about integrating the new diagnostic tool into the existing clinic workflow, especially related to the physical placement of the instrument and the responsibility for conducting the test



Staff Training and Workload

The need for comprehensive clinical & diagnostic training when rolling out a new algorithm is emphasized in the feedback. However, concerns about staff workload and associated resistance to new responsibilities may be barriers



Patient Sample Collection

Acceptability of tongue swab sensitivity vs. sputum was raised as a concern. It can be countered when difficult sputum collections are eased with a tongue swab, and new testing sites can be added where sputum collection sites aren't feasible

Resistance to Change

Resistance to change is a common barrier in adopting new technologies. Clinicians may be accustomed to existing diagnostics. Roll-out of a new algorithm requires full advocacy from national to district level of DOH leadership

Deployment Considerations | Recommendations and best practices for streamlined product adoption (1/2)

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1 **Needs Assessment and Stakeholder Engagement**

Identify the key stakeholders, such as the TB Technical working group and guideline committees and engage them early in the process. Understand their needs and expectations.

2 **Advocacy and Training Planning**

Drive advocacy through the identified groups to create awareness and generate support for the new diagnostic tool. Plan comprehensive training sessions to ensure that laboratory staff and clinicians understand the benefits of the tool.

3 **Site-Specific Workflow Assessment**

Conduct a thorough assessment of the existing clinic workflow. Understand where the instrument will be located and co-located within the clinic setting. Consider the physical placement, such as having one unit per clinic or one unit per consulting room.

4 **Overcoming Workflow Challenges**

Address site-level challenges related to workflow, including determining which staff cadre is responsible for conducting the test and collecting samples. Consider the experience with other diagnostic tools, such as TB urine LAM and Single Cartridge Xpert, to inform strategies for overcoming potential barriers.

5 **Training Implementation and On-Site Support**

Implement on-site training sessions for laboratory and clinic staff. Emphasize the benefits of the test being quick, with easy steps and components. Leverage previous experiences, like the roll-out of TB LAM in South Africa, to establish a precedent for on-site training.

Deployment Considerations | Recommendations and best practices for streamlined product adoption (2/2)

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6 Integration into Primary Health Care Services & Community Services

Highlight the potential integration of the new diagnostic tool into Primary Health Care services. Address concerns of clinicians about workload by emphasizing the benefits of point-of-care diagnosis. Showcase successful precedents, such as the TB LAM test. Nationally distributed mobile health units (±1,300) increase the opportunity for greater access to communities.

7 Continuous Monitoring and Feedback Loop

Establish mechanisms for continuous monitoring and feedback. Gather insights from users regarding the usefulness and relevance of the diagnostic tool. Address specific concerns, such as workflow challenges and the need for sample collection from patients who struggle to produce sputum.

8 Adaptation and Iteration

Based on feedback and real-world usage, be prepared to adapt the training and implementation process iteratively. Overcome challenges related to specificity, sensitivity thresholds, and any barriers identified during the initial stages.

9 Change Management Strategies

Implement change management strategies to address resistance. Clearly communicate the benefits of the new diagnostic tool, involve staff in decision-making processes, and create a culture that embraces innovation and improvement.

Appendices

1 Glossary

Appendix 1: Glossary

Term	Definition
1. Active TB Disease:	Active TB disease occurs when the TB bacteria become active and cause symptoms. It can affect the lungs or other organs and is contagious.
2. Adverse Drug Reactions (ADR):	Adverse drug reactions refer to undesired or harmful effects resulting from the use of TB medications. Monitoring and managing ADRs are crucial for patient safety.
3. Care Coordination:	Care coordination involves organizing and facilitating the delivery of healthcare services across different providers and settings to ensure that patients receive seamless and efficient care.
4. Chest X-ray:	Chest X-rays are imaging tests that allow healthcare providers to visualize the lungs and identify abnormalities, such as the presence of TB infection or disease.
5. Community Health Workers:	Community health workers are trained individuals within the community who play a crucial role in facilitating TB testing, educating community members, and providing support for those diagnosed with TB.
6. Community TB Testing:	Community TB testing refers to the systematic screening for tuberculosis within a specific community or population, aiming to identify individuals with TB infection or disease early on.
7. Contact Investigation:	Contact investigation involves identifying and testing individuals who have been in close contact with a person diagnosed with infectious TB to prevent further transmission.
8. First-Line Test:	A first-line test is an initial diagnostic procedure, often the most straightforward and widely used, to detect the presence of a disease. In TB diagnostics, this might include techniques like microscopy or rapid molecular tests.
9. GeneXpert MTB/RIF:	GeneXpert MTB/RIF is a molecular diagnostic test that simultaneously detects Mycobacterium tuberculosis (MTB) and rifampin resistance. It provides rapid results, aiding in timely diagnosis and treatment.
10. Health Literacy:	Health literacy is the ability of individuals to understand and use health information to make informed decisions about their health. It involves a person's knowledge, skills, and confidence in managing their health.
11. Index Case:	The index case is the first identified case of TB within a community. Identifying and treating the index case is crucial for preventing the spread of TB.
12. Induced Sputum Sample:	Induced sputum involves using a nebulizer to administer a solution that induces coughing, facilitating the collection of sputum for TB testing.
13. Invalid Rate:	The invalid rate of a diagnostic test indicates the proportion of test results that are deemed inconclusive or unreliable, often due to issues with sample collection, processing, or technical errors.
14. Latent TB Infection (LTBI):	Latent TB infection occurs when a person is infected with the TB bacteria but does not show symptoms. The bacteria are dormant, and the person is not contagious. However, the infection can become active later.
15. LED Fluorescence Microscopy:	LED fluorescence microscopy is a diagnostic technique that uses specific wavelengths of light to detect fluorescence in stained TB bacteria, aiding in their visualization.

Appendix 1: Glossary

Term	Definition
16. **Loop-Mediated Isothermal Amplification (LAMP):**	LAMP is a molecular technique used for the detection of TB DNA. It is known for its simplicity and ability to provide quick results.
17. **Loss to Follow-Up:**	Loss to follow-up occurs when patients who have started the TB diagnostic process or treatment do not complete the required steps, leading to a gap in their care and potential challenges in monitoring and managing the disease.
18. **Mass Testing:**	Mass testing, also known as mass screening, involves testing a large number of individuals in a community simultaneously to identify TB cases quickly.
19. **Mobile TB Testing Unit:**	A mobile TB testing unit is a vehicle or mobile clinic equipped to provide TB testing services in various locations within a community, reaching individuals who may have limited access to healthcare facilities.
20. **Molecular Diagnostics:**	Molecular diagnostics involve the detection and analysis of genetic material (DNA or RNA) to identify specific pathogens, such as Mycobacterium tuberculosis, with high sensitivity and specificity.
21. **Multi-Disease Testing Platform:**	A multi-disease testing platform is a diagnostic system capable of testing for multiple diseases simultaneously. In the context of TB diagnostics, it may offer the flexibility to test for various pathogens or conditions in a single assay.
22. **Multidrug-Resistant TB (MDR-TB):**	MDR-TB is a form of drug-resistant TB where the bacteria are resistant to at least isoniazid and rifampin, two of the most potent TB drugs.
23. **Nucleic Acid Amplification Test (NAAT) Sample:**	NAAT samples are used in molecular diagnostic tests, such as PCR (polymerase chain reaction) or LAMP (loop-mediated isothermal amplification), to detect the genetic material of the TB bacteria in a collected specimen.
24. **Patient-Centric Care:**	Patient-centric care is an approach to healthcare that prioritizes the individual needs, preferences, and values of the patient. It involves actively involving patients in their healthcare decisions and considering their perspectives in the planning and delivery of services.
25. **Patient Engagement:**	Patient engagement refers to the active participation of patients in their own healthcare, including decision-making, goal setting, and management of their health.
26. **Patient Experience:**	Patient experience encompasses the interactions, perceptions, and satisfaction levels of patients with the healthcare system, including their interactions with healthcare providers and the overall healthcare environment.
27. **Presumptive TB Cases:**	Presumptive TB cases refer to individuals who are suspected of having tuberculosis based on clinical symptoms, exposure history, or preliminary diagnostic results, but have not yet been confirmed through definitive testing.
28. **Rapid Diagnostic Tests:**	Rapid diagnostic tests for TB include various techniques that quickly identify the DNA or RNA of Mycobacterium tuberculosis, allowing for swift diagnosis.
29. **Rapid Molecular Tests:**	Rapid molecular tests for TB include various techniques that quickly identify the DNA or RNA of Mycobacterium tuberculosis, allowing for swift diagnosis.
30. **Sample Prep Module:**	A sample preparation module is a component of a diagnostic system that is designed to process and prepare collected samples, such as sputum, for subsequent testing in molecular diagnostics or other analytical platforms.

Appendix 1: Glossary

Term	Definition
31. Secondary Facility:	A secondary facility in the context of TB diagnostics is a healthcare facility that is equipped to handle certain diagnostic procedures, such as sample processing and testing, but may refer more complex cases to a tertiary facility.
32. Second-Line Test:	A second-line test is a more specialized or confirmatory diagnostic procedure used when the results of the first-line test are inconclusive or when a higher level of accuracy is required.
33. Screening Campaign:	A screening campaign is a targeted and organized effort to test individuals within a community for TB, usually involving mobile clinics, community health workers, or specific testing events.
34. Serological Tests:	Serological tests for TB detect antibodies in the blood. However, their use in TB diagnosis is controversial, and they are not recommended as primary diagnostic tools.
35. Shelf Life:	Shelf life refers to the period during which a diagnostic product, such as reagents or test kits, is expected to remain stable and effective when stored under specified conditions.
36. Sputum Sample:	Sputum is the mucus and other material coughed up from the lungs and airways. A sputum sample is commonly used in TB testing to detect the presence of Mycobacterium tuberculosis.
37. Stock Outs:	Stock outs occur when healthcare facilities experience a depletion of their inventory, leading to a lack of essential diagnostic supplies or equipment, potentially impacting the continuity of testing services.
38. Multi-Disease Testing Platform:	A multi-disease testing platform is a diagnostic system capable of testing for multiple diseases simultaneously. In the context of TB diagnostics, it may offer the flexibility to test for various pathogens or conditions in a single assay.
39. TB Clinic:	A specialized healthcare facility or unit that focuses on the diagnosis, treatment, and management of tuberculosis.
40. TB LAMP:	TB LAMP (Loop-Mediated Isothermal Amplification) is a molecular diagnostic technique used for the rapid detection of Mycobacterium tuberculosis DNA. It operates under isothermal conditions, allowing for quicker and simpler testing.
41. TB Screening:	TB screening involves the testing of individuals for tuberculosis infection or disease, often using methods such as chest X-rays, tuberculin skin tests (TST), or interferon-gamma release assays (IGRAs).
42. TB Testing Algorithm:	A TB testing algorithm is a step-by-step process or flowchart that outlines the sequence of diagnostic tests and procedures used to identify and confirm cases of tuberculosis.
43. Tertiary Facility:	A tertiary facility is a high-level healthcare institution that provides specialized and advanced medical care, including complex diagnostic services and treatment. In the context of TB diagnostics, it may handle cases referred from secondary facilities.
44. Time to Result:	Time to result is the duration it takes for a diagnostic test to provide a conclusive outcome from the moment the sample is collected. Shorter time to result is often desirable for prompt patient management.
45. Tuberculosis (TB):	Tuberculosis is an infectious disease caused by the bacterium Mycobacterium tuberculosis. It primarily affects the lungs but can also affect other parts of the body.

Appendix 1: Glossary

Term	Definition
46. Truenat:	Truenat is a molecular diagnostic platform that uses real-time polymerase chain reaction (PCR) technology for the detection of various pathogens, including Mycobacterium tuberculosis. It provides rapid and accurate results.
47. Urine Sample:	Urine samples may be used in specific tests, such as the urine lipoarabinomannan (LAM) assay, which detects a component of the TB bacteria in the urine of individuals with advanced HIV infection and active TB.
48. X-ray Computerized Tomography (CT) Scan:	A CT scan provides detailed cross-sectional images of the chest, allowing for a more comprehensive assessment of lung abnormalities, including TB-related changes.
49. Xpert MTB/RIF Sample:	The Xpert MTB/RIF test typically uses sputum samples but can also use other respiratory specimens. It is a molecular test that simultaneously detects Mycobacterium tuberculosis and rifampin resistance.