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ORIGINAL ARTICLE

# Policy to practice: impact of GeneXpert MTB/RIF implementation on the TB spectrum of care in Lilongwe, Malawi

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**Background:** While previous research has provided evidence of the diagnostic accuracy of the GeneXpert MTB/RIF (GeneXpert), further information is needed about implementation in the real-world. This study evaluated the impact of the introduction of GeneXpert testing in a tertiary medical center according to the testing algorithm proposed by the National TB Control Program (NTP) guidelines.

**Methods:** All adult medical inpatient persons with presumptive TB admitted between November 2013 and March 2014 were eligible for GeneXpert sputum testing and followed to TB treatment initiation status.

**Results:** We identified 932 persons with presumptive TB, of which 307 (32.9%) were GeneXpert tested. Those tested had an average age of 40 years, 49.2% (151) were male, 34.5% (106) were HIV positive, and 84.1% (249) presented with a cough. Of those GeneXpert tested, 28/307 (9.1%) tested positive, a 55.5% increase in detection compared to smear microscopy. However, the majority (44/72, 61%) of TB diagnoses were made by other modalities and not confirmed microbiologically. Of the 58 patients recommended to start treatment and discharged from the hospital, only 23 (40%) were documented to have started treatment at regional directly observed treatment, short course (DOTS) centers.

**Conclusions:** GeneXpert contributed minimally to overall TB diagnosis and the cascade of care due to implementation challenges of sputum collection, empiric treatment, and weak linkage to care between inpatient and outpatient settings.

**Keywords:** Diagnosis, GeneXpert, GeneXpert negative TB, HIV, Malawi, Pulmonary tuberculosis

## Introduction

TB is a leading cause of mortality among HIV co-infected individuals, with a disproportionate burden in Sub-Saharan Africa.[1] Improving TB diagnostics is one strategy to reduce TB morbidity and mortality.[1] The conventional procedure for TB diagnosis is AFB smear microscopy, which is a low-cost test with a high specificity (90%).[2,3] However, it is only able to identify 20–60% of incident TB cases, with decreased detection abilities among HIV infected individuals.[2–4] The GeneXpert MTB/RIF (GeneXpert) is a molecular diagnostic tool that has a rapid sample processing turnaround time (less than 2 hours), high sensitivity (89%) and specificity (99%), and the ability to detect rifampicin drug resistance.[4,5] GeneXpert increases TB case detection by 23% compared to AFB smear.[5]

While previous research has provided strong evidence of the diagnostic accuracy of the GeneXpert,[4] further information is needed about real-world implementation in resource challenged settings. GeneXpert implementation poses challenges related to both infrastructure requirements for testing[6–8] as well as healthcare delivery related factors[9,10] suggesting that expected gains in treatment outcomes may be difficult to achieve. In clinics in South Africa, while more TB cases were confirmed, overall mortality and TB treatment initiation rates did not change after implementation of GeneXpert.[11]

In concordance with the WHO recommendation, Malawi has also adopted GeneXpert testing into national health policy.[4,7,12] The Malawi National TB Control Program (NTP) has endorsed screening hospitalized persons with presumptive TB with GeneXpert.[12] In this setting, the dual burden of HIV and TB, representing 38%[13] and 16%[14] of admission diagnoses, emphasizes the potential importance of the assay in this population.

This study evaluated the impact of the introduction of GeneXpert testing in a tertiary medical center according to the testing algorithm proposed by the NTP guidelines.[12] In addition, we evaluated the cascade of care for TB, from screening to detection to treatment status.

## Materials and methods

### Study setting and population

Kamuzu Central Hospital (KCH) is a 1000 bed tertiary referral facility in Lilongwe, Malawi with approximately 5000 admissions to the adult medical wards per year.[14] All patients admitted to the medical wards and >14 years of age, from November 2013 through March 2014, were eligible. The NTP protocol recommends GeneXpert testing for all patients that present with 'danger signs' and have TB-related symptoms.[12] 'Danger signs' were defined as 'respiratory rate >30 per min, temperature >39°C, heart rate >120 beats per minute, patient confused or agitated, respiratory distress, systolic blood pressure <90 mmHg or inability to walk unassisted.'[12] Patients self-reporting with recent fever, cough, night sweats or weight loss for any period of time should be suspected of and tested for TB.[12]

### Study design

We conducted a prospective study of all KCH adult inpatients to assess the impact of GeneXpert detection of TB cases in the wards and initiation of TB treatment.

### Screening and testing procedures

Routine HIV testing was conducted in the wards by trained HIV testing (HTC) counselors. The counselors systematically screened and offered testing to all patients admitted to the wards. Patients with an unknown HIV status or a negative HIV test (>3 months ago) were offered opt-out HTC by the counselor (serial testing with HIV 1/2 and Unigold HIV 1/2).[15] The results of the test were then recorded in the patient's file.

Before implementation of the new guidelines, TB testing was initiated by the medical provider and sputum samples were tested using AFB smear at the KCH lab. Provider-initiated diagnostic methods such as chest x-ray, ultrasound, or fine needle aspiration were also utilized to aid in TB diagnosis. TB diagnosis and management was followed according to standard hospital protocol.

### Kamuzu Central Hospital and the Malawi National TB Control Program protocols

During implementation, we conducted TB screening and applied the NTP GeneXpert testing protocol.[12] All patients triaged from the short stay, or acute care, and subsequently admitted as an inpatient were presumed to meet the criteria for 'danger signs' based on hospital threshold for admission. A clinical officer, an existing Ministry of Health staff, was trained as the 'TB screening champion.' The clinical officer identified all admissions within the past 24 hours (recorded in the ward nurse's admission logs) and screened for all patients with TB symptomology. These admitted patients that initially presented with 'danger signs' and had relevant symptomology were defined as 'persons with presumptive TB'. Patients were asked to produce one sputum sample into a labeled container. Samples were collected by the clinical officer or placed in a designated collection location in the wards by the patient's guardian, if the patient could not expectorate immediately. No sputum induction process was available as per standard hospital protocol.[16] Clinic aides transported samples from the wards to the lab facility and testing at the lab facility took place Monday through Friday, 08:00 to 17:00 h. Results were communicated with the patient's medical care team as soon as they were available, between 08:00 and 17:00 h during weekdays.

In concordance with Malawi guidelines for GeneXpert, one sputum specimen per patient was obtained with coaching from the clinical officer.[12,16] The sample was processed adhering to the standardized protocol and quality control procedures of the UNC Project laboratory. GeneXpert testing was performed on the sputum sample according to the manufacturer's operation instructions. Additionally, fluorescence microscopy was used to examine smears for AFB. Smear positive results were determined by reporting *Mycobacterium tuberculosis* density, defined as scanty, 1+, 2+, or 3+. All test results were interpreted by trained laboratory personnel who were not blinded to the GeneXpert test result. The time of sample collection in the wards, receipt of sample at the lab, and processing of results was recorded.

### Data collection

A survey tool was used to collect demographic characteristics, address, patient ID number, symptoms and date of admission. The patient's phone contact information was recorded, in the event that test results were not available until after their discharge. HIV status was obtained from patient medical files, as HIV status was noted on medical charts by the HTC counselors. Review of patient files was performed weekly to abstract hospitalization outcome (death, discharge, abscond or transfer), date of outcome, and results of additional diagnostics (chest x-ray, ultrasound or fine needle aspiration). Any missing information of clinical characteristics was also extracted from the patient medical files.

Date of TB diagnosis was gathered from the patient medical files as treatment is not initiated on the wards. When the diagnosis of TB is confirmed, patients are transferred for inpatient hospitalization or discharged to receive outpatient therapy at the local directly observed treatment, short course (DOTS) center. All inpatient and outpatient TB patients register at one of the regional DOTS centers in order to receive therapy.

Patients were traced to a DOTS center in the Lilongwe District, where they were most likely to receive care based on their address. TB officers at each of the 15 sites were sent a list of patients who were diagnosed with TB at KCH. The officers then cross-referenced the patient information provided (patient's name, age and address) to the listings in the registry to determine if the patient had initiated treatment. The TB officers scanned the chronologically organized registries matching patients based on their date of discharge from KCH up to one month post-discharge. The Central District TB Officer of Bwaila

District Hospital in Lilongwe, Malawi also conducted random site visits to check on the accuracy of the matching.

### Statistical analysis

The primary outcome measures were the number of persons with presumptive TB tested, GeneXpert-positive patients and number recommended to start TB treatment. We used frequency and percentages to describe patient characteristics. Categorical variables were compared using Pearson's $\chi^2$ test. The change in TB case detection during GeneXpert implementation phase was calculated by comparing the proportion of GeneXpert-positives to the proportion of smear positives, stratified by HIV status. Programmatic factors were assessed by the length of time between date of admission, date of sample collection and date of result availability. Lastly, the proportion of patients registered for TB therapy at the Central district DOTS facilities was compared to all recommended to start TB treatment at KCH to measure linkage to care. All data was entered into an Access database (Microsoft Corp., Redmond, WA, USA) and analyzed using STATA 13 (StataCorp LP, College Station, TX, USA).

### Ethics

No consent process was necessary as TB testing is part of standard of care. Ethics approval was obtained from the Malawi National Health Science Research Committee and the University of North Carolina Medical School institutional review board.

## Results

### Characteristics

During the 4 month study period, 1936 patients were admitted to the medical wards, and 932 (48.1%) were identified as persons with presumptive TB (Figure 1); 51.8% (483) of persons with presumptive TB were under 30 years of age with a male to female ratio of 1.2:1. The most common symptoms were cough (454, 48.7%) and fever (604, 64.8%). Among persons with presumptive TB, 288 (30.4%) were HIV reactive, 236 (25.3%) were HIV nonreactive, and 408 (43.8%) were of unknown status.

### Implementation assessment

Of the 932 persons with presumptive TB, 307 (32.9%) were GeneXpert tested. In general, the gender distribution and HIV status among the persons with presumptive TB who were GeneXpert tested versus not tested were similar (Table 1). The primary reason persons with presumptive TB were not tested was failure to produce sputum (351, 37.7%) and notably, this group had a decreased frequency of cough as a primary symptom compared to those tested (33.9% vs 84.1%, p<0.0001).

The median length of time from admission to the wards to sample collection was 1 day (IQR 0–3) (Table 2). The median time from admission to GeneXpert result was 3 days (IQR 2–5). Lastly, the median time between hospital admission to recommendation to start TB treatment, based on a GeneXpert positive result, was 6 days (IQR 4–8).

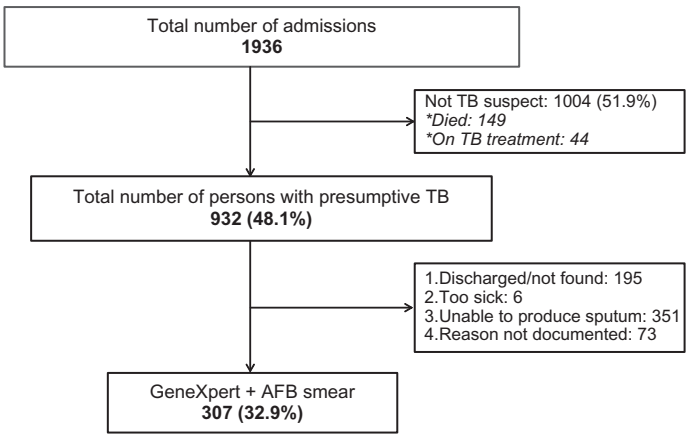


**Figure 1.** Flowchart of study participants. All inpatients admitted to the general male and female medical wards were screened for TB symptoms. They were defined as persons with presumptive TB if they met the criteria for danger signs and TB symptomology as described by the Malawi National TB Control Program (NTP) Manual.

### GeneXpert tested

Among the 307 inpatients tested, 28 (9.1%) were GeneXpert positive (Table 3). No rifampicin resistance mutations were detected.

The GeneXpert detected an additional 10 TB cases or increased TB detection by approximately 55.5%, compared to AFB smear. All AFB smear positives were also GeneXpert positive. Of the 11 GeneXpert positive-HIV positive patients, only six (54.5%) were detected by AFB smear. Demographics, symptoms and HIV status were similar according to GeneXpert status (Table 1)

### TB treatment

Out of 932 suspects, a total of 72 (7.7%) were recommended to start TB treatment. Of these, 28 (39%) were diagnosed with TB based on a positive GeneXpert results. Forty-four (61%) TB diagnosis were based on other modalities or clinical suspicion, of which 22 (31%) of patients were diagnosed on clinical suspicion and 22 (31%) were diagnosed with TB on evidence of radiological/histological evidence. All patients with a positive GeneXpert were started on TB therapy regardless of clinical, histological or radiological findings.

A total of 17 patients were GeneXpert-negative and recommended to start TB treatment. Twelve (71%) had radiographic evidence of TB (11 chest x-ray suggestion of TB, one abdominal ultrasound suggestion of TB). A majority of these GeneXpert-negative TB patients presented with cough (17, 100%) and were HIV positive (11, 65%).

A total of 27 patients were not GeneXpert tested and recommended to started TB treatment. 10/27(37%) had radiographic or histologic suggestion of TB. The remainder, 17 patients, were diagnosed based on clinical suspicion.

Of all patients recommended to initiate TB treatment, 14 (19%) died during the hospitalization. Of the 58 patients recommended to start treatment and discharged from the hospital, only 23 (40%) were documented to have initiated treatment at TB registration facilities in the Lilongwe district within 1 month of discharge from KCH.

**Table 1.** Demographic and clinical characteristics of all persons with presumptive TB (n=932)

| Characteristics | Persons with presumptive TB | | | |
|---|---|---|---|---|
| | Not GeneXpert tested (n=625) | GeneXpert tested (n=307) | GeneXpert positive (n=28) | GeneXpert negative (n=279) |
| | Frequency (%) | | | |
| Gender | | | | |
| Male | 363 (58.1%) | 151 (49.2%) | 13 (46.4%) | 138 (49.5%) |
| Female | 262 (41.9%) | 156 (50.8%) | 15 (53.6%) | 141 (50.5%) |
| Age[a] | | | | |
| 14–20 | 241 (44.1%) | 19 (6.2%) | 1 (3.6%) | 18 (6.5%) |
| 21–30 | 136 (24.9%) | 87 (28.3%) | 12 (42.9%) | 75 (26.9%) |
| 31–40 | 62 (11.4%) | 84 (27.4%) | 11 (39.3%) | 73 (26.2%) |
| 41–50 | 42 (7.7%) | 47 (15.3%) | 1 (3.6%) | 46 (16.5%) |
| >50 | 65 (11.9%) | 70 (22.8%) | 3 (10.7%) | 67 (24.0%) |
| Clinical features[b] | | | | |
| Cough | 205 (33.9%) | 249 (84.1%) | 23 (85.2%) | 226 (84.0%) |
| Fever | 482 (79.8%) | 122 (41.2%) | 9 (33.3%) | 113 (42.0%) |
| Night sweats | 79 (12.6%) | 47 (15.9%) | 7 (25.9%) | 40 (14.9%) |
| Weight loss | 115 (19.1%) | 50 (16.9%) | 7 (25.9%) | 43 (16.0%) |
| Hemoptysis | 14 (2.3%) | 14 (4.7%) | 1 (3.7%) | 13 (4.8%) |
| Shortness of breath | 99 (16.4%) | 37 (12.5%) | 3 (11.1%) | 34 (12.6%) |
| HIV status | | | | |
| Positive | 182 (29.1%) | 106 (34.5%) | 11 (39.3%) | 95 (34.1%) |
| Negative | 171 (27.4%) | 65 (21.2%) | 1 (3.6%) | 64 (22.9%) |
| Unknown | 272 (43.5%) | 136 (44.3%) | 16 (57.1%) | 120 (43.0%) |
| Outcome[c] | | | | |
| Discharged | 413 (81.5%) | 213 (90.3%) | 13 (92.9%) | 200 (90.1%) |
| Death | 83 (16.4%) | 23 (9.8%) | 1 (7.1%) | 22 (9.9%) |
| Absconded | 4 (0.8%) | NA | NA | NA |
| Transferred | 7 (1.4%) | NA | NA | NA |

Patients could have more than one clinical feature, so percentages of patients with each feature does not add to 100%.
[a] 79 missing age values for persons with presumptive TB not tested.
[b] 21 missing clinical features values among persons with presumptive TB-not tested; 118 missing outcomes values for persons with presumptive TB-not tested.
[c] 11 missing clinical features values among persons with presumptive TB tested, 71 missing outcomes values among persons with presumptive TB tested.
[d] 1 missing clinical features value among GeneXpert positives, 14 missing outcome values among GeneXpert positives.
[e] 10 missing clinical features values among GeneXpert negatives, 57 missing outcome values among GeneXpert negatives.
NA: not available.

**Table 2.** Turnaround time of the GeneXpert MTB/RIF and TB diagnosis in routine inpatient care at Kamuzu Central Hospital (KCH)

| Time intervals | Median time, days | IQR 25–75 n=307 |
|---|---|---|
| Date of admission to sample collection | 1 | 0–3 |
| Date of admission to GeneXpert result (from lab) | 3 | 2–5 |
| Date of admission to diagnosis of TB at KCH (GeneXpert positive) | 6 | 4–8 |

**Table 3.** Comparison of GeneXpert MTB/ RIF vs AFB smear results, stratified by HIV status (n=307)

| | HIV positive n=106 (%) | HIV negative n=65 (%) | Unknown n=136 (%) |
|---|---|---|---|
| GeneXpert MTB/ RIF | | | |
| Positive | 11 (10.3) | 1 (1.5) | 16 (11.8) |
| Negative | 95 (89.7) | 64 (98.5) | 120 (88.2) |
| AFB Smear[a] | | | |
| Positive | 6 (5.6) | 1 (1.5) | 11 (8.0) |
| Negative | 100 (94.4) | 64 (98.5) | 125 (92.0) |

[a]Each patient had a GeneXpert MTB/RIF and AFB smear test on a sputum sample, so two observations per patient.

## Discussion

Our study evaluated the impact of GeneXpert roll-out on TB diagnosis and treatment among inpatients in a resource challenged health care facility in Sub-Saharan Africa. The overall contribution of GeneXpert testing was small due to initiation of empiric therapy based on clinical symptoms and other diagnostics. Furthermore, there was low diagnostic impact due to operational challenges, such as difficulty with sputum sampling and slow turnaround time in a high volume setting. We also noted gaps in the continuum of care after discharge from the hospital. These findings suggest that implementation of the GeneXpert may not provide substantial change in patient outcomes in real world settings unless additional barriers are addressed.

### Empiric treatment

In our study, TB case detection increased only modestly among persons with presumptive TB after the implementation of GeneXpert. Despite GeneXpert implementation, initiation of TB treatment was disproportionately based on empiric treatment (61%), a process of diagnosing TB based on clinical suspicion and radiological findings and without bacteriological confirmation.[17] Our findings are similar to other studies in South Africa and Uganda that also reported this paradoxical phenomenon of high utilization of empiric treatment in the GeneXpert era.[16,18,19] Notably, even in settings with extensive diagnostics, TB can be missed. Autopsy studies in both the pre and post ART eras have demonstrated high rates of undiagnosed TB infection.[20,21] Physicians working in such environments may start patients on empiric therapy based on factors such as failure of antibiotic treatment, clinical danger signs, low healthcare access environment, delay in GeneXpert results, positive results using other radiologic modalities, or high patient mortality rate.[22–24] Overall, these findings suggest that empiric TB therapy is prevalent although the impact on patient outcomes is currently the subject of clinical trials.

### Gaps in diagnosis

Among persons with presumptive TB started on empiric TB treatment, a large proportion of patients were GeneXpert-negative or sputum scarce. Multiple previous studies have also documented this phenomenon.[25] In high HIV-TB burden environments, empiric treatment is often used to offset the diagnostic limitations and provide, possibly, same day treatment to decompensating patients.[21–25] The few studies presenting diagnostic information on GeneXpert negative individuals suggest that smear microscopy and chest x-ray have limited utility in detecting culture positive, Xpert negative, extrapulmonary or disseminated TB.[6,11] For sputum scarce patients, rapid diagnostics using other samples such as urine (urine LAM or urine GeneXpert) or blood may prove more feasible for testing. Overall, further guidelines are needed to address these gaps in diagnosis for GeneXpert negative and sputum scarce patients.[25]

### Mortality

We observed high in-hospital mortality rates among TB cases. First, our observed rate was congruent with TB mortality rates in other high-HIV prevalence settings (18–27%).[17,26,27] GeneXpert testing is expected to affect a decrease in mortality, presumably due to earlier diagnosis, thus earlier treatment. However, in hospital settings, TB disease may be sufficiently advanced that adverse outcomes are difficult to modify. Factors such as delay to presentation[28] or atypical presentation[29] may contribute to severe hospital presentations. The high in-hospital mortality rate confirms the need intensified case finding with GeneXpert further upstream, at the patient's first encounter with the healthcare system, in contrast to our referral medical facility.[17] Multiple healthcare environment factors and patient characteristics are important to consider and target in order to reduce mortality among patients with TB.

### Programmatic challenges

The 6 day turnaround time from admission to GeneXpert result, performed in a controlled research lab, was reduced compared to the 8 days for AFB smear results as reported in 2005.[30] Programmatic challenges were similar to previous reports, including delays with updated patient logs, sample submission, lab forms, transport of samples, result-to-clinical decision, and result-to-patient linkage.[31–33] This shows that hospital related work flow factors need to be improved simultaneously in order to gain full benefit of rapid diagnosis, particularly if sample volume is high. Task shifting TB screening to HTC counselors could

leverage existing infrastructure and staff capacity to manage increased TB suspect workload.[33–35] Other hospital related factors that could be targeted for improvement include communication between clinical staff and patients, documentation, coordination of care, and patient flow and tracking.[19,30,31]

### Linkage to care

While GeneXpert diagnosis did contribute to increased TB case detection, only 40% (23/58) were documented to have initiated treatment by registering at a TB registration center. This may be an underestimate as patients may have registered at a Central Region facility or inconsistency in matching names between registries. However, this finding is consistent with previous findings of loss to care in the TB care cascade.[36] Significant barriers to care include transportation costs, stigma and increased burden due to concomitant TB therapy and ART.[37–39] We suggest that TB control strategies should integrate strategies to eliminate gaps in the spectrum of care.

Our study is reflective of the programmatic challenges with implementation of an intervention in a routine hospital care setting and assessment of linkage to care, which presents some limitations. Approximately 20% of patient files were missing, leading to incomplete information regarding hospital outcomes. However, all patient files of those who had died were retained by the hospital ward clerks, such that we had 100% mortality ascertainment. Lastly, verification bias was present as not all persons with presumptive TB were GeneXpert tested and no confirmatory testing with culture was conducted. Likewise, sputum induction and collection of >1 sputum sample may increase diagnostic yield. However, this aligned with the NTP guidelines, which do not include culture for initial diagnosis, and impact evaluation directly relevant to our setting.

### Conclusions

Our pragmatic study of the implementation of the GeneXpert revealed only modest improvements in confirmed TB diagnosis and was limited by challenges in the implementation of the NTP algorithm. The current GeneXpert testing guidelines do not address the existing gaps in TB diagnosis, which are bridged by empiric-based TB diagnosis. Although our sample size was small, the blunted impact of the GeneXpert on diagnosis and initiation of TB treatment further emphasizes the need to identify alternative screening strategies to maximize utility and cost effectiveness of GeneXpert test.

Further investigation in the inpatient setting is needed to understand the accuracy of empirical TB treatment.

**Authors' contributions:** KSC: conception, design, acquisition, analysis, and interpretation of data, and drafting and revision; CK: conception, design, interpretation of data, revision; AB: acquisition of data; MM: conception, acquisition of data, and revision; IH: revision; JN: acquisition of data; MCH: conception, design, data analysis and interpretation, and drafting and revision. All authors provided final approval. KSC and MCH are the guarantors of the paper.

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