World Health Organization

TUBERCULOSIS DIAGNOSTICS

MOLECULAR LINE-PROBE ASSAY FOR THE DETECTION OF RESISTANCE TO SECOND-LINE ANTI-TB DRUGS (SL-LPA)

BACKGROUND

- Multidrug-resistant tuberculosis (MDR-TB) is a public health crisis and a global health security risk carrying grave consequences for those affected.
- An estimated 480 000 people developed MDR-TB in 2014 and 190 000 people died as a result of it.
- Early detection of people with MDR-TB is one of the major bottlenecks in tackling this epidemic. Of the 480 000 MDR-TB cases estimated to have occurred in 2014, only about a quarter – 123 000 – were detected and reported to national authorities.
- In May 2016, WHO issued new recommendations on the use of a rapid diagnostic test – a line probe assay to detect resistance to second-line anti-TB drugs (SL-LPA).
- WHO recommends this rapid diagnostic test for identifying those MDR- or rifampicin-resistant TB patients who can be placed on the shorter MDR-TB regimen. The results of this test will also be critical in placing patients on targeted conventional MDR-TB regimens with improved outcomes.

ABOUT THE TEST

- The novel diagnostic test - called MTBDRsl – is a DNA-based test that identifies genetic mutations in MDR-TB strains, making them resistant to fluoroquinolones and injectable second-line TB drugs.
- This test is the first and only WHO-recommended rapid test for detection of additional resistance in MDR-TB patients as well as XDR-TB. It is the most reliable way to rule out resistance to second-line drugs.

For more information please visit: www.who.int/tb

BENEFITS OF THE SL-LPA

- The SL-LPA produces results in just 24-48 hours, a vast improvement over the 3 months or longer currently required.
- It allows quick triage of confirmed rifampicin-resistant or MDR-TB patients into either the shorter MDR-TB regimen or the conventional longer regimen.
- Excluding second-line drug resistance a critical prerequisite for identifying patients who can be placed on the shorter MDR-TB regimen.
- Detection of any second-line resistance by the SL-LPA means that MDR-TB patients should not be enrolled on the shorter regimen as this could jeopardise their treatment outcome and fuel the development of XDR-TB.
- Patients detected with XDR-TB by the SL-LPA should also not be enrolled on the shorter regimen but require carefully designed individual regimens to optimise their chances of success.

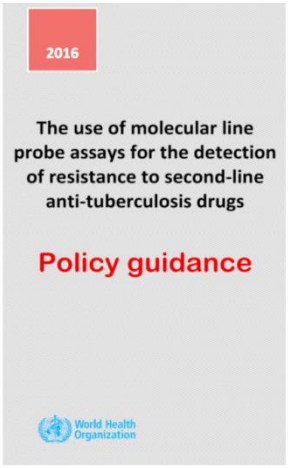
COSTS

- FIND has negotiated a preferential price of Euro 7.50 (approximately USD10) for the MTBDRsl strips in 138 countries (http://www.finddx.org/pricing/); however, doing the test requires other laboratory consumables and supplies which may push the cost up to between USD20 and USD30.
- The cost of the equipment to perform the test ranges between approximately USD8,000 and USD40,000 depending on the size of the equipment and whether results are read automatically or not.

WHO RECOMMENDATIONS

ON THE USE OF THE SL-LPA

http://www.who.int/tb/areas-of-work/laboratory/policy_statements

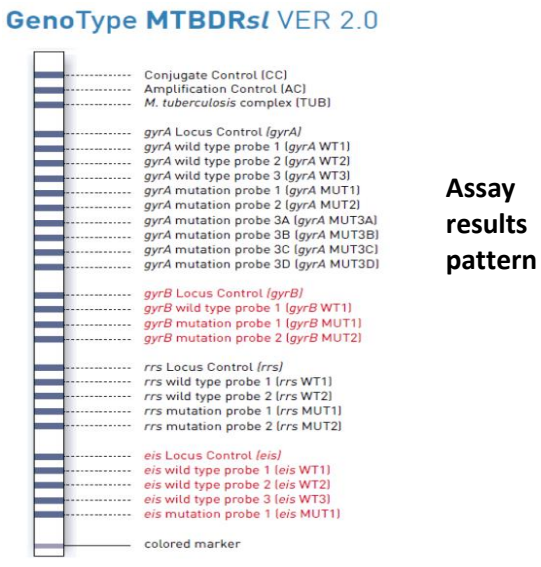


POLICY RECOMMENDATION

WHO recommends the use of the SL-LPA for patients with confirmed rifampicin-resistant TB or MDR-TB as the initial test to detect resistance to fluoroquinolones and the second-line injectable drugs, instead of phenotypic culture-based drug-susceptibility testing (DST).

CONDITIONS

- These recommendations apply to the use of SL-LPA for the direct testing of sputum specimens as well as indirect testing on culture isolates from rifampicin-resistant or MDR-TB patients, including adults and children (irrespective of the smear status).
- For second-line injectable results, resistance conferring mutations detected by SL-LPA are highly correlated with culture-based phenotypic resistance.
- For fluoroquinolones, resistance confirming mutations detected by SL-LPA are better correlated with culture-based phenotypic resistance to ofloxacin/levofloxacin in comparison to moxifloxacin; inclusion of moxifloxacin in a rifampicin-resistant or MDR-TB regimen is therefore best guided by phenotypic testing.
- Theses recommendations do not eliminate the need for phenotypic DST to confirm resistance to other drugs and to monitor the emergence of additional drug resistance during treatment.



Assay results pattern

ESTABLISHING SL-LPA AT COUNTRY LEVEL

- Countries with existing LPA capacity can immediately adopt the SL-LPA as the laboratory methods are the same as for first-line LPA.
- LPA is suitable for use at national/central reference laboratories or those with proven capability to conduct molecular testing. Expansion to more decentralised laboratories could be considered depending on availability of suitable laboratory infrastructure, specially trained personnel and adequate quality assurance of testing.
- Adequate and appropriate laboratory infrastructure and equipment must be available, including the necessary biosafety precautions and prevention of contamination: specimen processing for culture and manipulation of cultures require TB containment laboratories with appropriate biological safety cabinets. Laboratory facilities for LPA require at least three separate rooms - one each for DNA extraction, pre-amplification procedures, and amplification and post-amplification procedures. Restricted access to molecular facilities, unidirectional work flow, and stringent cleaning protocols must be established to avoid contamination.
- Appropriate laboratory staff should be trained to conduct LPA procedures. Supervision of staff by a senior individual with adequate training and experience in molecular assays is strongly recommended. A programme for external quality assessment of involved laboratories should be developed as a priority. Mechanisms for rapid reporting of LPA results to clinicians must be established to provide patients with the benefit of an early diagnosis.
- By 2014 approximately 400 LPA laboratories had been established in low and middle-income countries, as reported to WHO.