# CHALLENGES IN THE DIAGNOSIS OF DRUG- RESISTANT TUBERCULOSIS BY GENE-XPERT MTB/RIF IN NEPAL

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## ABSTRACT

**Introduction:** GeneXpert MTB/Rif assay is an automated, cartridge-based nucleic acid amplification test that can accurately detect both tuberculosis and Rifampicin resistance. Since its introduction, there has been a steady uptake of this technology by the National Tuberculosis Program of Nepal. Nevertheless, a large number of drug-resistant TB cases remains undiagnosed. This study aims to examine the challenges in diagnosis of drug-resistant tuberculosis by the GeneXpert MTB/Rif assay in Nepal and explore the possible solutions.

**Methods:** This was a cross-sectional study consisting of two parts – a quantitative part assessing the individual details and a qualitative part assessing the challenges on the diagnosis of drug-resistant TB by GeneXpert MTB/Rif assay. Data were collected from the GeneXpert operators, clinicians and program managers from 16 centers across the country and analyzed by IBM SPSS for Windows v23 and QDA Miner 4 Lite. Descriptive statistics were used to summarize the sociodemographic and other characteristics of the study participants using mean, standard deviation and proportions as appropriate.

**Results:** A total of 48 technical manpower participated in the study. The mean age was 39.95 years and a majority of them (77.3%) were male. The major challenges identified were inadequate training, frequent power failure, difficulty in maintaining appropriate steady temperature, module failure which is often not replaced in time, issues with calibration and timely availability of cartridges as well as appropriate ways to store the new cartridges and safe disposal of the used cartridges.

**Conclusion:** A number of challenges limit the optimal utilization of GeneXpert MTB/Rif assay warranting action.

**Key words:** Drug-resistant tuberculosis, GeneXpert MTB/Rif assay, challenges

## INTRODUCTION

TB (TB) remains a leading cause of death and the recent epidemic of drug-resistant TB presents a major public health challenge. In 2017, an estimated 10 million people developed TB disease, of which the TB disease of 558 000 was resistant to Rifampicin (RR TB) or to both Rifampicin as well as Isoniazid (MDR TB).[1] The South East Asia region bears a huge burden of TB – in 2015, nearly half of the global TB cases occurred in this region, of which 200000 cases were MDR/RR TB.[2] In Nepal, TB is the sixth leading cause of death and 2.2% of the new TB cases and 15% of the previously treated TB cases have been estimated to have MDR/RR TB.[3]

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Globally, the priorities of TB control programs are to improve early case-detection and to enhance the capacity to diagnose drug-resistant TB. To help achieve this goal, the World Health Organization (WHO), in 2010, approved and endorsed an automated, cartridge-based nucleic acid

amplification test that is based on the GeneXpert multi-disease platform – GeneXpert MTB/Rif assay (Cepheid, Sunnyvale, CA, USA).[4] It can detect both TB and resistance to Rifampicin in less than 2 hours and has been hoped to be a game changer in the TB diagnosis.[5]A Cochrane systematic review and meta-analysis has reported that the sensitivity of the GeneXpert MTB/Rif assay is 89% when used as an initial test, 67% when tested in smear-negative samples and 79% when tested in the samples from HIV positive patients. The specificity is 99%. In comparison with smear microscopy, GeneXpert MTB/RIF increased TB detection by 23%.[6] The recent WHO policy update on GeneXpert MTB/Rif assay has recommended it for lymph node aspirate, gastric aspirate and Cerebrospinal fluid (CSF) as well with the sensitivities of 84.9%, 83.8%, and 79.5% respectively.[7]

In Nepal, GeneXpert services were introduced in December 2011 through the TB REACH Wave 2 funding of the Stop TB partnership.[8] At present, there are more than 50 GeneXpert machines in different locations across the country. Nevertheless, a large number of drug-resistant TB cases still remain undiagnosed. In 2017, out of 496 estimated cases of drug-resistant TB, only 343 cases were diagnosed and enrolled in the treatment program.[3] This study aims to identify the context-specific challenges in the diagnosis of drug-resistant TB in Nepal by the GeneXpert MTB/Rif assay within the existing National TB Control Program framework and explore the possible solutions to the problems identified to provide recommendations to the program.

## MATERIALS & METHODS

This was a cross-sectional study consisting of two parts – a quantitative part assessing the individual demographic details and the relevant information based on his or her experience with the GeneXpert MTB/Rif and a qualitative part comprising of a Focus Group Discussion (FGD) on the challenges on the diagnosis of drug-resistant TB by GeneXpert MTB/Rif assay. Data were collected on July 2018 from the GeneXpert operators, clinicians and program managers from 16 representative GeneXpert centers across the country who gathered in five data collection sites.

(Table 1) Two trained data collectors in each of the study sites collected the data. A sign in sheet collected the information on the basic demographics, details on their work experience and the challenges faced in GeneXpert MTB/Rif assay utilization. It also served as an informed consent. The second part of the data collection consisted of an FGD using a structured format and recording the output of the discussion in the form of note-taking. A set of questions guided the discussions facilitated by probe questions when necessary.

The data obtained from the sign-in sheets were entered in Microsoft Excel (MS Office 2013, Microsoft Corporation, Washington, United States), cleaned, transported to and analyzed by IBM SPSS for Windows v23 (IBM Statistical Package for Social Sciences, 2015 IBM Corporation, New York, United States). For the analysis of FGD data, the transcripts were entered into and analyzed by QDA Miner 4 Lite (QDA Miner 4 Lite, 2012 Provalis Research, Montreal, Canada). Descriptive statistics were used to summarize the sociodemographic and other characteristics of the study participants using mean, standard deviation and proportions as appropriate.

## RESULTS

A total of 48 participants were included in the study (Table 2). The information on age and sex

**Table 1.** Study centers and data collection sites.

| Development Regions | Data collection sites | Additional study centers | Total no. of centers |
|---|---|---|---|
| Eastern | NATA Morang, Biratnagar | BPKIHS, Okhaldhunga | 3 |
| Central | NTC, Bhaktapur | GENETUP, Dhulikhel, HERD | 4 |
| Western | RTC, Pokhara | UMN Palpa, Lumbini Zonal | 3 |
| Mid-Western | TB Nepal, Nepalgunj | Kohalpur Medical College, Dailekh | 3 |
| Far-Western | Seti Zonal, Dhangadhi | Bayalpata Achham, Doti DHO | 3 |
| Total | | | 16 |

was available for 44 participants. The mean age was 39.95 years (SD ± 11.5) and a majority of the participants (77.3%) were male. The mean work experience in TB was 11.7 years (SD ± 9.9) and that with the GeneXpert MTB/Rif assay was 3.61 years (SD ± 2.19).

**Table 2.** Details of the study participants.

| Position | Service area | Number | Total |
|---|---|---|---|
| Operators of GeneXpert Machine | National Reference Labs | 8 | 22 |
| | Teaching Hospitals | 3 | |
| | Community Hospitals | 3 | |
| | Government Centers | 4 | |
| | Non-Government Organizations | 4 | |
| Clinicians | | | 13 |
| Program Managers | | | 13 |
| | | Total | 48 |

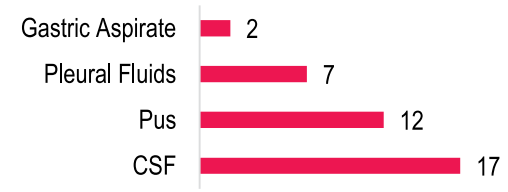
## Operators:

Five of the 22 respondents (22.7%) reported that they had not received any formal training on the operations of GeneXpert MTB/Rif assay. Most of GeneXpert MTB/Rif operators reported that they run two (45.5%) or three (50%) cycles of GeneXpert MTB/Rif assays in a typical working day (Table 3).

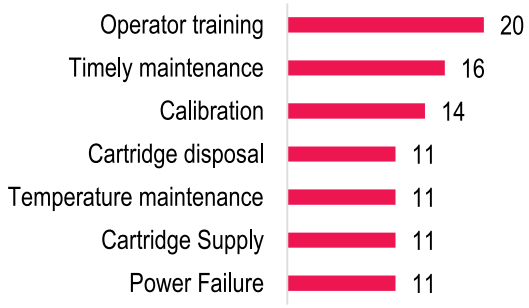
**Table 3.** Number of cycles of GeneXpert MTB/Rif tests per day.

| SN | Number of cycles | Frequency | Percent |
|---|---|---|---|
| 1 | 2 | 10 | 45.5 |
| 2 | 3 | 11 | 50 |
| 3 | 4 | 1 | 4.5 |

Just over half of the operators reported that they dispatched the GeneXpert MTB/Rif assay reports on the same day while the rest did on the next working day. All the participant operators responded that they had been conducting the GeneXpert MTB/Rif analysis of extra-pulmonary samples as well with CSF being the most commonly analyzed extra-pulmonary sample (Figure 1).




Among the problems reported by the operators, the most common was inadequate operator training (20 out of 22 responses) (Figure 2).




## Clinicians:

The average number of presumptive cases of drug-resistant TB encountered was reported to be 1.31 (SD ± 0.48) and the average number of GeneXpert MTB/Rif assay requests made in a typical working day was 4.85 (SD ± 2.82). Only two (15.3%) of the 13 respondents reported that they were confident in selecting appropriate patients for GeneXpert MTB/Rif assay analysis and/or interpreting the test results.

All the respondents reported that they had been sending extra-pulmonary samples as well for GeneXpert MTB/Rif analysis with CSF being the most common extra-pulmonary sample for whom GeneXpert MTB/Rif assay was requested (12 respondents) followed by pleural fluid (9 respondents) (Figure 3).

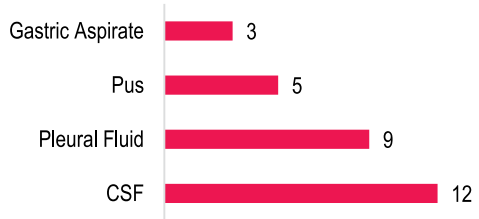



**Figure 3.** Extra-pulmonary samples requested for GeneXpert by clinicians.

Among the problems reported by the clinicians, the most common was the delayed availability of the GeneXpert MTB/Rif assay results and long waiting time to submit a sample for GeneXpert MTB/Rif assay (9 out of 13 responses) (Figure 4).

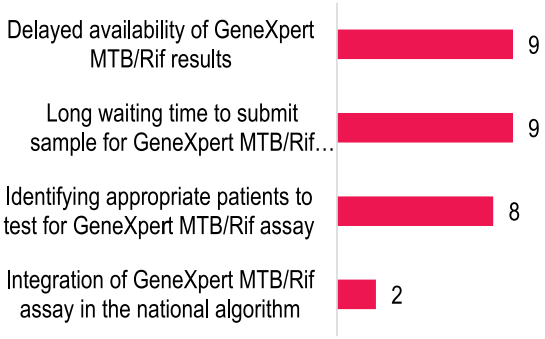



**Figure 4.** Challenges on GeneXpert identified by clinicians.

**Program managers:**

The average number of GeneXpert MTB/Rif assay test centers in the catchment program areas were reported to be 8.45 (SD ± 8.39). All except one participant responded that they thought the GeneXpert MTB/Rif assays were placed at the appropriate level of healthcare delivery system and the cost incurred justified the benefits (12 respondents each).

Among the problems reported by the program managers, the most common was lack of decentralization in the distribution of the GeneXpert MTB/Rif assay centers within their program areas (9 responses) (Figure 5).

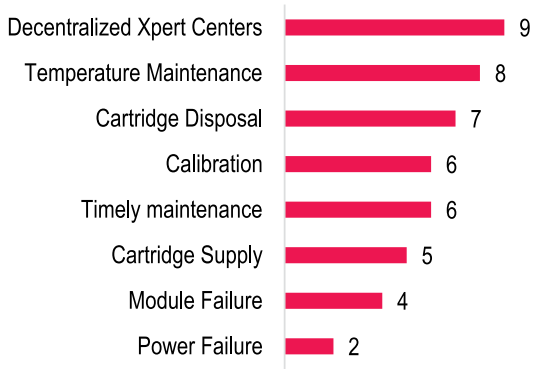



**Figure 5**. Challengeson GeneXpert identified by the program managers.

**Focus Group Discussion**

There were five sessions of the Focus Group Discussions conducted – one session each in the five development region capitals. Each Focus Group comprised of three operators, three clinicians, and two program managers. The Program managers were Regional and District level managers in the four development region capitals and National level managers in the Focus Group of the session at the National TB Center. The discussions lasted about one to two hours and were moderated by the two trained facilitators from the National TB Center, who were themselves operators or clinicians or program managers. A set of questions guided the discussions and note-taking accompanied the discussions. The moderators facilitated the discussions where necessary with aid of probe questions.

**Key findings**

Challenges in human resource and diagnostic algorithms

Most of the FGD participants shared that the human resource utilizing the GeneXpert MTB/Rif assay have not been well oriented to the updated diagnostic algorithms. The reported need for training support included that of basic operations, software handling, testing strategies and interpretation of the test results, especially when there is discordance.

Challenges in the maintenance and operations of GeneXpert MTB/Rif assay

The major challenges shared in the Focus Group Discussions were a frequent power failure, difficulty in maintaining appropriate steady temperature, module failure that is often not replaced in time, issues with calibration and timely availability of cartridges as well as appropriate ways to store the new cartridges and safe disposal of the used cartridges. These issues have been shown to have an impact on the erroneous reports.

Managerial challenges

One of the important managerial issues identified was the lack of decentralized availability of the GeneXpert machines across the country. The sputum courier system intended to fill the gap has often been inadequate. As a result, many patients with presumptive drug-resistant TB fail to be tested by GeneXpert. Often, the central TB lab has poorly responded to the requests for machine

maintenance or cartridge supply or calibration issues. Appropriate facilities to store the cartridges also seem to be lacking in many locations.

**Recommendations and solutions**

The focus Group Discussions have come up with a number of possible solutions to the challenges identified. First, ensure wide dissemination of the updated diagnostic algorithms among the clinicians as well as operators to minimize the confusions. This can be done by refresher training for the operators and workshops for the clinicians. Identify a focal point in the central TB reference lab in National TB Center, which can be a person or a group of persons who will respond to the requests for maintenance, cartridge supply, machine calibration etc. from the GeneXpert centers and proceed accordingly. The GeneXpert centers should be encouraged to manage the problems which can be managed locally. It was recommended to maintain a buffer stock of the modules (at least 25% of the total number of modules being operated) at the center so that they can be replaced soon to avoid or minimize lapses in services. These GeneXpert machines and the modules should be established according to the caseloads to avoid prolonged waiting times. National TB Center has been urged to come up with nationally agreed algorithms and recommendations in the use of extra-pulmonary samples for the diagnosis of TB, particularly drug-resistant TB.

## DISCUSSION

Though GeneXpert machines can be placed anywhere, from a peripheral clinic to a reference laboratory, the selection of a site depends on the workload, efficiency of referral networks, the infrastructure requirements, the human resources capacity and running costs. These considerations often result in GeneXpert machines being placed above the peripheral level, which requires the establishment of the reliable specimen or patient-referral networks.[4] A study from India showed that the installation and operations of the GeneXpert MTB/Rif assay in the lower levels of health systems were feasible and required minimal infrastructural modifications.The Program Managers participated in the study felt that the GeneXpert MTB/Rif assays have been placed at the appropriate level of healthcare delivery system in Nepal.

Available studies have demonstrated that the diagnosis of TB is cost-effective in different settings from low-income countries like Tanzania to high-income low TB burden countries like the United States.[10,11] A study assessing the cost of TB and drug-resistant TB diagnosis by GeneXpert globally as well as in 36 high-burden countries reported that diagnosis of drug-resistant TB by GeneXpert would cost US$70–90 million per year globally and be lower cost than conventional diagnostics.[12] No studies could be found that have examined the cost-effectiveness of the GeneXpert within the National TB Control Program of Nepal. However, the TB Program managers studied have been involved in the planning and budgeting activities of the programs and all except one respondent were of the opinion that the cost incurred by the GeneXpert MTB/Rif assays was justified for the benefits obtained.

Among the operators who participated in the study, 95.5% reported that they run 2 to 3 cycles of GeneXpert testing in a typical working day. While the number of test outputs in a day also depends on the number of modules available, given the less than 2 hour turn-around time, the World Health Organization estimates 16 tests in an 8-hour working day using 4 module GeneXpert machine that amounts to 4 cycles of tests per day.[4] Increasing the number of test cycles per day, therefore, could potentially maximize the use of GeneXpert MTB/Rif assay. Considering the average number of GeneXpert MTB/Rif assay requests made by clinicians studied in a typical working day as 4.85, the number of test cycles per day needs to be balanced against the number of requests of GeneXpert received for optimal outcome

Among the extra-pulmonary samples reportedly being tested for GeneXpert MTB/Rif assay, CSF was the most common sample, followed by pus and gastric aspirate. The policy update on GeneXpert MTB/Rif assay by the WHO now recommends considering CSF, pus, gastric aspirate only for GeneXpert analysis.[7] Seven operators and nine clinicians participating in our study reported that they have been obtaining GeneXpert MTB/Rif assay samples for pleural fluids as well. While this may be justified for a limited number of reference labs or academic centers, routine testing of pleural

fluids and other body fluids should be limited. Perhaps, updating the operators and clinicians with the latest national algorithms and evidence base can help achieve this goal.

Although the GeneXpert MTB/Rif assay procedure takes less than 2 hours, many clinicians report that they receive their results days later. Frequently cited problems include laboratory operations issues, including limited staff, practices of batching specimens, and other logistical barriers such as inefficient specimen referral and transport networks. In order to expedite the test results delivery to the clinicians, an SMS based tool called XpertSMS has been rolled out in TB REACH projects in a number of countries, including Pakistan and Bangladesh.[13] These services can potentially minimize the delays in treatment decision by the clinicians.

The National TB Center conducts periodic training on identifying the individuals to test for GeneXpert MTB/Rif assays, the test results interpretations and clinical decision-making. However, these activities seem to be inadequate in building up the confidence in operations and/or test results interpretations. While an escalation of training activities seem to be an obvious initial response, a further assessment of the specific needs and tailored approaches would ensure optimal utilization of the available resources. A short-term hands-on training at National Reference Labs by the trained colleagues/superiors can be an option for the selected operators. For clinicians, wider dissemination of the most up-to-date diagnostic algorithms is recommended. Workshops for clinicians can be especially helpful in minimizing the use of GeneXpert MTB/Rif assay for treatment response monitoring, guiding the interpretations of discordant results and clinical decision-making. An easy access to the technical advisory group can supplement in the clinical decision-making process.

The GeneXpert machine requires a stable electric power supply. Interruptions in power may cause damage to the machine, results to be lost, cartridges to be wasted, and the need to obtain another specimen.[4] Therefore, a power stabilizer and an uninterrupted power supply unit (UPS) are recommended for the GeneXpert instrument. In the testing locations with frequent and longer power outages, an additional infrastructure to prevent the test cycle is needed. This will, in turn, prevent cartridges from being wasted and protect the equipment. Depending upon the frequency and duration of power outages, this may include an inverter with an external battery that can provide power for both the instrument and the computer for the average duration of the test – that is, 2 hours. An operational research in Uganda has demonstrated the feasibility of solar power at the district/sub-district level with abundant sunlight.[14] A guideline from the Foundation for Innovative New Diagnostics is available that provides a clear guidance on GeneXpert power backup solutions to meet different power supply scenarios.[15]

The power supply irregularities also have implications in the GeneXpert machine operations as well as cartridge storage conditions. The manufacturer recommends that the ambient operating temperature be maintained between 15 °C and 30 °C for the GeneXpert machine operations and the cartridges and the specimen reagent be stored at 2–28°C.[4] The operating temperature recommended is not different from the operating temperatures recommended for a wide range of other laboratory equipment, household appliances, and computers. Therefore, an airconditioningis required in many locations, especially with a humid climate, in Nepal, the Southern Terai region of the country. Ensuring that appropriate temperature is of utmost importance because operating outside the recommended temperature range may increase the error rates since extreme temperatures interfere with thermo-cycling during the test. Though the manufacturer has stated that the cartridges are stable if kept at 2-45 °C for less than 6 weeks at 75% relative humidity, an uninterrupted power supply to the refrigerator storing the cartridges is important.

Equipment maintenance is an important problem in many resource-limited settings, including in Nepal. One of the important maintenance issues is the module failure. One possible solution is the provision of buffer modules and spare parts within the country, which can potentially minimize or prevent service interruptions. Resources from the manufacturer can be a useful resource to try tackling the maintenance problem locally.[16] The GeneXpert modules require annual calibration.

A remote calibration option is available that uses a kit containing special cartridges that are run on each module without specimens. The process lasts approximately 20 minutes and each kit can calibrate 4 modules. However, in some cases, remote calibration will not be sufficient. Therefore, provision of maintenance services and support for shipping and distribution of supplies, including calibration have been identified as key demands.

## CONCLUSION

While GeneXpert MTB/Rif assay is an important tool in the diagnosis of drug-resistant TB, various challenges limit its optimal utilization. Several recommendations can be formulated based on the current study. These include training support for operators, wider dissemination of the updated diagnostic algorithms among the clinicians as well as operators, identification of a focal point in the central TB reference lab in National TB Center who will respond to the requests for maintenance, cartridge supply, machine calibration etc. from the GeneXpert centers and proceed accordingly. Maintain a buffer stock of the modules (at least 25% of the total number of modules being operated) at the center is also recommended so that they can be replaced soon to avoid or minimize lapses in services.

## CONFLICT OF INTEREST

None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## REFERENCES


1. WHO. WHO | Global tuberculosis report 2018 [Internet]. WHO. [cited 2018 Nov 25]. Available from: http://www.who.int/tb/publications/global_report/en/
2. Asia RO for S-E, Organization WH. Bending the curve - ending TB: Annual report 2017 [Internet]. WHO Regional Office for South-East Asia; 2017 [cited 2017 Oct 27]. Available from: http://www.who.int/iris/handle/10665/254762
3. National TB Program Nepal. Annual Report NTP Nepal 2018 [Internet]. [cited 2018 Nov 25]. Available from: https://nepalntp.gov.np/wp-content/uploads/2018/03/Final-Annual-Report-NTPN-2018.pdf
4. WHO. Xpert mtb/rif implementation manual: technical and operational "how-to." Geneva: World Health Organization; 2014.
5. Evans CA. GeneXpert—A Game-Changer for Tuberculosis Control? PLOS Med. 2011 Jul 26;8(7):e1001064.
6. Steingart KR, Schiller I, Horne DJ, Pai M, Boehme CC, Dendukuri N. Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. Cochrane Database Syst Rev. 2014 Jan 21;(1):CD009593.
7. WHO Global TB Programme. Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children. [Internet]. 2013 [cited 2018 Jul 27]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK258608/
8. TB REACH Project with GeneXpert [Internet]. [cited 2018 Aug 3]. Available from: http://nepal.iom.int/jupgrade/index.php/en/aboutus/18-topic-details/81-tb-reach-project-with-genexpert
9. Raizada N, Sachdeva KS, Sreenivas A, Vadera B, Gupta RS, Parmar M, et al. Feasibility of Decentralised Deployment of Xpert MTB/RIF Test at Lower Level of Health System in India. PLOS ONE. 2014 Feb 26;9(2):e89301.
10. Dheda K, Theron G, Welte A. Cost-effectiveness of Xpert MTB/RIF and investing in health care in Africa. Lancet Glob Health. 2014 Oct 1;2(10):e554–6.
11. Choi HW, Miele K, Dowdy D, Shah M. Cost-effectiveness of Xpert® MTB/RIF for diagnosing pulmonary tuberculosis in the United States. Int J Tuberc Lung Dis Off J Int Union Tuberc Lung Dis. 2013 Oct;17(10):1328–35.
12. Pantoja A, Fitzpatrick C, Vassall A, Weyer K, Floyd K. Xpert MTB/RIF for diagnosis of tuberculosis and drug-resistant tuberculosis: a cost and affordability analysis. Eur Respir J. 2013 Sep 1;42(3):708–20.
13. Interactive Research and Development A 17th 2013. XpertSMS – Introducing Automated MTB/RIF Reporting into running projects [Internet]. [cited 2018 Aug 4]. Available from: http://www.stoptb.org/wg/gli/assets/html/gli5/gli_2013_xpertsms_ird_v5.pdf

14. Solar energy powers GeneXpert IV Dx system for detection of tuberculosis and rifampicin resistance in district /sub-district public health care settings in Uganda [Internet]. 2011. Available from: https://www.ghdonline.org/uploads/Uganda-GX-solar_for-website_190420111-SOLAR_3.pdf

15. FIND. Providing Uninterrupted Power for GeneXpert® in Low and Middle Income Settings: A Practical Guide [Internet]. [cited 2018 Aug 4]. Available from: https://www.finddx.org/wp-content/uploads/2018/02/UPS-guide-XpertMTB-RIF_FINAL_07DEC16.pdf

16. Webmaster. Cepheid | GeneXpert Maintenance Videos [Internet]. [cited 2018 Nov 27]. Available from: http://www.cepheid.com/us/about-us/news-events/press-releases/30-site-pages-us/support/43-maintenance-videos