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Perspective

Refining Tuberculosis Diagnostics with Isoniazid Resistance Testing

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DESCRIPTION

The Xpert MTB/RIF Ultra (Xpert Ultra) assay, a molecular diagnostic tool, has significantly enhanced TB diagnosis and the detection of rifampicin resistance. However, its specificity for rifampicin resistance is suboptimal, often leading to false-positive results. This limitation highlights the need for complementary testing, such as isoniazid resistance testing, to improve treatment precision and patient outcomes. Xpert Ultra is a Nucleic Acid Amplification Test (NAAT) designed to detect *Mycobacterium tuberculosis* (*M. tb*) and mutations in the *rpoB* gene associated with rifampicin resistance. Compared to its predecessor, Xpert MTB/RIF, Ultra offers improved sensitivity for TB detection, particularly in paucibacillary cases, such as those with extrapulmonary TB or HIV co-infection. However, the increased sensitivity comes at the cost of reduced specificity, particularly for rifampicin resistance. False-positive results can occur due to non-pathogenic mutations in the *rpoB* gene or contamination. This can lead to misclassification of patients as having Rifampicin Resistant-TB (RR-TB), resulting in unnecessary initiation of more toxic and costly drug regimens. Xpert Ultra's lower specificity for rifampicin resistance can misclassify patients with drug-susceptible TB as having RR-TB. Such errors may occur due to delay the initiation of appropriate treatment, expose patients to second-line drugs, which have significant side effects and strain healthcare resources by allocating scarce drugs to non-resistant cases. Misdiagnosis complicates the global effort to combat Multidrug Resistant-TB (MDR-TB) and Extensively Drug Resistant-TB (XDR-TB), as it inflates resistance statistics and undermines confidence in diagnostic tools.

Importance of isoniazid resistance testing

Isoniazid (INH) is a foundation of first-line TB therapy, and resistance to it is a essential factor in determining treatment regimens. Testing for isoniazid resistance provides several benefits in the context of rifampicin resistance diagnostics:

Accurate diagnosis of MDR-TB: MDR-TB is defined as resistance to both rifampicin and isoniazid. Including isoniazid resistance testing ensures that true MDR-TB cases are identified, reducing the risk of over-treatment or under-treatment.

Guidance for therapy: Detecting isoniazid resistance allows clinicians to adjust treatment regimens appropriately. For example, patients with rifampicin resistance but isoniazid susceptibility may benefit from simplified regimens rather than full MDR-TB treatment. High-dose isoniazid can still be used in certain cases of low-level resistance, preserving its therapeutic value.

Improved outcomes and cost efficiency: Precise resistance profiling minimizes the use of unnecessary second-line drugs, reducing adverse effects and healthcare costs. It also optimizes treatment duration and enhances patient adherence.

Advances and integrating resistance testing into TB

Line Probe Assays (LPAs): LPAs, such as GenoType *Mycobacterium tuberculosis* Drug Resistant *plus* (MTBDR*plus*), are molecular tests capable of detecting resistance to both rifampicin and isoniazid. They identify mutations in the *rpoB*, *kat*G, and *inh*A genes, offering a comprehensive resistance profile. LPAs are especially useful as a follow-up to Xpert Ultra in cases of rifampicin resistance detection.

Whole Genome Sequencing (WGS): WGS provides detailed insights into the genetic basis of drug resistance, enabling the identification of both common and rare mutations. While not yet widely available in resource-limited settings, WGS represents a promising tool for future TB diagnostics.

Phenotypic Drug Susceptibility Testing (DST): Traditional culture-based DST remains the gold standard for confirming drug resistance. It is particularly useful for verifying Xpert Ultra results and providing definitive guidance in complex cases.

Algorithmic approach: A tiered diagnostic algorithm can optimize the use of available tools. For example, conducting initial screening with Xpert Ultra. Confirm rifampicin resistance with LPA or phenotypic DST. Perform isoniazid resistance testing to refine the diagnosis.

Capacity building: Expanding laboratory infrastructure and training healthcare workers in resistance testing techniques are essential for improving diagnostic accuracy and treatment outcomes.

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Enhanced diagnostic tools: Developing molecular assays with improved specificity for rifampicin resistance and integrated isoniazid resistance testing will streamline TB diagnostics.

CONCLUSION

While Xpert Ultra has revolutionized TB diagnostics, its low specificity for rifampicin resistance necessitates complementary testing, particularly for isoniazid resistance. Integrating isoniazid resistance testing into diagnostic algorithms ensures accurate identification of MDR-TB, guides tailored treatment, and improves patient outcomes. Advances in diagnostic tools and expanded access to resistance testing will strengthen global TB control efforts and pave the way for more effective management of drug-resistant TB.