Programmatic implementation of targeted next-generation sequencing (tNGS) for DR-TB management in South Africa

From pilot validation to routine national integration of an end-to-end Deeplex tNGS solution

Dr Shaheed V Omar
Centre Head
Centre for Tuberculosis, NICD/NHLS
National TB Reference Laboratory
WHO Supranational Reference Laboratory
Johannesburg, South Africa

SETTING THE SCENE

Why tNGS? tNGS WORKSTREAM BACKGROUND

- WHO-recommended platform for comprehensive detection of drug-resistance–associated mutations
- Mutation-level resistance profiling across multiple drug classes
- Seq&Treat Multi-country Study demonstrated clinical and operational feasibility for DR-TB management
- The South African implementation transitions tNGS from pilot validation to routine national integration

THE SOUTH AFRICAN CONTEXT

- Among the first LMICs implementing routine tNGS for DR-TB
- Integrated within the national DR-TB reflex testing algorithm
- ~7,000 DR-TB patients annually eligible for reflex resistance testing
- BDQ resistance (~6.5%) increases the need for rapid, comprehensive profiling

OBJECTIVE: establish programmatic tNGS capacity for all RR/DR-TB patients

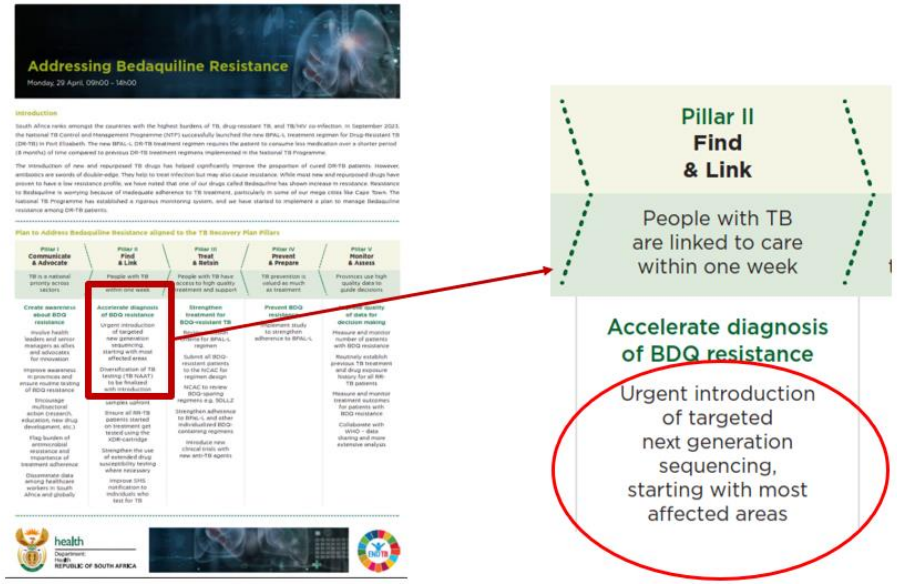
World Health Organization

Use of targeted next-generation sequencing to detect drug-resistant tuberculosis

Rapid communication, July 2023

Comprehensive DST Matrix

Simultaneous, 13-drug susceptibility profiling covering core first-line (INH, RIF), FQ, SLID, and critical newer agents (BDQ, LZD, CFZ).



SOUTH AFRICA Diagnostic Network

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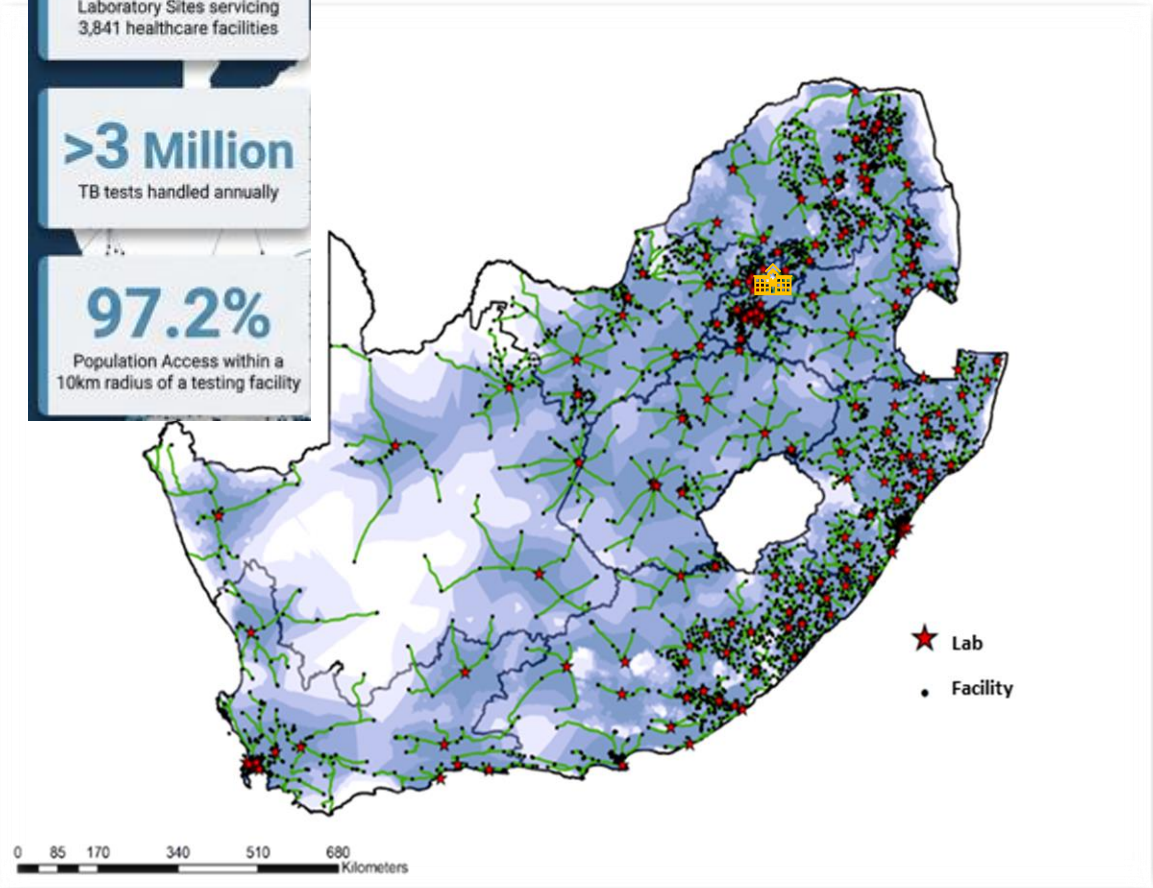
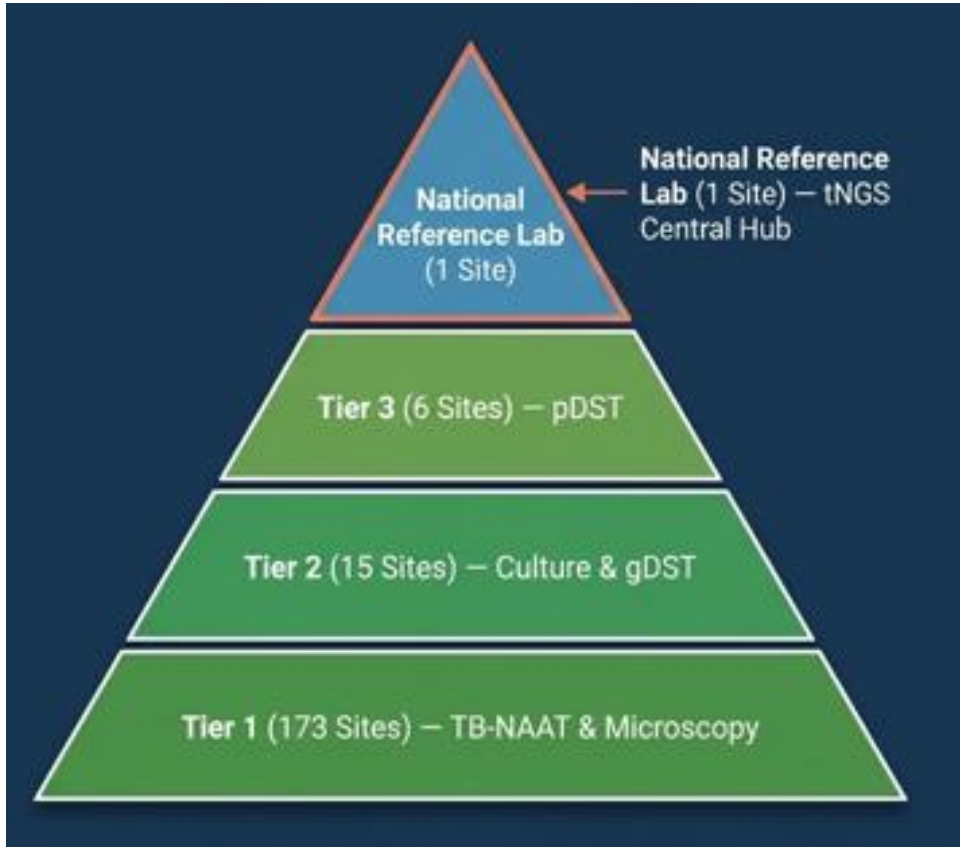
200+
Laboratory Sites servicing 3,841 healthcare facilities

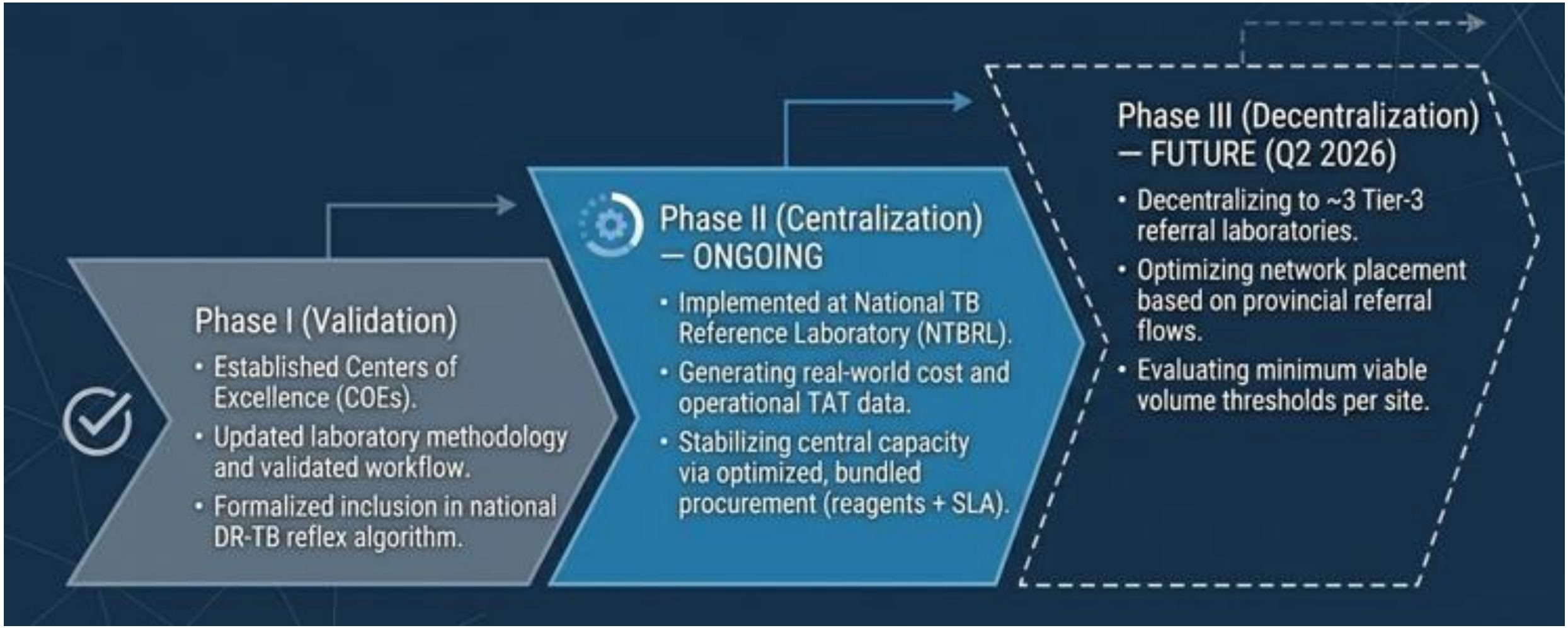
>3 Million
TB tests handled annually

97.2%
Population Access within a 10km radius of a testing facility

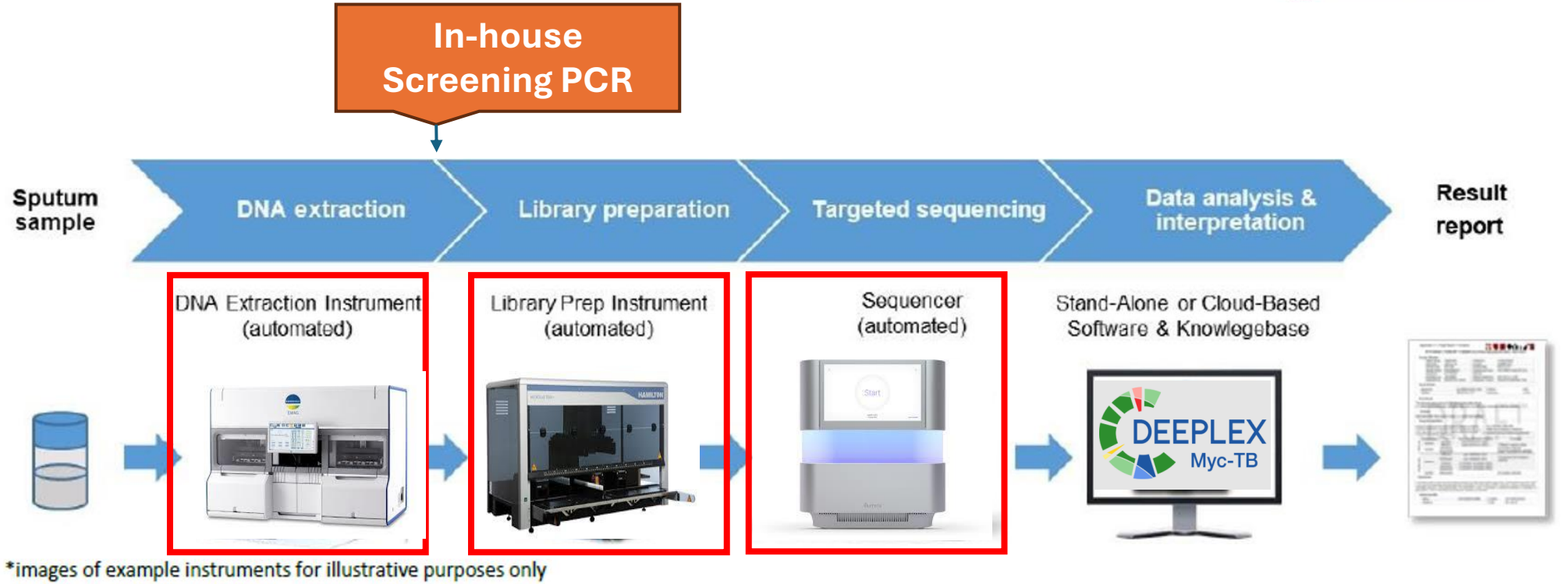




A PHASED approach from validation to sustainable integration

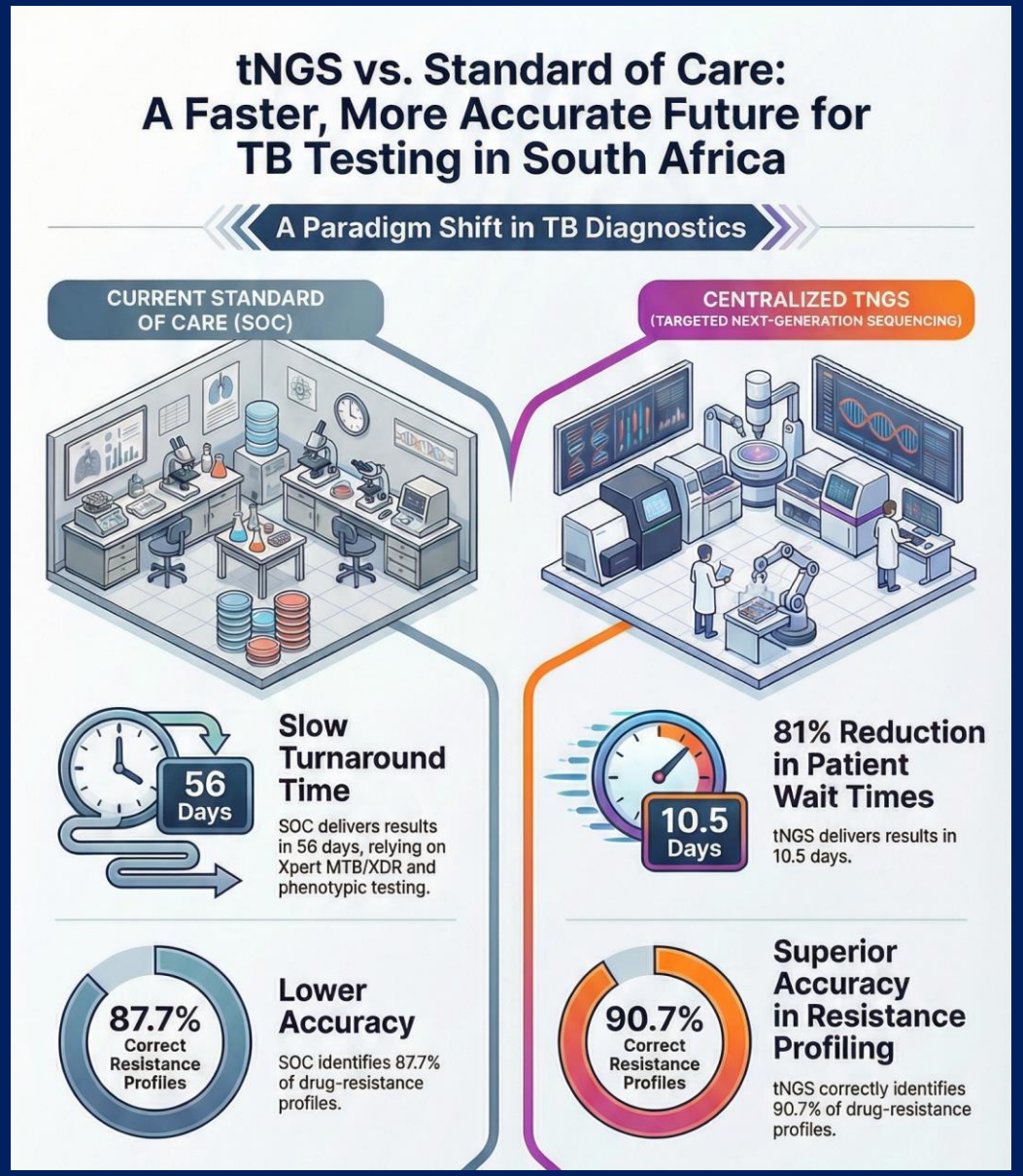


National Validation – Workflow Validation



Validations performed due to deviation for WHO Recommended END-TO-END Solutions:

- ✓ DNA Extraction System
- ✓ Automated Library Preparation
- ✓ Sequencing Platform



Cost-Effectiveness of tNGS Compared to Standard of Care (South African Context)

$50
Cost Savings per Patient

20%
Reduction vs SOC

- Economic Analysis: Health system cost-effectiveness study compared tNGS to standard phenotypic DST for rifampicin-resistant TB patients in South Africa
- Targeted NGS showed lower cost per patient ($195 USD) versus standard phenotypic DST ($245 USD), achieving $50 savings per patient tested
- Cost advantage driven by faster turnaround reducing pre-treatment default, fewer repeat tests, and elimination of prolonged culture infrastructure requirements
- Health System Impact: At 7,000 DR-TB patients annually, tNGS adoption could generate estimated $350,000 USD annual savings while improving diagnostic speed

de Nooy A, Omar SV, Ockhuisen T et al. Cost-effectiveness of Targeted Next-Generation Sequencing for Tuberculosis Drug-resistance Testing as an Alternative to the Standard of Care in South Africa. Clin Infect Dis. 2026 Feb 9;82(1):e119-e125.

National DR-TB Reflex Algorithm with tNGS

15
Xpert XDR Sites

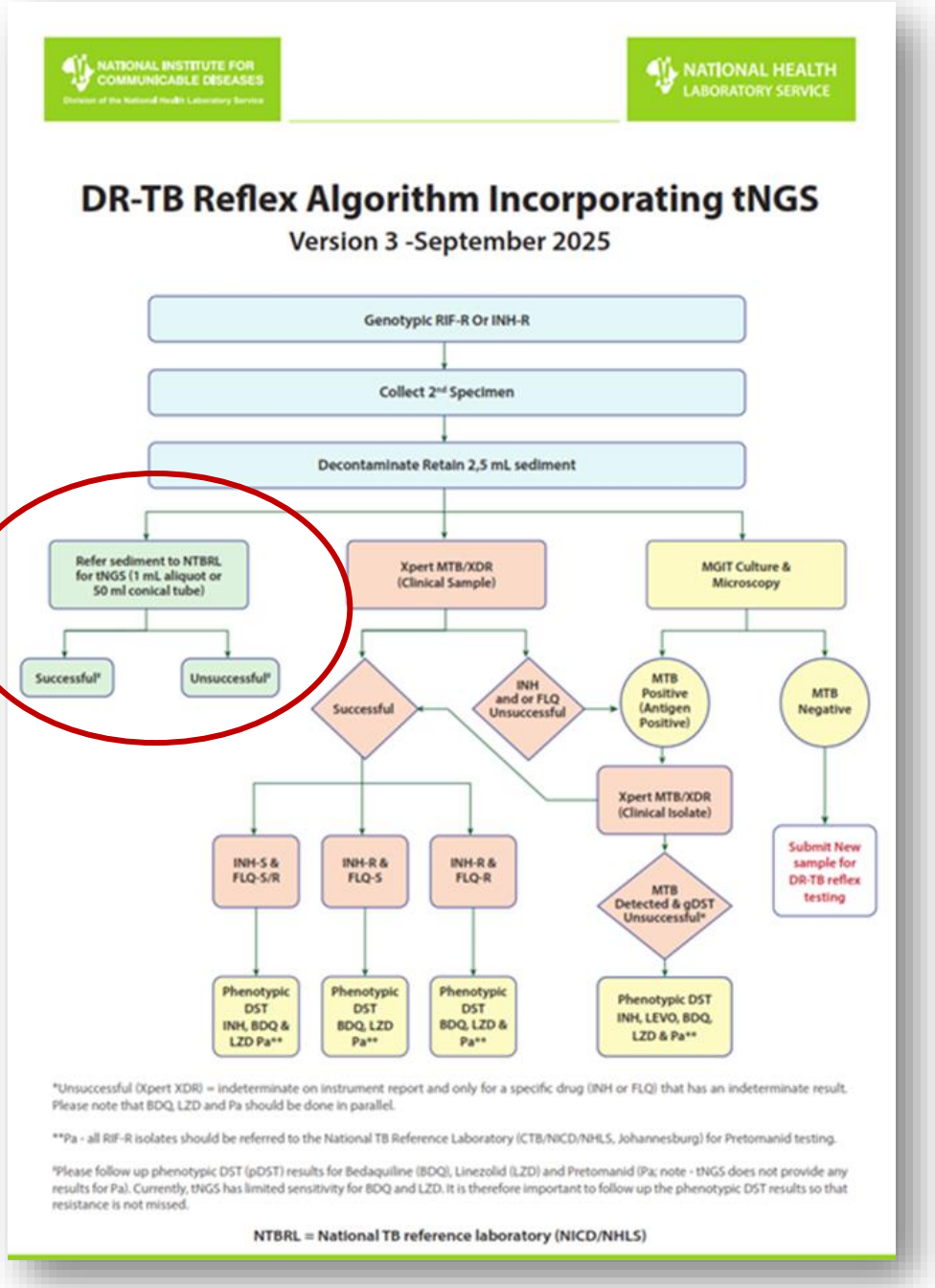
10-Day
tNGS TAT

Algorithm triggers tNGS automatically for rifampicin/isoniazid resistance cases, ensuring rapid comprehensive profiling for critical treatment decisions

Workflow Required Coordination Across 15 Sites Feeding Samples To Centralized NTBRL With Standardized Tracking Procedures

Reflex Algorithm Eliminated Manual Delays And Ensured Systematic Surveillance For All Eligible Patients

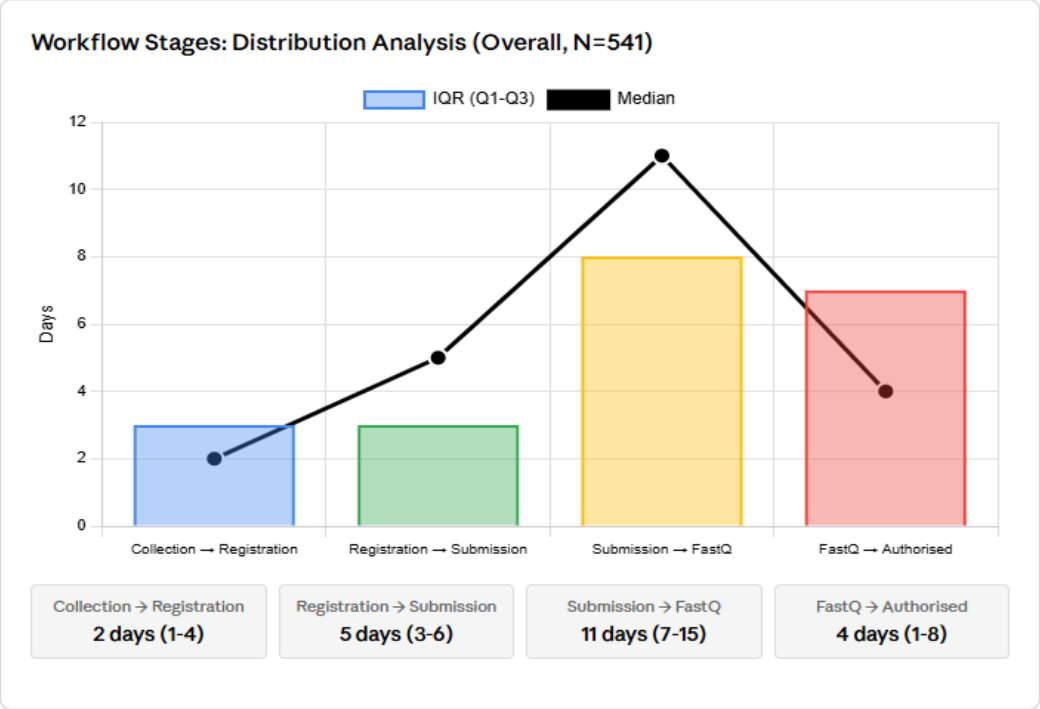
Target 10-day Turnaround Time Represents Substantial Improvement Over 56-day Phenotypic Testing For Treatment Optimization



MONITORING & EVALUATION

National tNGS performance

Total samples	Sites	End-to-end median	Processing median
541	7	23 days	11 days

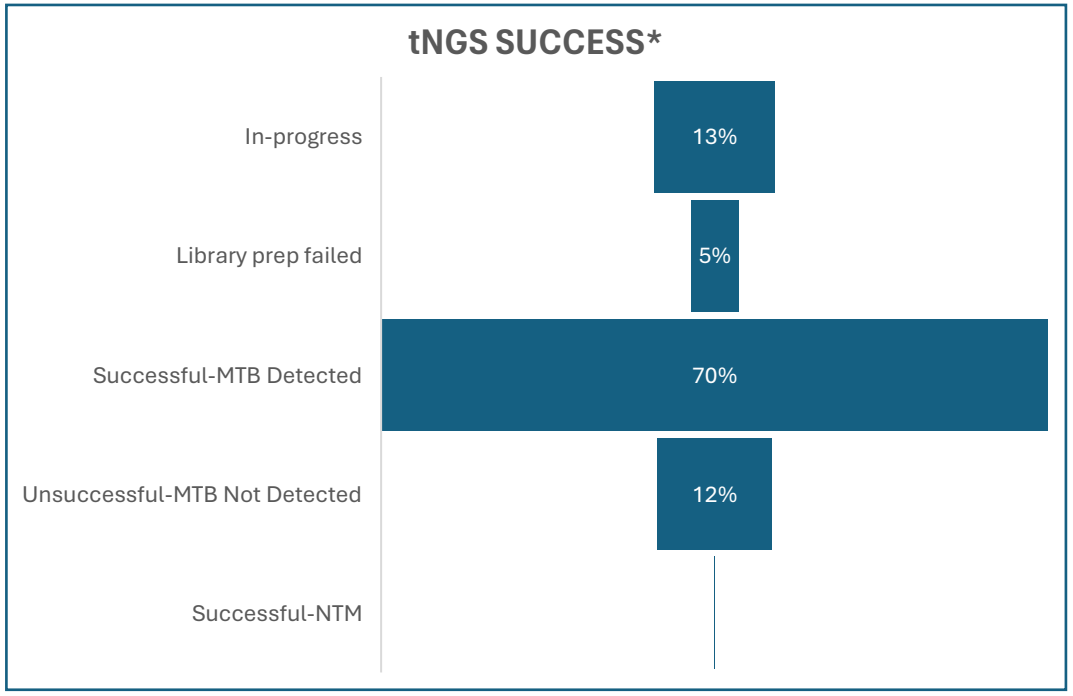


Drug Target	Reference	N	Anti-TB Drug Prevalence (95% CI)	Sensitivity(95% CI)	Specificity(95% CI)
Rifampicin	WGS	255	**86.7%** (81.9%–90.6%)	**98.2%** (95.4%–99.5%)	**76.5%** (58.8%–89.3%)
Isoniazid	WGS	224	**65.6%** (59.0%–71.8%)	**94.6%** (89.6%–97.6%)	**92.2%** (83.8%–97.1%)
	pDST	224	**67.4%** (60.8%–73.5%)	**91.4%** (85.7%–95.3%)	**95.9%** (88.5%–99.1%)
Fluoroquinolones	WGS	216	**27.8%** (21.9%–34.3%)	**86.7%** (75.4%–94.1%)	**95.5%** (91.0%–98.2%)
Bedaquiline	pDST	237	**21.5%** (16.5%–27.3%)	**94.1%** (83.8%–98.8%)	**84.4%** (78.4%–89.3%)
	WGS	237	**32.1%** (26.2%–34.3%)	**80.3%** (69.5%–88.5%)	**88.8%** (82.9%–93.2%)
Linezolid	pDST	227	**1.3%** (0.3%–3.8%)	**100.0%** (29.2%–100.0%)	**100.0%** (98.4%–100.0%)
	WGS	230	**1.3%** (0.3%–3.8%)	**100.0%** (29.2%–100.0%)	**100.0%** (98.4%–100.0%)

Overview of tNGS samples processed

2,476
samples processed

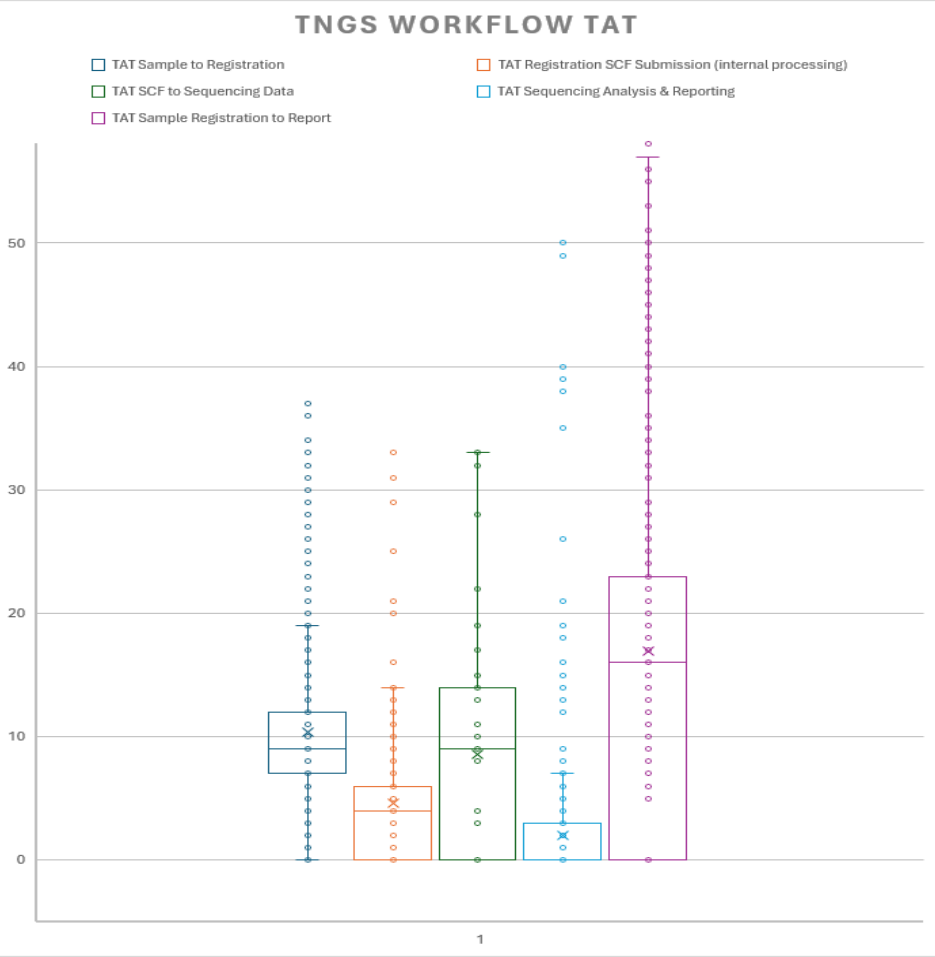
73% (1,614)
*tNGS successful



***EXCLUDES SAMPLES NOT MEETING THE CT-THRESHOLD, REJECTED OR NOT ELIGIBLE**

TURNAROUND TIME

Measured tNGS TAT by workflow stage



Sequencing analysis & reporting — ~3 DAYS

Fastest stage — a consistent, efficient process once sequencing is complete.

SCF submission (internal) — ~4 DAYS

Lowest median but moderate variability, with occasional processing delays.

SCF → sequencing data — ~9 DAYS

Occasional inconsistency in sequencing throughput or batching delays.

Sample registration → report — ~16 DAYS

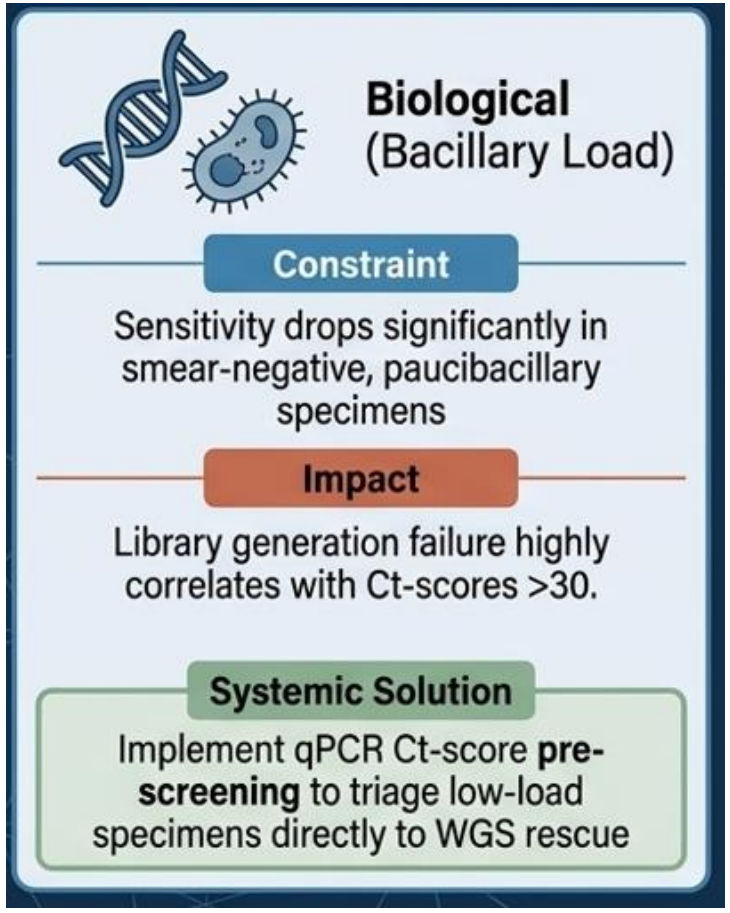
End-to-end TAT and greatest variability — the cumulative effect of upstream delays.

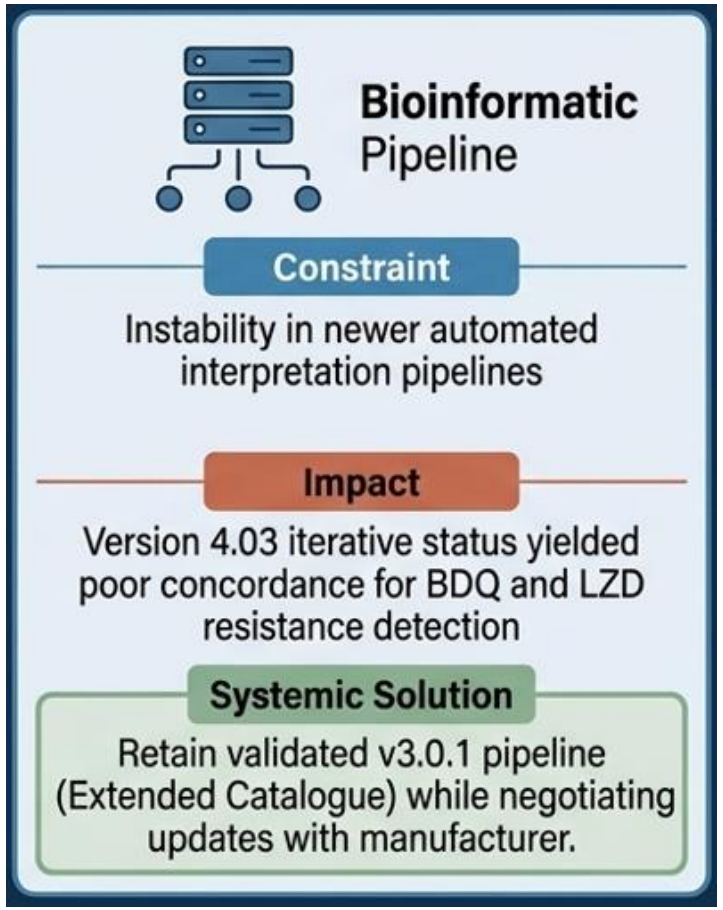
Benchmark: half of all samples fall within a 2-week window — a useful target for turnaround.

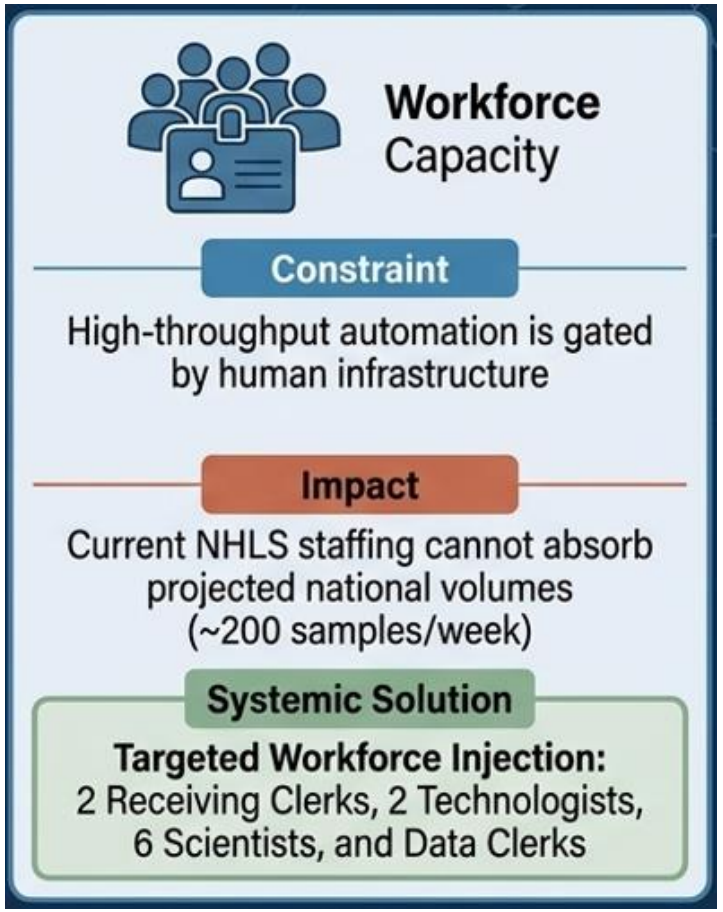
ROOT-CAUSE ANALYSIS

Workflow-level contributors to extended TAT

TAT reflects cumulative constraints across pre-analytical, analytical and post-analytical stages.







PHASE III - NETWORK DESIGN QUESTION

Evaluating the optimal network design for DR-TB tNGS

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OBJECTIVE

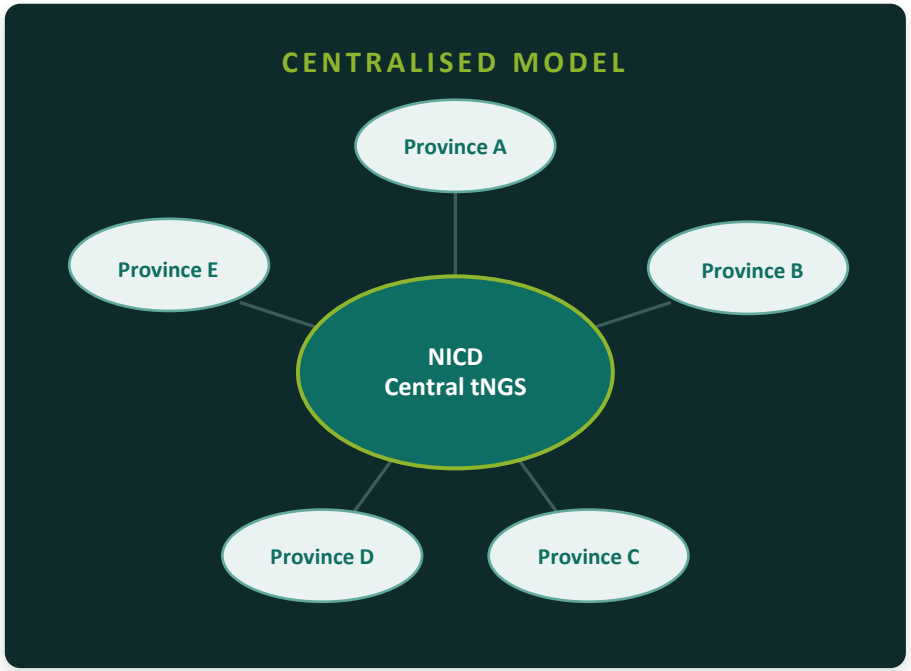
- What is the optimal balance between centralised efficiency and provincial access?
  - Centralised model — all testing at NTRL
  - Decentralised model — targeted platform decentralisation

ANALYTICAL APPROACH

- Calculate full end-to-end centralised cost (including transport)
- Map provincial volumes and referral flows
- Estimate minimum viable volume thresholds per site
- Model incremental HR, infrastructure and logistics requirements

EXPECTED OUTPUT

- Define the minimum viable volume threshold for provincial placement
- Quantify the incremental cost of decentralisation
- Inform optimal network placement



Key question: **does targeted decentralisation improve system performance relative to cost?**

Findings will guide sustainable scale-up decisions and inform broader global guidance on tNGS implementation models.

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YES! WE CAN #ENDTB

Commit, Invest, Deliver!