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BMJ Global Health

# Targeted next-generation sequencing for drug-resistant tuberculosis diagnosis: implementation considerations for bacterial load, regimen selection and diagnostic algorithm placement

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## ABSTRACT

**Introduction** Early and accurate diagnosis of drug-resistant tuberculosis (DR-TB) is essential for improving treatment outcomes. Phenotypic drug susceptibility testing (pDST) is comprehensive but slow, while rapid molecular assays provide resistance information for a limited number of drugs. Targeted next-generation sequencing (tNGS) offers the potential for broad and rapid resistance detection, but its integration into diagnostic algorithms has been hindered by uncertainty about its placement within existing workflows.

**Methods** This study evaluated the extent to which two tNGS solutions—Deeplex Myc-TB (GenoScreen) and TB Drug Resistance Test (Oxford Nanopore Technologies, ONT)—provided interpretable drug resistance results that could inform regimen design, in comparison to other WHO-recommended molecular assays and pDST. Data were collected from three high-burden DR-TB settings under the Seq&Treat study. Sequencing success rates and drug resistance detection were analysed based on: (1) the initial Xpert MTB/RIF result (very low, low, medium, high), (2) resistance results for drugs in WHO-recommended regimens and (3) performance relative to other WHO-endorsed assays. The potential impact of different algorithms on the estimates was also considered. Key factors influencing successful tNGS adoption within diagnostic pathways were identified, leveraging insights from the Seq&Treat diagnostic accuracy study.

**Results** Sequencing success rates were 88.5% (GenoScreen) and 93.1% (ONT) across 763 samples. While tNGS provided complete resistance data for 73%–86% of drugs in recommended regimens, pDST achieved 92%–93%. Both tNGS solutions matched or exceeded the sensitivity of WHO-recommended molecular assays.

**Conclusions** This study highlights the critical role of tNGS as a centralised tool for comprehensive drug resistance testing to inform DR-TB treatment decisions following initial screening assays. By complementing existing molecular tests with tNGS, diagnostic workflows can be optimised to ensure timely and comprehensive resistance detection. These findings support policy updates to integrate tNGS into global TB diagnostic algorithms.

**Trial registration number** NCT04239326.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ In 2023, the WHO issued a conditional recommendation for the use of targeted next-generation sequencing (tNGS) to rapidly detect genetic mutations linked to tuberculosis (TB) drug resistance. tNGS has been shown to perform robustly across a wide range of TB drugs, as demonstrated in a recent diagnostic accuracy assessment published in *The Lancet Infectious Diseases* (2024) (DOI: 10.1016/S1473-3099(24)00586-3). However, the article does not address patient outcomes or the integration of tNGS into diagnostic algorithms. Despite its potential, tNGS implementation in clinical settings has been slow due to uncertainty about its optimal placement in diagnostic workflows. A PubMed search identified only two relevant studies: one in Bangladesh demonstrating tNGS's utility in detecting drug resistance directly from clinical specimens and another in Namibia highlighting logistical challenges and offering insights for programmatic implementation.

## INTRODUCTION

In 2023, an estimated 10.8 million people fell ill with tuberculosis (TB), with 400 000 new TB cases already resistant to the first-line drug rifampicin (RIF).[1] The End TB Strategy relies on the early and rapid diagnosis and treatment of all forms of TB, including universal access to drug susceptibility testing (DST) and effective treatment of all drug-resistant TB (DR-TB) infections.[2] Reports of emerging resistance to new and highly effective drugs



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### WHAT THIS STUDY ADDS

⇒ This study uniquely utilises data from three diverse, high-burden clinical sites to evaluate the performance of tNGS. It identifies key factors influencing tNGS success, highlights its value in informing TB treatment regimens based on drug target sequencing and compares its diagnostic performance to other WHO-recommended molecular tests. These analyses provide a detailed understanding of how tNGS can optimise diagnostic pathways for drug-resistant TB.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The study supports integrating tNGS into diagnostic algorithms, with molecular tests providing limited resistance testing near patient entry points and tNGS delivering comprehensive results at centralised laboratories. This approach could streamline DR-TB diagnosis and improve treatment outcomes. By considering factors affecting tNGS success and the information it provides about treatment options, the diagnostic algorithm can be further tailored to specific settings, advancing research, policy and clinical practice.

like bedaquiline (BDQ) further call for antibiotic stewardship.[3 4] The rapid, appropriate and tailored treatment of TB and DR-TB infections is critical to preserve our limited arsenal of TB drugs and regimens.

The current reference standard for most resistance detection is phenotypic DST (pDST). However, pDST has a long turnaround time, so clinicians must treat patients empirically while waiting for information regarding drug susceptibility. Furthermore, access to new and repurposed drugs such as BDQ, linezolid (LZD) and pretomanid to perform pDST is limited in several countries, often leaving clinicians blind to drug susceptibility information for these critical components of effective, all-oral TB treatment regimens.[5] New rapid, molecular DR-TB assays with expanded resistance detection capabilities hold great promise to lower the time to resistance detection (eg, Xpert MTB/XDR and assays in the pipeline such as Hain FluoroType XDR and Bioneer RFIA),[6] but these assays still have important limitations, especially regarding drug coverage.[7]

Culture-free, targeted next-generation sequencing (tNGS) solutions have the potential to transform the diagnosis of DR-TB by enabling testing outside of biosafety level 3 facilities—following appropriate specimen inactivation—and by reducing the time required for pDST while providing resistance information for a broader range of drug targets.[8] In 2023, WHO convened a Guideline Development Group to review evidence on the performance of tNGS platforms. This led to a conditional recommendation for the use of two tNGS solutions—Deeplex Myc-TB (GenoScreen, Lille, France) and the TB Drug Resistance Test (Oxford Nanopore Technologies, Oxford, United Kingdom)—for rapid and accurate genetic analysis and detection of mutations associated with TB drug resistance. These platforms offer a novel, comprehensive approach to TB DST within a fraction of the time required for culture-based methods.[8 9]

Despite this progress, challenges remain in translating the utility of tNGS into clinical practice. Guidance is needed on how to optimally integrate tNGS into existing diagnostic algorithms, considering its technical and operational challenges, particularly in resource-limited settings.[10] The Seq&Treat study provided a robust evaluation of these two tNGS solutions, demonstrating their diagnostic accuracy across high-burden settings.[11] However, that evaluation focused on performance metrics and diagnostic accuracy, leaving questions about how actionable tNGS results can enhance patient care and fit within broader diagnostic workflows.

Building on Seq&Treat findings, we analyse key factors influencing the successful adoption of tNGS, including integration with existing WHO-recommended molecular tests, its role in informing treatment regimens and its applicability across diverse settings. We propose diagnostic algorithms incorporating tNGS solutions to optimise DR-TB detection and treatment, aiming to address the gaps in operational guidance and policy for effective implementation in global TB control programmes.

## METHODS

### Seq&Treat study overview

Three epidemiologically diverse clinical sites with high DR-TB burdens were selected for trialling of tNGS technologies through Seq&Treat,[11] reflecting intended use settings with the appropriate infrastructure for handling complex workflows. 832 patients with DR-TB or risk factors were enrolled, with 48 (5.8%) patients excluded due to TB-negative Xpert MTB/RIF results on the study sputum, leaving 784 patients. Of these 784, tNGS was not performed for 21 (2.7%) patients for any reason, and so results from 763 patients were available for both tNGS solutions.

All enrolled patients provided at least 5 mL of sputum, which was homogenised, decontaminated and resuspended in 4 mL final volume for downstream testing. Xpert MTB/RIF, acid-fast bacilli smear, MGIT and LJ culture, and Hain MTBDR*plus/sl* were performed on the sediment (figure 1). MGIT pDST for isoniazid (INH), RIF, streptomycin (SM), ethambutol (EMB), pyrazinamide (PZA), moxifloxacin (MFX), levofloxacin (LFX), amikacin (AMK), kanamycin (KAN), capreomycin (CAP), BDQ, LZD and clofazimine (CLF) was performed according to manufacturer's protocols using WHO-recommended critical concentrations.[12 13] Whole genome sequencing (WGS) was performed on the culture isolate for each clinical sample as previously detailed.[11 14] The first edition of the WHO catalogue of mutations associated with drug resistance in *Mycobacterium tuberculosis* was used to interpret variants as resistant to any given drug.[15]

### Targeted next-generation sequencing

End-to-end tNGS workflows were performed according to manufacturer instructions, as described previously.[11] tNGS was performed using batched, frozen sediments

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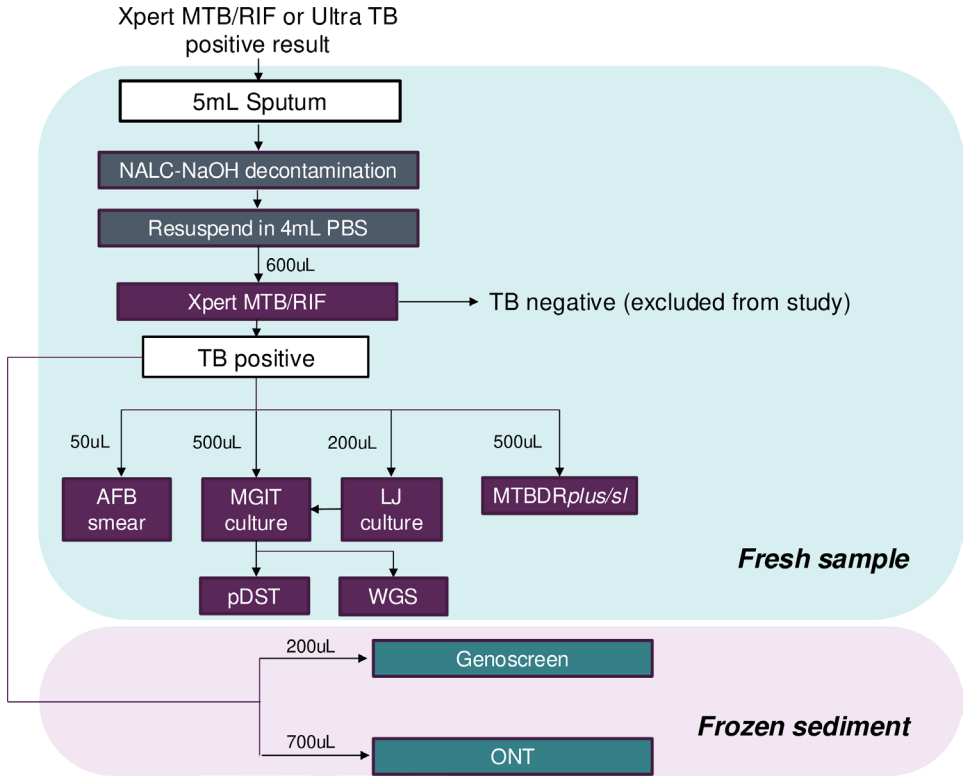



**Figure 1** Seq&Treat sample flow and testing scheme. AFB, acid-fast bacilli; LJ, Lowenstein Jensen; MGIT, mycobacterial growth indicator tube; NALC-NaOH, N-acetyl-L-cysteine and sodium hydroxide; ONT, Oxford Nanopore Technologies; PBS, phosphate buffered saline; pDST, phenotypic drug susceptibility testing; RIF, rifampicin; TB, tuberculosis; WGS, whole genome sequencing

once sufficient samples were collected. Generated FASTQ files were analysed with the solution-specific bioinformatics pipeline. For a mutation to be reported, it had to be represented in >20% of all the calls for that location in the genome for all gene targets except the *rrs* gene target, which required a higher minimum proportion of calls (≥50%) to identify mutations. Drug-resistance mutation lists used for the interpretation of mutations as resistant or susceptible came from the WHO mutation catalogue, first edition.[15]

### tNGS data generation

Given that tNGS solutions may be run in reflex to an upfront molecular assay result, the ability of each tNGS solution to generate sequencing data per drug target for Xpert MTB/RIF TB positive samples from both Oxford Nanopore Technologies (ONT) and GenoScreen tNGS-tested patients (n=763) was stratified by Xpert semiquantitative result (ie, very low, low, medium and high).

For each of seven recommended drug regimens (ie, HREZ, REZLv, BPaL/M, the new 6-month and 9-month regimens,[16] the short multidrug-resistant TB regimen and the longer multidrug-resistant TB regimen) as well as for a single compound (ie, fluoroquinolones), the ability of each tNGS solution to generate data for all relevant drugs included in the regimen was compared with pDST and WGS. The following drug information was considered necessary to inform each regimen selection: INH, RIF, PZA and EMB for HRZE; INH, RIF, PZA, EMB and LFX for REZLv; INH, RIF, PZA, EMB, LFX, BDQ and LZD for BPaL/M; INH, RIF, PZA, EMB, LFX, BDQ, LZD and CLF for the short regimen, new 6mo regimen (BDLLfxC) and 9-month regimens (BLMZ, BLLfxCZ and BDLLfxZ); and INH, RIF, PZA, EMB, LFX, BDQ, LZD, CLF, AMK and ETH for the long regimen. No test provided information for pretomanid or delamanid resistance, WGS did not provide information for BDQ or CLF, and pDST was not performed for ETH. These drugs were left out of the relevant calculations. Results were expressed as a percentage of the total enrolled patients tested by the given method (n=784 for WGS, pDST; n=763 for GenoScreen; n=766 for ONT; n=782 for line probe assay) using Clopper Pearson binomial confidence intervals. For example, for BPaLM selection based on ONT results, the number of samples with clear ONT results for INH, RIF, PZA, EMB, LFX, BDQ and LZD out of the 766 samples tested was determined.

### tNGS performance against other WHO-recommended molecular tests

The performance of tNGS for each drug target was compared with available WHO-recommended molecular tests. Results were expressed as the percentage of the samples generating both pDST and tNGS results for any drug, using Clopper Pearson binomial CIs. Data from the WHO consolidated guidelines on TB (module 3: Diagnosis) for WHO-recommended DR-TB assays were extracted and included to compare diagnostic



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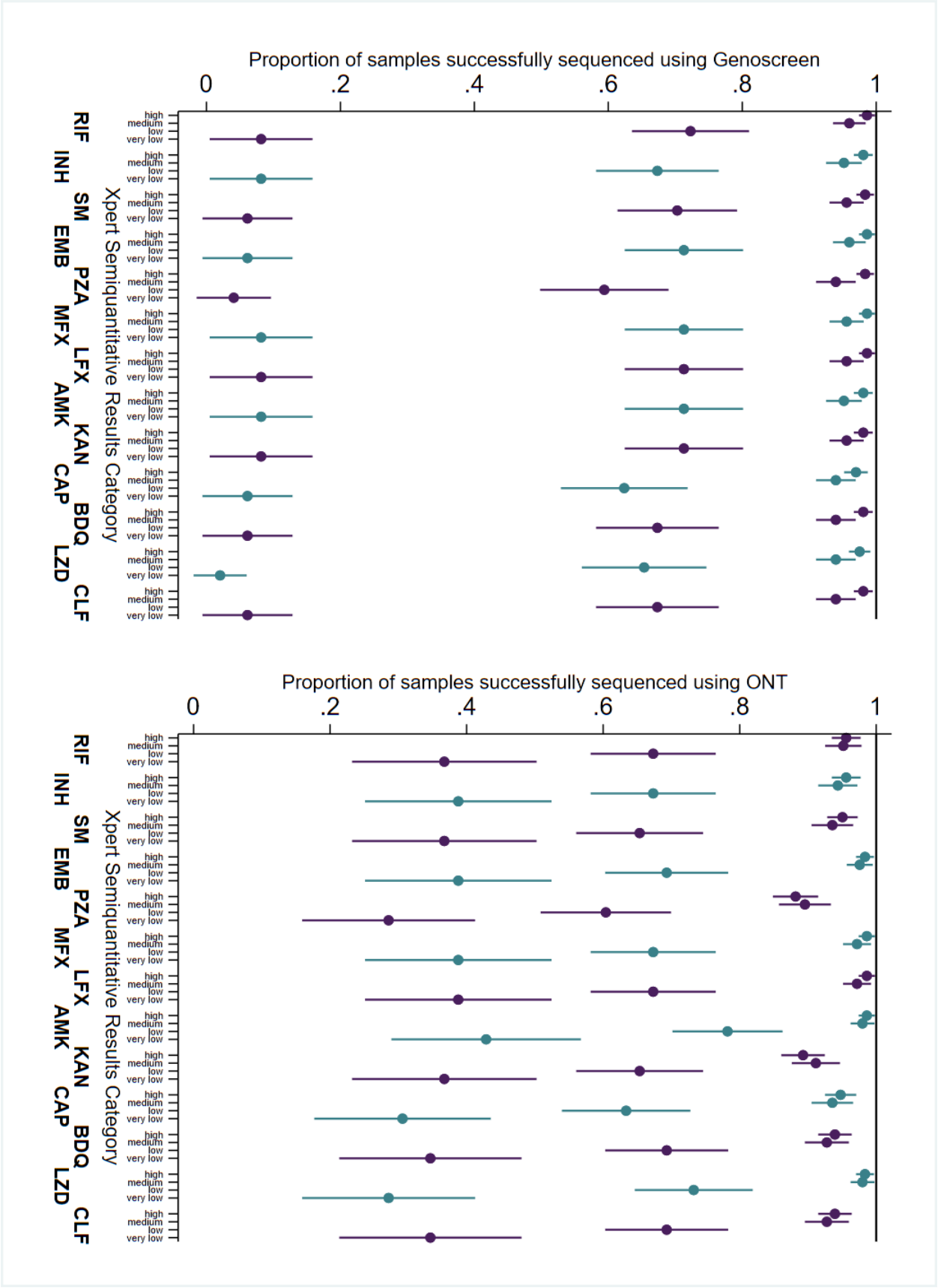



**Figure 2** Ability of tNGS to generate sequencing data by Xpert result for all enrolled patients tested by both tNGS solutions (n=763), stratified by drug target. AMK, amikacin; BDQ, bedaquiline; CAP, capreomycin; CLF, clofazimine; EMB, ethambutol; INH, isoniazid; KAN, kanamycin; LFX, levofloxacin; LZD, linezolid; MFX, moxifloxacin; ONT, Oxford Nanopore Technologies; PZA, pyrazinamide; RIF, rifampicin; SM, streptomycin; tNGS, targeted next-generation sequencing.

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performance. pDST was included as the reference standard for consistency across the various platforms per guidelines.

### tNGS diagnostic algorithm

Based on the tNGS resistance detection rates for relevant drug compounds and in the context of current regimens, suitable use cases of tNGS as a reflex and/or up-front test for TB and drug resistance detection in well-equipped, higher level referral laboratories were considered. The availability and use of other WHO-recommended molecular tests were also considered in recommending a suitable diagnostic algorithm.

### Human research conduct

Study conduct was approved by the Institutional Ethics Committee, P.D. Hinduja Hospital and Medical Research Center (1313–19-CR (SP)), the Ethics Committee of the National Center for Tuberculosis and Lung Diseases of Georgia (FWA00020831), and the Human Research Ethics Committee of the University of the Witswatersrand, Johannesburg (R14/49: M200113), as well as the WHO Research Ethics Review Committee (ERC.0003342).[11] The trial is registered at clinicaltrials.gov (NCT04239326).

### Patients and public involvement

Patients or the public were not involved in the design, or conduct, or reporting or dissemination plans of our research.

### Results tNGS data generation

GenoScreen generated sequencing data for 88.5% (675/763) while ONT generated sequencing data for 93.1% (710/763) of all samples tested across Xpert MTB/RIF semiquantitative result categories (figure 2), independent of smear or culture positivity. For all drugs assessed, GenoScreen generated sequencing data for >94% of all samples with high or medium Xpert semiquantitative results. For RIF, INH, SM, EMB, MFX, LFX, AMK, CAP, BDQ, LZD and CLF, ONT generated sequencing data for >90% of all samples with high or medium Xpert semiquantitative results. Both solutions generated sequencing data for >59% of all samples with low Xpert semiquantitative results. For samples with very low Xpert semiquantitative results, GenoScreen generated sequencing data for only 2%–8% of samples compared with 29%–43% of samples for ONT. Overall, a significantly higher percentage of samples in the Xpert high and medium categories generated sequencing data compared with those in the low and very low categories for both solutions (p<0.05).

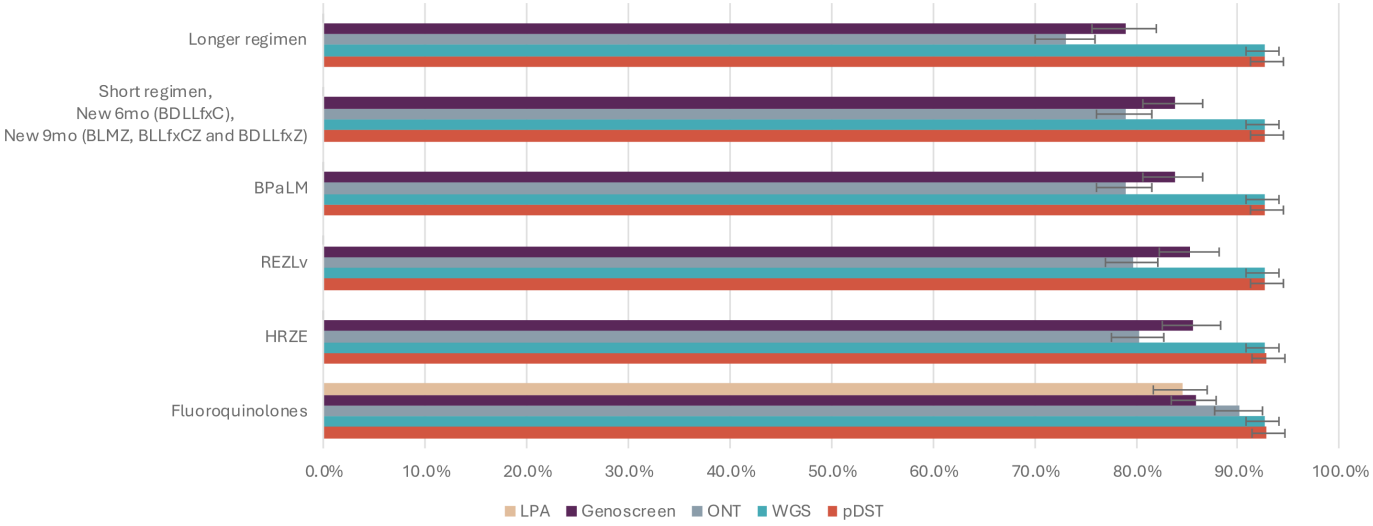



**Figure 3** Potential of tNGS to generate sequencing data to inform drug regimen selection compared with whole genome sequencing and phenotypic drug susceptibility testing reference standards. BPaLM, bedaquiline, pretomanid, linezolid and moxifloxacin; HRZE, isoniazid, rifampicin, pyrazinamide and ethambutol; LPA, line probe assay; ONT, Oxford Nanopore Technologies; pDST, phenotypic drug susceptibility testing; REZLv, rifampicin, ethambutol, pyrazinamide and levofloxacin; tNGS, targeted next-generation sequencing; WGS, whole genome sequencing. The following drug information was considered relevant to inform regimen selection: isoniazid, rifampicin, pyrazinamide and ethambutol for HRZE; isoniazid, rifampicin, pyrazinamide, ethambutol and levofloxacin for REZLv; isoniazid, rifampicin, pyrazinamide, ethambutol, levofloxacin, BDQ and linezolid for BPaLM; isoniazid, rifampicin, pyrazinamide, ethambutol, levofloxacin, BDQ, linezolid and clofazimine for the short regimen; and isoniazid, rifampicin, pyrazinamide, ethambutol, levofloxacin, BDQ, linezolid, clofazimine, amikacin and ethionamide for the long regimen. None of the tests provided information for pretomanid resistance. WGS did not provide information for BDQ or clofazimine, and phenotypic DST was not performed for ethionamide. These drugs were left out of the relevant calculations for BPaLM (eg, BDQ was not considered for the ability of WGS to generate data for the BPaLM regimen) and the short and long regimens. Results were expressed as a percentage of the total enrolled patients tested (n=784 for WGS, pDST; n=763 for GenoScreen; n=766 for ONT; n=782 for line probe assay) including 95% CIs.



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Of the total (n=763) number of samples sequenced by both tNGS solutions, 88.5% (95% CI 86.0 to 90.7) returned results for any drug target for the GenoScreen solution and 93.1% (95% CI 91.0 to 94.8) returned results for any drug target for the ONT solution. All 763 samples (including overall indeterminates) are reflected in figure 2, including 364 samples with 'high', 249 samples with 'medium', 101 samples with 'low' and 49 samples with 'very low' Xpert semiquantitative results.

For all relevant regimens, WGS and pDST-generated complete data to inform regimen selection for 92.6%–92.9% of tested patients (figure 3). The GenoScreen solution generated complete data for the respective drug targets to inform HRZE regimen (i.e. INH, RIF, PZA and EMB) selection for 85.6% (95% CI 82.9% to 88.0%) of patients, REZLv selection for 85.3% (95% CI 82.6%–87.8%) of patients, BPaLM, short regimen and the new 6-month and 9-month regimen selection for 83.7% (95% CI 80.9% to 86.3%) of patients, and long regimen selection for 78.9% (95% CI 75.8% to 81.7%) of patients. The ONT solution generated complete data for the respective drug targets to inform HRZE selection for 80.3% (95% CI 77.3% to 83.1%) of tested patients, REZLv selection for 79.6% (95% CI 76.6% to 82.4%) of patients, BPaLM, short regimen and the new 6-month and 9-month regimen selection for 79.0% (95% CI 75.9% to 81.8%) of patients, and long regimen selection for 73.1% (95% CI 69.8% to 76.2%) of tested patients. For a single drug compound (ie, fluoroquinolones), the tNGS solutions generated valid results as or more often than the MTBDR*sl* assay.

For RIF resistance detection, the two tNGS solutions demonstrated equivalent or higher sensitivity than the compiled, WHO-reviewed data for Xpert MTB/RIF, Xpert MTB/RIF Ultra, Truenat RIF, MTBDR*plus* V.2 or the collective moderate complexity assays (table 1). For INH resistance detection, the two tNGS solutions also demonstrated equivalent or higher sensitivity than the compiled, WHO-reviewed data for MTBDR*plus* V.2, the moderate complexity assays or Xpert MTB/XDR. For PZA resistance detection, the tNGS solutions demonstrated similar sensitivity to the Genoscholar PZA-TB II. For fluoroquinolone and second-line injectable (AMK, KAN and CAP) resistance detection, the tNGS solutions demonstrated equivalent or higher sensitivity than the MTBDR*sl* V.1 or the Xpert MTB/XDR assay.

Sensitivity estimates for WHO recommended molecular tests were taken from the WHO consolidated guidelines

**Table 1** Sensitivity of tNGS solutions against other WHO recommended molecular tests compared with a reference standard of phenotypic culture-based DST, stratified by drug target

| | ONT (1 study \| 763 participants) | GenoScreen (1 study \| 763 participants) | Xpert MTB/RIF (5 studies \| 921 patients) | Xpert Ultra (5 studies \| 930 patients) | Truenat RIF (1 study \| 309 specimens) | MTBDRplus v2 (4 studies \| 872 samples) | cDST Solutions (18 studies \| 2874 specimens) | Genoscholar PZA-TB II (7 studies \| 964 participants) | Xpert MTB/XDR (3 studies \| 1605 participants) | MTBDRsl v1 (9 studies \| 1771 smear-positive participants) |
|---|---|---|---|---|---|---|---|---|---|---|
| RIF | 97.4 (95.6, 98.6) | 99.0 (97.6, 99.7) | 95.3 (90.0, 98.1) | 94.9 (88.9, 97.9) | 84.3 (72.0, 91.8) | 95.8 (92.6, 97.6) | 96.7 (93.1, 98.4) | | | |
| INH | 95.3 (93.1, 97.0) | 96.5 (94.5, 98.0) | | | | 94.5 (91.4, 96.5) | 86.4 (82.1, 89.8) | | 94.2 (89.3, 97.0) | |
| SM | 81.2 (77.3, 84.8) | 98.8 (97.2, 99.6) | | | | | | | | |
| EMB | 85.0 (81.0, 88.4) | 95.6 (92.9, 97.5) | | | | | | | | |
| PZA | 74.9 (70.0, 79.4) | 89.3 (85.4, 92.4) | | | | | | 81.2 (75.4, 85.8) | | |
| MFX | 94.7 (91.6, 97.0) | 97.2 (94.6, 98.8) | | | | | | | 93.1 (88.0, 96.1) | 86.2 (74.6, 93.0) |
| LFX | 93.4 (90.1, 96.0) | 96.2 (93.4, 98.1) | | | | | | | 93.1 (88.0, 96.1) | 86.2 (74.6, 93.0) |
| AMK | 87.9 (76.7, 95.0) | 94.4 (84.6, 98.8) | | | | | | | 86.1 (75.0, 92.7) | 84.9 (79.2, 89.1) |
| KAN | 79.2 (69.7, 86.8) | 83.0 (73.8, 90.0) | | | | | | | 91.5 (83.1, 96.0) | 66.9 (44.1, 83.8) |
| CAP | 81.5 (68.6, 90.8) | 88.0 (75.7, 95.5) | | | | | | | 76.5 (55.7, 89.4) | 79.5 (58.3, 91.4) |
| BDQ | 5.7 (1.0, 19.2) | 81.3 (63.6, 92.8) | | | | | | | | |
| LZD | 46.9 (29.1, 65.3) | 44.4 (25.5, 64.7) | | | | | | | | |
| CLF | 0.0 (0.0, 10.9) | 87.5 (71.0, 96.5) | | | | | | | | |

AMK, amikacin; BDQ, bedaquiline; CAP, capreomycin; CLF, clofazimine; EMB, ethambutol; INH, isoniazid; KAN, kanamycin; LFX, levofloxacin; LPA, line probe assay; LZD, linezolid; MFX, moxifloxacin; ONT, Oxford Nanopore Technologies; PZA, pyrazinamide; RIF, rifampicin; SM, streptomycin; tNGS, targeted next-generation sequencing.

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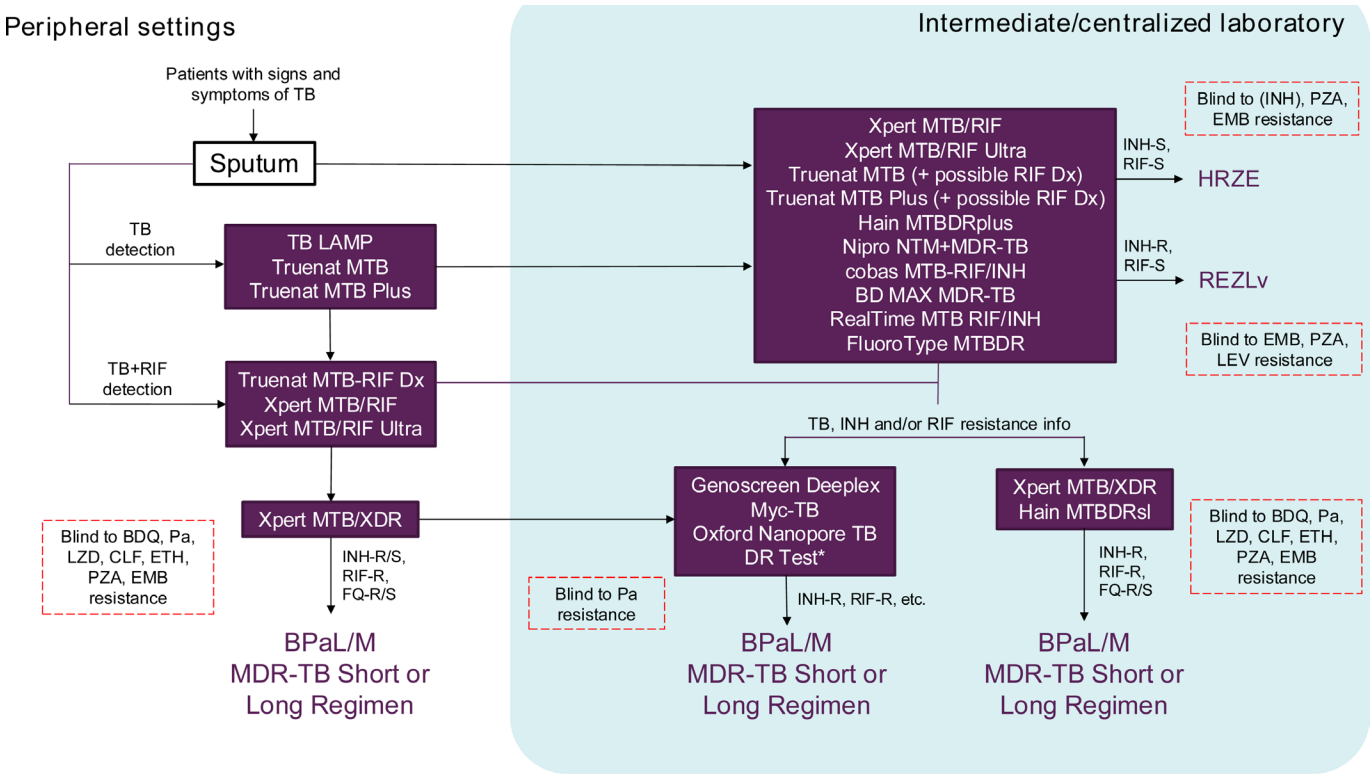



**Figure 4** Proposed diagnostic algorithm for centralised laboratories including tNGS. *It is envisioned that centralised workflows receive samples programmatically for high-throughput TB and resistance testing (ie, direct sample testing via entry tests such as Xpert MTB/RIF or moderate complexity assays or platforms such as BD MAX MDR-TB) or receive samples obtained following an initial TB positive result on an entry assay run in a peripheral testing centre (eg, using decentralised Truenat or GeneXpert platforms), or a combination of these two sample receipt pathways. If a sample generated a TB-positive result on an up-front assay that also generated a RIF resistance result, the sample might be directly tested by second-line resistance assays (eg, Xpert MTB/XDR, MTBDRsl or either of the two tNGS solutions), with tNGS providing the most comprehensive resistance profiling. Factors such as resistance prevalence should also be considered when considering how to run tNGS solutions in a given setting, as tNGS would be anticipated to have better positive predictive value for a high DR-TB burden setting (eg, a DR-TB referral centre such as Hinduja Hospital in Mumbai, India), where it might be run as an upfront assay with maximal impact without waiting for up-front DR-TB testing results, or TB samples from high burden settings might be otherwise included to fill up a tNGS run. Furthermore, given the relatively open design of tNGS solutions compared with existing rapid diagnostics, existing tNGS gene targets may be easily updated to accommodate new mutation calls through bioinformatics analysis, while additional tNGS gene targets (eg, for pretomanid) may be added to the initial multiplex as new information becomes available, further 'unblinding' clinicians to patient resistance profiles prior to treatment. The Nipro PZA line probe assay may also be run at any point of the centralised algorithm to inform PZA resistance. All 'blind' boxes reference rapid DST, as pDST should be performed in parallel. BDQ, bedaquiline; BPaL/M, bedaquiline, pretomanid, linezolid (and moxifloxacin); CLF, clofazimine; DR-TB, drug-resistant tuberculosis; DST, drug susceptibility testing; EMB, ethambutol; ETH, ethionamide; FQ, fluoroquinolone; HRZE, isoniazid, rifampicin, pyrazinamide and ethambutol; INH, isoniazid; LFX, levofloxacin; LZD, linezolid; MDR-TB, multidrug-resistant tuberculosis; ONT, Oxford Nanopore Technologies; Pa, pretomanid; pDST, phenotypic drug susceptibility testing; PZA, pyrazinamide; -R, resistant; REZLv, rifampicin, ethambutol, pyrazinamide and levofloxacin; RIF, rifampicin; -S, susceptible; TB, tuberculosis; tNGS, targeted next-generation sequencing.

on TB: module 3: diagnosis: rapid diagnostics for TB detection, 2021 update,[17] and web annexes with the exception of the sensitivity estimates for Xpert MTB/RIF and Ultra, which were taken from the Cochrane systematic review.[18] Specificity of the ONT solution was >99% for all drugs except SM (90.2%) by ONT. Specificity of the GenoScreen solution was >97% for all drugs except SM (95.9%). Of note, estimates for entry tests (ie, Xpert MTB/RIF and Ultra, Truenat RIF, even MTBDRplus and cDST solutions) include study populations screened based on TB symptoms, rather than DR-TB or risk factors for DR-TB as for tNGS solutions and other molecular reflex tests.

Given the relative complexity of tNGS and associated infrastructure and training requirements, a suitable diagnostic algorithm foresees tNGS being used within a centralised, referral laboratory in reflex to a positive result from either a peripherally performed TB detection test (eg, Xpert MTB/RIF or Truenat MTB) or a moderate complexity assay, including Xpert MTB/XDR, if resistance is detected to any drug (figure 4). Running a tNGS solution as the up-front test on a received TB-positive



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sputum specimen might also be considered given local DR-TB prevalence or incidence rates, patient DR-TB risk factors or other suspicion of resistance.

## DISCUSSION

The global rollout of new TB drugs and regimens, including BPaL/M, requires appropriate diagnostic tools to ensure effective patient treatment and preserve these important compounds. The GenoScreen Deeplex Myc-TB and ONT TB Drug Resistance Tests are accurate for resistance detection to an expanded array of first-line and second-line TB drug compounds,[11] and unlike any other WHO-recommended molecular test to date, also provide valuable information regarding BDQ and LZD resistance to inform clinical management decisions. Using the largest dataset underlying the WHO review of these tNGS solutions,[8 9] we found that tNGS results were generated for the vast majority (> ~90%) of samples with Xpert MTB/RIF high and medium semiquantitative calls and the majority (> ~60%) with low calls. The tNGS solutions generated data for all drugs in recommended regimens (with the exception of pretomanid) for >73% of the total samples tested. To inform BPaL/M regimen eligibility, the two tNGS solutions generated data for >79% of the total samples tested. Furthermore, the tNGS solutions had equivalent or superior performance in terms of sensitivity for resistance detection for every drug reported compared with all other WHO-recommended molecular tests to date. Together, these results suggest that the evaluated tNGS solutions provide valuable information in reflex to an upfront DR-TB result and support tNGS positioning in clinical testing algorithms, with WHO-recommended molecular tests providing limited DST closer to patient entry into the care cascade and tNGS solutions offering comprehensive DST at a more centralised level.

Although the overall tNGS success rate was high, there was a significant correlation between sample bacillary load and the ability to obtain a tNGS result. It is well established that paucibacillary samples can be challenging for optimal molecular testing,[17] and the ability of the tNGS solutions to generate results for the majority of samples with Xpert MTB/RIF low, medium or high calls is notable, and similar to MTBDR*sl* performance on Xpert cartridge extracts.[19] The MTBDR*plus* already features in WHO algorithm 1, where a WHO-recommended molecular test is used as the initial TB diagnostic test.[17] In this algorithm, if a non-trace TB detection call is obtained by Xpert MTB/RIF Ultra but RIF is indeterminate and the melt curve is not consistent with the presence of a deletion or multiple mutations, LPA or sequencing may be performed to confirm or exclude resistance. The ability of the tNGS solutions to generate data for the vast majority of samples with low to high Xpert MTB/RIF semiquantitative TB detection results supports a similar positioning of tNGS as a reflex test to confirm initial test results with the advantage of providing resistance information for many additional drug compounds. It is also notable that only Xpert MTB/RIF-positive samples were included in the Seq&Treat assessment. Although 48 samples were excluded due to a negative Xpert on the second (study) sample, it is likely that the upfront testing of samples prior to tNGS potentially eliminated downstream tNGS failures. Thus, the upfront testing of samples with entry assays may save significant time and cost. Further studies are needed to determine whether semiquantitative results for upfront molecular tests may also be reliable predictors of tNGS success and used to further optimise the diagnostic algorithm.

With regards to recommended regimens,[7] the tNGS solutions fully informed regimen selection in 73%–86% of cases, compared with 92%–93% of cases for pDST or WGS. Notably, both culture and WGS repeats were allowed in this study, likely inflating reference test performance, whereas tNGS was performed once per sample.[11] Furthermore, the tNGS platforms had comparable performance to the MTBDR*sl* assay for a single drug (ie, fluoroquinolones). One limitation of this analysis was the equal weighting of drugs in the calculations (eg, a result for BDQ resistance was weighted equally to a result for AMK resistance, although BDQ treatment is preferred and thus features more prominently in recommended regimens). Nonetheless, considering the long time to result of pDST and WGS and the additional limitations of each reference test, tNGS solutions present a valuable option to generate timely results for a wide portfolio of drugs direct from sputum samples, informing regimen selection while waiting for pDST or WGS, methods which are dependent on a culture pre-step, to return results.

In terms of performance for drug resistance detection, the two tNGS solutions had equivalent or superior performance to all existing WHO-recommended molecular tests for all drugs included in the readout. Notably, both tNGS solutions met target product profile minimal criteria for relevant first-line and second-line drugs[12 20] and generated sequencing data for BDQ, LZD and CLF for a large portion of samples against a results calling algorithm that can easily be updated as more information becomes available regarding identified mutations' association with resistance.[21] In the interim, interpreting sequencing information for some drugs as 'ruling out' resistance, or screening for the absence of relevant mutations, deletions or frameshifts in the genes covered by the tNGS solutions, rather than 'ruling in' or specifically detecting well-defined resistance-associated mutations, might be a valid strategy for drugs such as BDQ.[6]

Despite the strong performance of tNGS solutions compared with WHO-recommended molecular tests, there are important placement considerations for tNGS technologies that were not considered in this evaluation.[10 22] In particular, this class of tests is not meant to replace assays intended for initial diagnosis given concerns regarding complexity and accessibility. Rather, tNGS represents a valid alternative to pDST for comprehensive drug resistance predictions.[23] Notably, tNGS solutions are available with various

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throughput capabilities, depending on which sequencer is selected for the workflow (eg, batching requirements anticipate the routine sequencing of 22 samples per run on ONT MinION/GridION flow cells and 13 samples per run on Illumina iSeq 100/MiSeq (Micro kit) platforms).[9] Higher throughput is possible using larger kits and platforms, and multidisease testing is also encouraged in settings where few priority samples are handled to save costs across programmes. Sample throughput, as well as the degree of high-level infrastructure and skill requirements for performance of tNGS, currently limit these technologies to central (referral) laboratories, similar to the LPA and moderate complexity assays, where batching requirements might be met for reflex testing in low-DR-TB to high-DR-TB burden settings for a range of patient population sizes. Studies on cost-effectiveness are needed to identify the optimal batch sizes, turnaround times and sequencing solutions while considering the drug resistance burden, referral systems, testing volumes, capital investments and maintenance. As current moderate complexity assays such as the Abbott RealTime MTB RIF/INH, FluoroType MTBDR, BD MAX MDR-TB and cobas MTB-RIF/INH only report resistance for first-line drugs INH and RIF but have more rapid turnaround times than either tNGS solution, it is envisioned that in centralised healthcare settings incoming samples might first be tested by any one of these moderate complexity solutions if an initial result was not already obtained by Xpert MTB/RIF or Truenat MTB+RIF at the peripheral level, with TB samples testing RIF-resistant by one of these initial assays then reflexed to tNGS as an alternative to Xpert MTB/XDR or Hain MTBDR*sl* for full resistance profiling.

Another limitation of the analysis was the failure to include additional DR-TB comparator tests other than MTBDR*sl*. Additional studies focused on head-to-head performance of tNGS solutions against other WHO-recommended molecular tests (eg, Xpert MTB/XDR) as direct reflex tests to entry test results will allow for direct performance comparisons and increase confidence in use of tNGS solutions with or in place of other molecular tests in centralised settings. Additionally, the performance of the tNGS solutions is expected to improve given the recent release of the second edition of the WHO catalogue of mutations associated with drug resistance,[23] which may be used for an updated, in silico analysis of the tNGS solutions and composite reference standard. Work has begun on a third edition to further fill knowledge gaps for pretomanid and other relevant TB drugs, and it remains a global priority to strengthen the evidence base for phenotypic and genotypic correlations. For pretomanid, the ONT TB drug resistance test might be easily updated to report resistance, as the assay already includes delamanid resistance genes implicated in cross-resistance. An additional limitation of the current assessment is that the usability and clinical utility of the tNGS solutions were not specifically evaluated in Seq&Treat, which would inform implementation of these assays and further support their use in diagnostic algorithms and in the context of current regimens, especially for efficient triage of patients to all-oral DR-TB treatments.[9] Future studies investigating the time to result, cost-effectiveness and especially patient outcomes associated with tNGS triage to specific regimens will be critical to support tNGS positioning in national diagnostic algorithms. Furthermore, sample referral network analyses and turnaround times were not estimated in the Seq&Treat study, although sample transport networks should be strengthened in combination with well-established, regional sequencing facilities to ensure effective scale-up and implementation of tNGS.

Although certain sequencing-based strategies exist that provide a more comprehensive picture of TB drug resistance than tNGS, they are not yet readily available for clinical decision-making. WGS, for example, has been demonstrated direct from sputum using target enrichment steps, thereby lowering the time-to-result.[24] However, sample preparation remains a challenge to ensure adequate sensitivity for resistance detection as well as complete and deep coverage of genomes. Due to these limitations and other technical complexities, including bioinformatics, the approach remains largely removed from clinical care. Other sequencing approaches, such as Qiagen's QIAseq xHYB *M. tuberculosis* panel, which relies on probe-based target enrichment for culture-free WGS of TB may prove valuable to generate reads for a range of TB sample types, although data from the full workflow testing of clinical samples is needed to support this approach.[25] Alternative phenotypic approaches, such as microbroth dilution plates,[26] are still in development and require extensive validation and development prior to availability for programmatic use.

## CONCLUSION

Overall, the GenoScreen Deeplex Myc-TB and ONT TB Drug Resistance Test generated sequence data to inform TB and DR-TB regimen selection for the majority of all Xpert MTB/RIF-positive patients tested. For all drugs, the two tNGS solutions demonstrated equivalent or higher sensitivity than all available WHO-recommended molecular tests, and tNGS performance is only expected to improve. Operational and implementation research on these technologies will be key to further inform positioning of these technologies in DR-TB diagnostic algorithms and guide implementation.

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**Contributors** REC, AS and MR conceived the study. REC and SBG led the study design and implementation. SBG coordinated data analysis and interpretation with support from MS, AMC and NI. SBG and MS curated and analysed the data. NT, CR and SVO contributed to the laboratory components and assay implementation. REC, AS, MR, SU and AMC provided oversight and critical revision of the manuscript. SBG drafted the manuscript with input from all co-authors. All authors reviewed and approved the final version of the manuscript. SBG is the guarantor for this manuscript.

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**Competing interests** REC received salary support and travel cost reimbursement according to the terms of a service contract between FIND and their home institution, UC San Diego. REC has additionally received funding for a grant through NIH/NIAID to develop and evaluate a tNGS solution for drug resistant TB (R01AI176401). REC is a co-inventor on a patent associated with the processing of TB sequencing data (European Patent Application number 14840432.0 & USSN 14/912,918). REC has agreed to 'donate all present and future interest in and rights to royalties from this patent' to Translational Genomics Research Institute.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Ethics approval** This study involves human participants. Study conduct was approved by the Institutional Ethics Committee, P.D. Hinduja Hospital and Medical Research Center (1313-19-CR (SP)), the Ethics Committee of the National Center for Tuberculosis and Lung Diseases of Georgia (FWA00020831) and the Human Research Ethics Committee of the University of the Witswatersrand, Johannesburg (R14/49: M200113), as well as the WHO Research Ethics Review Committee (ERC.0003342). The trial is registered at clinicaltrials.gov (NCT04239326). Participants gave informed consent to participate in the study before taking part. Participants gave informed consent to participate in the study before taking part.

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**Data availability statement** Data are available upon reasonable request. The relevant data are presented in the manuscript. All sequence data can be found on the NCBI Sequence Read Archive (SRA) under the accession number PRJNA1160005. Additional data are available upon request. Available documents include the Seq&Treat study protocol and statistical analysis plan. Templates of the informed consent forms may also be shared upon request. Please contact the corresponding author with reasonable requests.

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