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Truenat®

MTB-RIF Dx

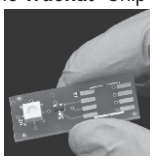
Chip-based Real Time PCR Test for Rifampicin Resistant
Mycobacterium tuberculosis

1. INTENDED USE

Truenat® MTB-RIF Dx (REF 601210005 / 601210020 / 601210025 / 601210050 / 601210100 / 601210200) is an automated point-of-care or near patient Chip-based Real Time Polymerase Chain Reaction (PCR) test for the detection of Rifampicin resistance in *Mycobacterium tuberculosis* (MTB) in **Truenat® MTB/MTB Plus** positive human specimen and aids in the diagnosis of MDR-TB. This test detects the presence of major mutations (SNPs) in the MTB genome that are known to cause resistance to rifampicin. **Truenat® MTB-RIF Dx** runs on the **Truelab®** Real Time Quantitative micro PCR Analyzers. This is a follow on test, to be performed only on the extracted DNA from **Truenat® MTB/MTB Plus** positive sample. **Truenat® MTB-RIF Dx** is a single use *in vitro* diagnostics test meant for professional use in near-patient, laboratory or any healthcare settings, by healthcare professionals or any user appropriately trained by a representative of Molbio Diagnostics.

2. INTRODUCTION

Multidrug-resistant *Mycobacterium tuberculosis* (MDR-TB) has emerged as a major public health problem worldwide. The WHO estimates that in 2014 an estimated 480 000 people developed MDR -TB across the globe. MDR-TB is defined as TB that is resistant to both Isoniazid (INH) and Rifampicin (RMP). In many countries and regions, these resistant strains constitute a serious threat to the efficacy of tuberculosis control programs. One of the main reasons for treatment failure and fatal clinical outcome in patients with tuberculosis is resistance to rifampicin. Rifampicin resistance is most invariably associated with resistance to isoniazid. Hence, detection of rifampicin resistance is recommended as a reliable surrogate marker for diagnosis of MDR-TB. Drug Susceptibility Testing (DST) by culture methods are the most common method used for detecting drug resistance. Culture methods require specialized and controlled laboratory facility and highly skilled manpower and takes 3 to 6 weeks to provide the result. Molecular techniques such as line probe assay and polymerase chain reaction (PCR) or Real Time PCR are accurate and much faster than culture. However molecular techniques have so far been restricted to centralized reference laboratories as they require skilled manpower and elaborate infrastructure. Also the turnaround time for results could take a few days. The **Truelab®** Real Time Quantitative micro PCR System enables decentralization and near patient detection of rifampicin resistance, by making real time PCR technology rapid, simple, robust and user friendly and offering "sample to result" capability even at resource limited settings. This is achieved through a combination of lightweight, portable, mains/battery operated **Truelab®** Real Time Quantitative micro PCR Analyzer and **Trueprep® AUTO / AUTO v2** Universal Cartridge Based Sample Prep Device and room temperature stable **Truenat®** Chip-based Real Time PCR test and **Trueprep® AUTO / AUTO v2** Universal Cartridge Based Sample Prep Kit so that even the peripheral laboratories with minimal infrastructure and minimally trained technicians can easily perform these tests routinely in their facilities and report PCR results in less than an hour. Moreover, with these devices PCR testing can also be initiated in the field level, on site. **Truenat® MTB- RIF Dx** is a disposable, room temperature stable, Chip-based Real Time PCR test with dried $MgCl_2$ in reaction well and freeze dried PCR reagents in microtube for performing Real Time PCR test for detection of Rifampicin resistant *Mycobacterium tuberculosis* and runs on the **Truelab®** Real Time Quantitative micro PCR Analyzer.



It requires only six (6) µL of purified **Truenat® MTB / MTB Plus** positive DNA to be added to the reaction well for the analysis. The intelligent chip also carries test and batch related information and stores information of used test to prevent any accidental re-use of the test.

NOTE: Truelab® / Truenat® / Trueprep® / Truepet® are all trademarks of Molbio Diagnostics Private Limited.

The Truelab® Real Time micro PCR Analyzer is protected by the following patents and patents granted: IN 2313/CHE/2007 (Patent No. 281573), WO2009/047804 and corresponding claims of any foreign counterpart(s) thereof.

The Truenat® micro PCR chip is protected by the following patents and patents pending: IN 2312/CHE/2007, WO 2009/047805 and corresponding claims of any foreign counterpart(s) thereof.

3. PRINCIPLE OF THE TEST

Truenat® MTB-RIF Dx works on the principle of Real Time Polymerase Chain Reaction. The DNA from the patient sample is first extracted using **Trueprep® AUTO / AUTO v2** Universal Cartridge Based Sample Prep Device and **Trueprep® AUTO / AUTO v2** Universal Cartridge Based Sample Prep Kit and assayed for MTB using **Truenat® MTB/MTB Plus** test (refer **Truenat® MTB/Truenat® MTB Plus** pack insert).

If the sample tests positive for MTB, Six (6) µL of the purified DNA is then dispensed using the provided micropipette and tip into the microtube containing freeze dried PCR reagents and allowed to stand for 30-60 seconds to get a clear solution. ⚠ No mixing by tapping, shaking or by reverse pipetting should be done. Six (6) µL of this clear solution is then pipetted out using the same pipette and tip and dispensed into the reaction well of the **Truenat® MTB- RIF Dx** chip and the test is started. Presence of mutations (SNPs) within the RRDR region of *rpoB* gene target are detected using a probe melt assay. At the end of the test run, a "Rif Resistance Detected" or "Rif Resistance Not detected " result is displayed. The results can be printed via Bluetooth using the **Truelab®** micro PCR printer or transferred to the lab computer/or any remote computer via Wifi network or 3G/GPRS network. Upto 20000 results can be stored on the analyzer for future recall and reference.

4. TARGET SELECTION

The target sequence for this kit is the RRDR region of the *rpoB* gene and the codon region coverage is MTB Codon Numbering [H37Rv]: Codon **428 - 435** & Codon **445 - 452** (*E. coli* Codon Numbering: Codon **509 - 516** & Codon **526 - 533**), representing mutation hot spots known to be related to rifampicin resistance.

5. CONTENTS OF THE Truenat® MTB - RIF Dx KIT

A. Individually sealed pouches
B. Package Insert
   Each individually sealed pouch contains:
   1. **Truenat® MTB-RIF Dx** micro PCR chip (1 Nos.)
   2. Microtube with freeze dried PCR reagents (1 Nos.)
   3. DNase & RNase free pipette tip (1 Nos.)
   4. Desiccant pouch (1 Nos.)

REF	601210005	601210020	601210025	601210050	601210100	601210200
⧖	5T	20T	25T	50T	100T	200T

6. STORAGE AND STABILITY

Truenat® MTB-RIF Dx chip is stable for two (2) years from the date of manufacture if stored between 2-30°C. It is also stable for upto (1) month at temperatures up to 45°C. Avoid exposure to light. Do not freeze.

7. MATERIALS REQUIRED BUT NOT PROVIDED WITH THE KIT

Truelab® Real Time micro PCR Workstation (REF 623010001 / 633010001 / 643010001 / 653010001) consisting of,

1. **Trueprep® AUTO/AUTO v2** Universal Cartridge Based Sample Prep Device (REF 603041001 / 603042001).
2. **Truelab® Uno Dx / Truelab® Duo / Truelab® Quattro** Real Time micro PCR Analyzer (REF 603021001 / 603022001 / 603023001).
3. **Truelab®** micro PCR Printer (REF 603050001).
4. **Truepet®** SPA fixed volume precision micropipette - 6 µl (REF 604070006).
5. **Truelab®** Microtube Stand (REF 603070001)

Also required additionally are: **Truenat® MTB/MTB Plus** Chip-based Real-Time PCR test for *Mycobacterium tuberculosis*, **Trueprep® AUTO MTB** Sample Pre-treatment Pack (REF 60204AS05 / 60204AS20 / 60204AS25 / 60204AS50 / 60204AS100 / 60204AS200), **Trueprep® AUTO** Universal Cartridge Based Sample Prep Kit (REF 60203AR05 / 60203AR25 / 60203AR50 / 60203AR100 / 60203AR200) or **Trueprep® AUTO v2** Universal Cartridge Based Sample Prep Kit (REF 60207AR05 / 60207AR25 / 60207AR50 / 60207AR100 / 60207AR200), **Truenat®** Positive Control Kit Panel - I (REF 801010008), Powder free disposable gloves, waste disposal container with lid.

8. SPECIMEN PREPARATION FOR EXTRACTION WITH Trueprep® AUTO/AUTO v2

Truenat® MTB-RIF Dx requires purified nucleic acids from sputum/EPTB specimen that are extracted using the **Trueprep® AUTO / AUTO v2** Universal Cartridge Based Sample Prep Device and **Trueprep® AUTO / AUTO v2** Universal Cartridge Based Sample Prep Kit that have tested positive by **Truenat® MTB/MTB Plus** (Refer to the User Manual of **Trueprep® AUTO / AUTO v2** Universal Cartridge Based Sample Prep Device and the package inserts of **Trueprep® AUTO / AUTO v2** Universal Cartridge Based Sample Prep Kit, **Trueprep® AUTO MTB** Sample Pre-treatment Pack and **Truenat® MTB/MTB Plus** for details).

9. SAFETY PRECAUTIONS

1. For *in vitro* diagnostic use only.
2. Bring all reagents and specimen to room temperature (20 - 30°C) before use.
3. Do not use kit beyond expiry date.
4. Carefully read the user manuals, package inserts and material safety data sheets (MSDS) of all the components of the **Truelab® Real Time micro PCR System** before use
5. All materials of human origin should be handled as potential infection hazards.
6. Do not pipette any material by mouth.
7. Do not eat, drink, smoke, apply cosmetics or handle contact lenses in the area where testing is done.

8. Use protective clothing and wear disposable gloves when handling samples and while performing sample extraction.

10. PROCEDURAL PRECAUTIONS

1. Check all packages before using the kit. Damage to the packaging does not prevent the contents of the kit from being used. However, if the outer packaging is damaged the user must confirm that individual components of the kit are intact before using them.
2. Do not perform the test in the presence of reactive vapours (e.g. from sodium hypochlorite, acids, alkalis or aldehydes) or dust.
3. While retrieving the **Truenat® MTB-RIF Dx** micro PCR chip, microtube and the DNase & RNase free pipette tip from the pouch, ensure that neither bare hands nor gloves that have been used for previous tests run are used.
4. Ensure that the colour of the dessicant pouch is orange after opening a sealed **Truenat®** chip pouch. If the colour of the desiccant pouch changes from orange to white due to the absorption of moisture, do not use the contents of the **Truenat®** chip pouch.

11. PROCEDURAL LIMITATIONS

1. Optimal performance of this test requires appropriate specimen collection, handling, storage and transport to the test site.
2. Though very rare, mutations within the highly conserved regions of the target genome where the **Truenat®** assay primers and/or probe bind may result in the under-quantitation of or a failure to detect the presence of the concerned pathogen.
3. The instruments and assay procedures are designed to minimize the risk of contamination by PCR amplification products. However, it is essential to follow good laboratory practices and ensure careful adherence to the procedures specified in this package insert for avoiding nucleic acid contamination from previous amplifications, positive controls or specimens.
4. A specimen for which the **Truenat®** assay reports "Not Detected" cannot be concluded to be negative for the concerned pathogen. As with any diagnostic test, results from the **Truenat®** assay should be interpreted in the context of other clinical and laboratory findings.

12. CLEANING AND DECONTAMINATION

1. Spills of potentially infectious material should be cleaned up immediately with absorbent paper tissue and the contaminated area should be decontaminated with disinfectants such as 0.5% freshly prepared Sodium hypochlorite [10 times dilution of 5% Sodium hypochlorite (household bleach)] before continuing work.
2. Sodium hypochlorite should not be used on an acid-containing spill unless the spill-area is wiped dry first. Materials used to clean spills, including gloves should be disposed off as potentially bio-hazardous waste e.g. in a bio-hazard waste container.

13. TEST PROCEDURE

(Please also refer the **Truelab®** Real Time Quantitative micro PCR Analyzer user manual)

1. The **Truenat® MTB-RIF Dx** test is a follow-on test to be performed using the nucleic acid elute extracted from the **Truenat® MTB/MTB Plus** positive samples.
2. The **Truenat® MTB-RIF Dx** test option is available on the result page of a **Truenat® MTB/MTB Plus** test with a MTB positive ("MTB Detected") report.
3. Select the "MTB-RIF" tab displayed on the result page of the corresponding **Truenat® MTB/MTB Plus** test.
4. The patient details shall get carried over for the **Truenat® MTB-RIF Dx** test.
5. Press Start Test.
6. For **Truelab® Uno Dx,** press the eject button to open the chip tray. For **Truelab® Duo/Quattro**, the chip tray opens automatically on tapping the "Start Test" button.
7. Open a pouch of **Truenat® MTB-RIF Dx** and retrieve the Chip-based Real Time PCR test and the microtube. Do not open the pouch until ready to test.
8. Place the **Truenat® MTB-RIF Dx** chip on the chip tray without touching the white reaction well. The reaction well should be facing up and away from the analyzer. Gently place the chip on the chip tray by aligning it in the slot provided.
9. Place the microtube containing freeze dried PCR reagents in the microtube stand provided along with the **Truelab®** Real Time micro PCR workstation after ensuring that white pellet of freeze dried PCR reagents remains at the bottom of the microtube. Remove the microtube cap and dispose it off as per the section on "Disposal and Destruction" (Section 16). Using the filter barrier tip provided in the pouch, pipette out six (6) µL of the purified DNA from the Elute Collection Tube into the microtube. Allow it to stand for 30-60 seconds (in-use time) to get a clear solution. ⚠ Do not mix it by tapping, shaking or by reverse pipetting. Using the same filter barrier tip, pipette out six (6) µL of this clear solution and dispense into the centre of the white reaction well of the **Truenat® MTB-RIF Dx** chip. Take care not to scratch the internal well surface and not to spill elute on the outside of the well. Dispose off the microtip as per the section on "Disposal and Destruction" (Section 16).
10. For **Truelab® Uno Dx**, slide the chip tray containing the **Truenat® MTB-RIF Dx** Chip-based Real Time PCR test loaded with the sample into the **Truelab®** analyzer. Press "YES" on the "Please Load Sample" prompt. For **Truelab® Duo/Quattro**, select "YES" at the "Please Load Sample" prompt. Chip tray will close automatically and the reaction will start. ⚠ Make sure to start the test promptly after 30-60 seconds of adding the elute to the microtube.
11. Read the result from the screen.
12. After the reaction is completed, for **Truelab® Uno Dx,** push the Eject button to eject the chip tray. For **Truelab® Duo/Quattro**, tap the "Open/Close Tray" button to eject the chip tray.
13. Take out the **Truenat® MTB-RIF Dx** micro PCR chip at end of the test and dispose it off as per the section on "Disposal and Destruction" (Section 16).
14. Turn on **Truelab®** micro PCR printer and select print on the screen for printing out hard copy of the results. Test results are automatically stored and can be retrieved any time later. (Refer to **Truelab®** Analyzer manual).
15. Switch off the **Truelab®** Real Time micro PCR Analyzer.

14. RESULTS & INTERPRETATIONS

This test uses a real time PCR assay followed by melt protocol to find probe melt Tm values. At the end of the test run, the results screen will display "Rif Resistance Detected" if mutations are detected or "Rif Resistance Not Detected" if mutations are not detected. "Indeterminate" or "Error" will be displayed when the obtained Tm values don't meet the requirements for resistance calculation.

15. QUALITY CONTROL PROCEDURES

To ensure that the **Truelab®** Analyzer is working accurately, run positive and negative controls from time to time. The **Truenat®** Positive Control Kit Panel - I (REF 801010008) containing Positive Control and Negative Control must be ordered separately. It is advisable to run controls under the following circumstances:
● Whenever a new shipment of test kits is received. ● When opening a new test kit lot. ● If the temperature of the storage area falls outside of 2-30°C. ● By each new user prior to performing testing on clinical specimen.

16. DISPOSAL AND DESTRUCTION

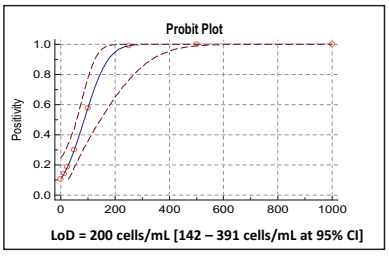
1. Submerge the used **Truenat® MTB-RIF Dx** chip, microtube, microtube cap, pipette tips etc. in freshly prepared 0.5% sodium hypochlorite solution for 30 minutes before disposal as per the standard medical waste disposal guidelines.
2. Disinfect the solutions and/or solid waste containing biological samples before discarding them according to local regulations.
3. Samples and reagents of human and animal origin, as well as contaminated materials, disposables, neutralized acids and other waste materials must be discarded according to local regulations after decontamination by immersion in a freshly prepared 0.5% of sodium hypochlorite for 30 minutes (1 volume of 5% Sodium hypochlorite for 10 volumes of water).
4. Do not autoclave materials or solutions containing Sodium hypochlorite.
5. Chemicals should be handled in accordance with Good Laboratory Practice and disposed off according to the local regulations.

17. SPECIFIC PERFORMANCE CHARACTERISTICS

Limit of Detection (Analytical Sensitivity):

MTB strain H37Rv from Zeptometrix was used for LoD determination. The LoD was determined by testing **Trueprep® AUTO** extracts, using dilutions of H37Rv strain (500 cells/ml, 250 cells/ml, 100 cells/ml, 50 cells/ml, 25 cells/ml, 12 cells/ml, 0 cells/ml) in negative sputum. Each dilution was tested as indicated in following table. Probit analysis of the data was used to determine the concentration with 95% probability of detection. The LoD was found to be 200 cells/mL of sputum for **Truenat® MTB-RIF Dx** assay.

Cells/mL	Total Runs	Detected
0	10	0
12	10	2
25	10	3
50	10	3
100	10	5
250	10	10
500	10	10



Reproducibility:

The reproducibility of **Truenat® MTB-RIF Dx** assay was determined between three different users and between three different devices. In this study three different users performed the extraction of three pre-characterized samples on **Trueprep® AUTO** Universal Cartridge Based Sample Prep Device and the DNA elutes were tested on **Truelab® Uno Dx** Real Time Quantitative micro PCR analyzer using **Truenat® MTB-RIF Dx** chips. For three device variation check, DNA extracts of pre-chracterized samples were run on three different **Truelab® Uno Dx** Real Time Quantitative micro PCR analyzer using **Truenat® MTB-RIF Dx** chips. The reported results showed uniformity for three users and three device study.

Accuracy of Truenat® MTB-RIF Dx assay:

Accuracy was determined by performing DNA extractions and PCR for characterized samples from TDR Bank, ITM, Antwerp in **Truenat® MTB-RIF Dx.** The results of

Truenat® MTB-RIF Dx assay was in concordance with the characterized panel data.

Trueness of Truenat® MTB-RIF Dx assay:
For this study, pre-chracterized sample panel from FIND was used. Samples bearing mutations in the *rpoB* gene tested in **Truelab® Uno Dx** Real Time Quantitative micro PCR Analyzer using **Truenat® MTB-RIF Dx** chips. The results of **Truenat® MTB-RIF Dx** assay was in concordance with the pre-characterized panel data.

Clinical Validation 1:
Truenat® MTB-RIF Dx is a reflux test that used to determined Rifampicin resistance in samples detected as positive by **Truenat® MTB** or **Truenat® MTB Plus** assay. 10 positive sputum samples were tested on three different lots of **Truenat® MTB-RIF Dx** assay at National Institute for Research in Tuberculosis, Chennai against WHO approved system as comparator.
All 05 samples were Rifampicin resistance was detected by comparator assay also yielded similar results by **Truenat® MTB-RIF Dx** assay. In all the samples where Rifampicin resistance was not detected by comparator assay, similar results were obtained by **Truenat® MTB-RIF Dx.** These results showed 100% concordance between the two assays. No variation was observed across three lots of **Truenat® MTB-RIF Dx** chips tested.

Clinical Validation 2:
Multicentric Clinical evaluation study for Truenat® MTB-RIF Dx test:
A multicentric prospective clinical evaluation study was conducted in 19 clinical sites and 7 reference laboratories in 4 countries [India, Peru, Ethiopia, Papua New Guinea] to determine the diagnostic accuracy of the Truenat assays when performed in the intended settings of use (i.e.microscopy centres), relative to microbiological confirmation (culture) as the reference standard. The performance of the Truenat assays was also compared head-to-head (on the same specimens) to Xpert or Ultra in reference laboratories as part of this assessment. The study was coordinated by **FIND** [Foundation for Innovative New Diagnostics].
The prospective, multicenter, diagnostic accuracy study in which the performance of the **Truenat® MTB** assays and **Truenat® MTB-RIF Dx** assay – was assessed in four countries using solid and liquid culture as the reference standard for diagnosis of TB, and MGIT SIRE as the reference standard for the detection of RIF resistance.
The study had two objectives:

1. Estimate diagnostic accuracy of the **Truenat® MTB-RIF Dx** assay for RIF resistance detection among individuals undergoing evaluation for pulmonary TB and DR-TB, using phenotypic DST as the reference standard.
2. Compare the diagnostic accuracy of the **Truenat® MTB-RIF Dx** assay to that of Xpert, using a reference phenotypic DST for detection of RIF resistance.

Diagnostic Accuracy of the Truenat® MTB-RIF Dx detection assay [Intended use settings]
The **Truenat® MTB-RIF Dx** assay done on sputum in the microscopy centres had a sensitivity of 84.2% and 95.2% specificity for RIF resistance detection (relative to RIF DST).
The **Truenat® MTB-RIF Dx** assay done on sputum in the reference laboratories had a sensitivity of 84.3% and specificity of 97.3%.

Table 1 : Performance of Truenat® MTB-RIF Dx at the microscopy centre

Test	Sensitivity% (95% CI)	Sensitivity % Smear Pos (95% CI)-N	Sensitivity % Smear Neg (95% CI)-N	Specificity % (95% CI)
Truenat® MTB-RIF Dx	84.2 [62.4,94.5]	87.5 [64.0,96.5]-N:16	66.7 [20.8,93.8]-N:3	95.2 [90.8,97.5]
Ref lab sputum **Truenat® MTB-RIF Dx**	84.3 [72.0,91.8]	86.4 [73.3,93.6]-N:44	71.4 [35.9,91.8]-N:7	97.3 [94.5,98.7]

Diagnostic accuracy of Truenat assays compared to Xpert and Ultra
The sensitivities of **Truenat® MTB-RIF Dx** and Xpert assays for RIF-resistance detection were 82% and 84% respectively; and specificity was 98% for both assays. The sensitivities of **Truenat® MTB-RIF Dx** and Xpert Ultra assays for RIF-resistance detection sensitivity was 100% and specificity 96% for both **Truenat® MTB-RIF Dx** and Ultra tests.

Table 2: Performance of Truenat® MTB-RIF Dx in comparison with Xpert

Test	Sensitivity% (95% CI)	Sensitivity % Smear Pos (95% CI)-N	Sensitivity % Smear Neg (95% CI)-N	Specificity % (95% CI)
Xpert	84.2 [69.6,92.6]	88.6 [74.1,95.5]-N:35	33.3 [6.2,79.2]-N:3	97.8 [94.4,99.1]
Truenat® MTB-RIF Dx	81.6 [66.6,90.8]	85.7 [70.6,93.7]-N:35	33.3 [6.2,79.2]-N:3	97.8 [94.4,99.1]

Table 3: Performance of Truenat® MTB-RIF Dx in comparison with Ultra

Test	Sensitivity% (95% CI)	Sensitivity % Smear Pos (95% CI)-N	Sensitivity % Smear Neg (95% CI)-N	Specificity % (95% CI)
Ultra	100 [67.6,100.0]	100 [61.0,100.0]-N:6	100 [34.2,100.0]-N:2	95.9 [86.3,98.9]
Truenat® MTB-RIF Dx	100 [67.6,100.0]	100 [61.0,100.0]-N:6	100 [34.2,100.0]-N:2	95.9 [86.3,98.9]

18. REFERENCES

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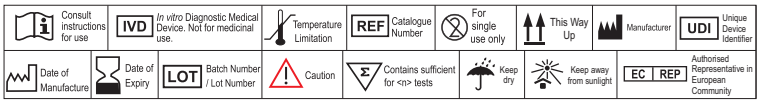
SYMBOL KEYS



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