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MOLECULAR DETECTION OF DRUG-RESISTANT TUBERCULOSIS AND ITS ASSOCIATION WITH TREATMENT OUTCOMES

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Abstract

Molecular diagnosis of drug-resistant tuberculosis (DR-TB) involves identifying genetic mutations in Mycobacterium tuberculosis associated with resistance to anti-tuberculosis drugs. Early detection of these mutations enables clinicians to select appropriate treatment regimens and avoid delays in therapy. Multidrug-resistant tuberculosis (MDR-TB) is defined as resistance to at least rifampicin and isoniazid.

Molecular techniques include Xpert MTB/RIF, line-probe assays, and sequencing methods. These approaches provide results more rapidly than conventional culture-based drug-susceptibility testing, which may take several weeks. However, their accuracy depends on the mutations covered by the assay, and discrepancies with phenotypic testing may occur, sometimes requiring additional confirmation.

Rapid molecular detection can facilitate earlier initiation of appropriate treatment. Although studies have reported associations with faster culture conversion and improved outcomes, a direct causal effect has not been established. Furthermore, the clinical significance of heteroresistance, characterized by the coexistence of susceptible and resistant bacterial populations, remains uncertain.

Introduction

Drug-resistant tuberculosis (DR-TB) represents a significant public health challenge and contributes to the growing problem of antimicrobial resistance. Early identification of drug resistance is essential for selecting effective treatment regimens, reducing transmission, and preventing the development of additional resistance. Multidrug-resistant tuberculosis (MDR-TB) is defined as resistance to at least rifampicin and isoniazid.

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Drug susceptibility testing includes phenotypic and molecular approaches. Phenotypic methods evaluate bacterial growth in the presence of specific anti-tuberculosis drugs but are often time-consuming and technically demanding. In contrast, molecular techniques detect genetic mutations associated with drug resistance and generally provide faster results. However, their diagnostic accuracy depends on the genetic targets included in each assay, meaning that mutations outside the targeted regions may remain undetected.

Molecular testing supports earlier treatment decisions, although detected mutations alone cannot fully predict individual treatment outcomes. Particular attention should also be given to isoniazid-resistant, rifampicin-susceptible tuberculosis, which remains an important form of drug resistance. Since molecular assays differ in their diagnostic targets and performance, additional phenotypic susceptibility testing may be necessary to obtain a more comprehensive resistance profile.

Molecular Testing Methods. Molecular drug-susceptibility testing (DST) is based on detecting Mycobacterium tuberculosis nucleic acid and identifying genetic mutations associated with resistance to anti-tuberculosis medications. These diagnostic approaches are generally divided into probe-based and sequencing-based methods. Compared with conventional culture-based phenotypic DST, molecular techniques provide considerably faster results and support earlier identification of drug-resistant tuberculosis.

Probe-Based Assays. Probe-based molecular assays use nucleic acid amplification and hybridization techniques to detect M. tuberculosis and specific mutations associated with drug resistance. Important examples include Xpert MTB/RIF and line-probe assays (LPAs), such as GenoType MTBDR. These methods are widely used because they provide relatively rapid diagnostic results. Xpert MTB/RIF can identify tuberculosis and rifampicin resistance within approximately two hours, whereas LPAs may require up to two days from specimen processing to result interpretation. Both approaches offer substantial time advantages over conventional culture-based methods, which may require several weeks.

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LPAs are particularly useful for identifying mutations associated with rifampicin and isoniazid resistance. However, their diagnostic performance may be reduced in smear-negative specimens, and uncommon mutations located outside the targeted genetic regions may remain undetected. Furthermore, these assays require appropriate laboratory infrastructure, trained personnel, and standardized procedures to ensure reliable results.

Sequence-Based Assays. Sequence-based methods, including targeted gene sequencing and next-generation sequencing (NGS), identify resistance-associated mutations by analyzing specific genomic regions or broader portions of the bacterial genome. Whole-genome sequencing (WGS) provides more comprehensive genetic information and can detect a wider range of resistance-associated mutations than assays based on a limited number of molecular probes. Targeted NGS has attracted considerable attention because it may allow resistance detection directly from clinical specimens without relying exclusively on conventional culture-based procedures. Several studies have demonstrated diagnostic performance comparable to WGS for identifying known resistance-associated mutations. In addition to clinical diagnosis, sequencing technologies contribute to epidemiological surveillance by providing information about transmission patterns, bacterial genetic diversity, and the emergence of new resistance mutations.

Despite these advantages, the implementation of sequencing-based methods in routine clinical practice remains challenging because of relatively high costs, specialized laboratory requirements, complex data interpretation, and the need for trained professionals. Nevertheless, technological improvements and decreasing sequencing costs may facilitate their broader application in tuberculosis diagnostics. Importantly, the reliability of all genotypic methods depends on the genetic regions examined and the accuracy with which detected mutations are interpreted in relation to phenotypic drug resistance.

Resistance Targets and Classifications. Molecular diagnostic assays identify drug resistance in Mycobacterium tuberculosis by detecting mutations within specific genetic regions associated with reduced susceptibility to anti-tuberculosis medications. For rifampicin (RIF), the most commonly investigated target is the

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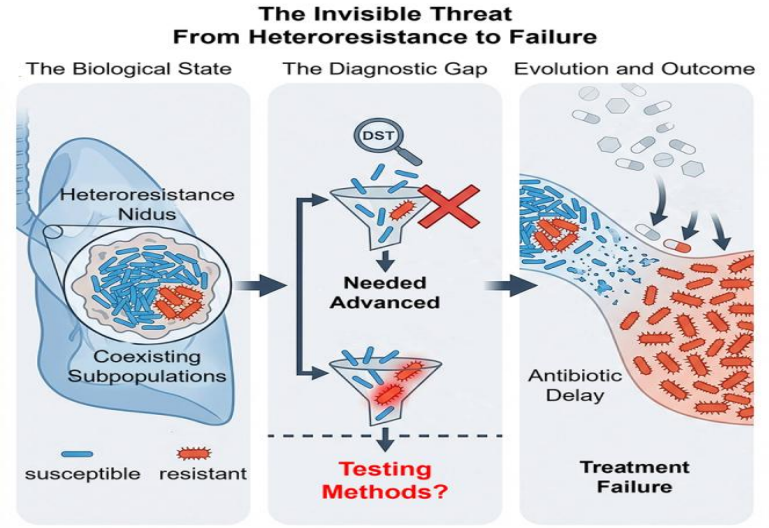
rpoB gene, particularly its 81-base-pair rifampicin resistance-determining region (RRDR), where the majority of clinically relevant resistance-associated mutations are located.

First-line line-probe assays (LPAs) also identify genetic alterations associated with isoniazid (INH) resistance, primarily within the katG gene, especially at codon 315, and the promoter region of the inhA gene. Second-line LPAs are designed to detect mutations in the gyrA gene associated with fluoroquinolone resistance, as well as genetic changes linked to resistance against injectable drugs, including amikacin, kanamycin, and capreomycin.

However, molecular testing has certain limitations because it examines predefined genetic regions and may fail to identify mutations located outside the targeted sequences. In addition, some mutations are associated with relatively low levels of resistance and may not be detected by conventional phenotypic drug-susceptibility testing (pDST) at standard critical concentrations. The World Health Organization refers to specific mutations associated with this phenomenon as borderline resistance mutations. Seven recognized rifampicin-associated mutations include L430P, D435Y, H445L, H445S, H445N, L452P, and I491F. Collectively, these mutations account for approximately 12% of rifampicin-resistant isolates. Differences between genetic detection and phenotypic resistance expression may therefore result in discrepancies between molecular and conventional susceptibility testing.



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Phenotypic resistance can also be evaluated using the resistance-ratio method, which compares the minimum inhibitory concentration (MIC) of a clinical isolate with that of the reference M. tuberculosis H37Rv strain. A resistance ratio of 2 or lower generally indicates susceptibility, whereas a ratio of 4 represents an intermediate result requiring repeat assessment. Values of 8 or higher are considered indicative of resistance. Nevertheless, this approach has limitations in distinguishing low-level and intermediate resistance, and its results may be influenced by the bacterial inoculum size.

Differences in critical concentrations can also affect the classification of isoniazid resistance. One investigation reported that previously applied critical concentrations of 0.2 and 1.0 mg/L were considerably higher than proposed breakpoints of 0.0312 mg/L for low-level resistance and 0.125 mg/L for high-level resistance. These findings highlight the importance of appropriately selected diagnostic thresholds and the integration of molecular and phenotypic methods to achieve a more accurate characterization of drug-resistant tuberculosis.

Table 1 Definitions, WHO Classification of Anti-Tuberculosis Drugs for MDR-TB, and the Development Pipeline for Novel TB Therapies

Definitions	
Resistant Bacteria	A bacterial population with a genetic mutation that facilitates survival against antibiotic treatment
Bacterial Tolerance	Bacteria that are able to phenotypically survive antibiotic challenge, with no genetic mutations directly associated with drug resistance
Persistent Bacteria	A subpopulation of bacterial cells that display a tolerant phenotype towards antibiotics
Acquired Resistance	Bacteria that develop drug resistance due to host or antibiotic pressure while infecting the lung
Transmitted Resistance	The infection of naïve lungs with bacteria already having a resistance genotype
Multidrug Resistant TB (MDR-TB)	Infection with tubercle bacilli genetically resistant to rifampicin and isoniazid
Pre-Extensively Drug Resistant TB (pre-XDR-TB)	MDR-TB with additional resistance to any fluoroquinolone OR a second line injectable
Extensively Drug Resistant TB (XDR-TB)	MDR-TB with resistance to any fluoroquinolone AND a further Group A drug

WHO TB Drug Classification for use in the treatment of MDR-TB			
Group A:	Group B:	Group C:	
Levofloxacin/moxifloxacin Bedaquiline Linezolid	Clofazimine Cycloserine/terizidone	Ethambutol Delamanid Pyrazinamide Imipenem-cilastatin/meropenem	Amikacin/streptomycin Ethionamide/prothionamide P-aminosalicylic acid Other agents

Candidate Pipeline for New Anti-TB Drugs					
Phase I:		Phase II:		Phase III: (drug regimen human trials)	
BVL-GSK098 GSK-286 PBTZ-169	TBAJ-587 TBAJ-876 TBI-223	BTZ-043 Delpazolid (LCB01-0371) GSK 3036656 OPC-167832 Pyrifazimine (TBI-166) SPR720 (Fobrepodacin)	SQ109 Sudapyridine (WX-081) Sutezolid TBA-7371 Telacebec (Q203)	Bedaquiline Clofazimine Delamanid Levofloxacin	Linezolid Moxifloxacin Pretomanid Rifapentine

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Diagnostic Performance and Interpretation of Molecular and Phenotypic Tests

Molecular diagnostic assays enable the rapid identification of genetic mutations associated with anti-tuberculosis drug resistance. However, their diagnostic performance differs according to the antimicrobial agent being tested, the assay platform, and the type of clinical specimen. DNA microarray-based methods have demonstrated high accuracy for detecting isoniazid (INH) and rifampicin (RIF) resistance in clinical isolates, with reported sensitivity and specificity reaching 100% for both drugs. Nevertheless, their performance may be less consistent when detecting resistance to other anti-tuberculosis agents. Reported sensitivity was 90% for fluoroquinolone resistance and 95.7% for resistance to second-line injectable drugs, whereas specificity reached 90.9% and 90.2%, respectively. For ethambutol resistance, sensitivity was 89.9%, while specificity was considerably lower at 57%. When applied to sputum specimens, microarray assays achieved sensitivities above 90% for several drugs, although specificity varied between 60% and 95%.

The diagnostic accuracy of individual molecular platforms may also differ. For example, the mfloDx™ pre-XDR-TB assay demonstrated 86.2% sensitivity and 99.2% specificity for detecting INH resistance when compared with MGIT-based drug-susceptibility testing (DST). These findings highlight the importance of considering the performance characteristics of each assay when interpreting molecular results and selecting appropriate diagnostic strategies.

Despite advances in molecular diagnostics, phenotypic drug-susceptibility testing (pDST) continues to play an essential role in the identification of drug-resistant tuberculosis, particularly when molecular findings are negative, inconclusive, or inconsistent with the patient's clinical presentation. By evaluating bacterial growth in the presence of specific anti-tuberculosis drugs, pDST provides functional evidence of drug susceptibility. However, conventional solid-culture methods are time-consuming, generally requiring three to six weeks to produce results, and depend on well-equipped laboratory facilities and specialized technical expertise.

It is important to recognize that neither genotypic nor phenotypic testing represents an entirely reliable reference standard in every clinical situation.

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Discrepancies may arise because molecular assays detect only selected resistance-associated mutations, whereas phenotypic methods assess bacterial growth under predefined laboratory conditions. Consequently, diagnostic findings should not be interpreted independently but rather evaluated in conjunction with the patient's treatment history, clinical manifestations, epidemiological background, and other available laboratory data.

When molecular and phenotypic results are inconsistent, a systematic approach is required to establish the most reliable interpretation. This may involve repeating the relevant tests, verifying specimen identity and quality, and performing additional molecular investigations. Where available, high-resolution whole-genome sequencing (WGS) can provide more comprehensive information about the genetic characteristics of Mycobacterium tuberculosis and mutations potentially associated with resistance. Continued access to reliable pDST is also important, as it may reveal resistance patterns that are not covered by the targets of currently available molecular assays.

Another important challenge in interpreting drug-resistance results is heteroresistance, which refers to the coexistence of drug-susceptible and drug-resistant Mycobacterium tuberculosis populations within the same patient. This phenomenon may occur when resistant bacterial variants emerge within an initially susceptible population or when different bacterial populations coexist. Conventional diagnostic techniques may fail to identify resistant subpopulations present at low frequencies, resulting in an incomplete characterization of the patient's resistance profile. If such variants remain undetected, treatment may create selective pressure that favors their subsequent expansion.

Phenotypic DST alone may also be insufficient to distinguish heteroresistance from infection involving multiple genetically distinct M. tuberculosis strains. In this context, sequencing-based approaches can provide additional information about the composition and genetic diversity of bacterial populations. Deep sequencing and other highly sensitive molecular techniques may identify low-frequency resistance-associated variants that remain undetected by conventional diagnostic methods.

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The relationship between heteroresistance and treatment outcomes remains an area of ongoing investigation. Available evidence suggests that the reported association may depend partly on the analytical sensitivity of the diagnostic methods used. In one review, studies employing highly sensitive techniques capable of detecting resistant variants at frequencies of approximately 1–5% reported a stronger association between heteroresistance and unfavorable treatment outcomes than studies using methods with higher detection thresholds. The same analysis indicated that patients in whom heteroresistance was identified and appropriately addressed through treatment had outcomes comparable to those observed in patients with homogeneous drug resistance.

Clinical Implications of Molecular Drug-Susceptibility Testing

Rapid molecular drug-susceptibility testing (DST) plays an important role in the early management of drug-resistant tuberculosis by substantially reducing the time required to obtain clinically actionable resistance information. Compared with conventional phenotypic methods, molecular assays can provide results much earlier, enabling clinicians to identify appropriate treatment options and initiate effective therapy without unnecessary delays.

The implementation of molecular DST has been associated with shorter intervals to sputum culture conversion and more favorable treatment outcomes in some studies. For instance, investigations involving Xpert MTB/RIF and line-probe assays demonstrated that molecularly detected resistance could subsequently be confirmed by phenotypic DST. The use of Xpert MTB/RIF as an initial diagnostic tool facilitated the identification of multidrug-resistant tuberculosis (MDR-TB) among newly diagnosed patients, potentially preventing the administration of ineffective first-line regimens and limiting opportunities for continued disease transmission.

Although molecular findings can substantially influence treatment decisions, their interpretation requires consideration of the clinical context and the limitations of individual diagnostic platforms. Some genotypic assays detect only predefined mutations and may therefore fail to identify newly recognized or uncommon resistance-associated variants. In contrast, broader sequencing-based approaches can reveal non-canonical mutations that are not covered by

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conventional molecular tests. Such findings may require additional investigation, including phenotypic DST, to clarify their clinical significance and determine their contribution to the resistance profile.

Accordingly, molecular test results can provide an important basis for initiating or modifying treatment while further confirmatory investigations are being conducted. This approach may reduce dependence on slower conventional testing and support more timely therapeutic decisions. Nevertheless, molecular findings should be integrated with phenotypic susceptibility results whenever necessary, particularly when unusual mutations or inconsistencies between laboratory findings and clinical response are identified.

Association Between Molecular Detection of Drug Resistance and Treatment Outcomes

The early identification of drug resistance through molecular diagnostic methods may contribute to improved tuberculosis management by allowing patients to receive an appropriate treatment regimen sooner than would be possible with conventional culture-based DST. Phenotypic testing can require several weeks, during which patients may remain untreated or continue receiving regimens that are ineffective against the resistant bacterial strain. Such delays may compromise treatment effectiveness and increase the likelihood of loss to follow-up before an appropriate regimen is initiated. Therefore, rapid molecular diagnosis is considered an important component of strategies aimed at improving patient care and reducing the transmission of drug-resistant tuberculosis.

In addition to supporting initial treatment selection, molecular DST can assist clinicians in reassessing therapeutic strategies when patients demonstrate an inadequate response to treatment. The identification of previously unrecognized resistance may explain persistent microbiological positivity or delayed culture conversion. However, suspected treatment failure generally requires a comprehensive evaluation, potentially combining molecular and phenotypic DST with clinical and microbiological assessment.

Reported treatment outcomes vary considerably across study populations and therapeutic regimens. In one cohort, favorable outcomes were documented in 37.8% of patients, whereas 31.3% experienced unfavorable outcomes. An

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additional 20.7% had no outcome assigned or were still awaiting final classification. Importantly, the unfavorable outcome category included loss to follow-up, which should not automatically be interpreted as microbiological treatment failure. The investigators emphasized that earlier recognition of resistance and timely initiation of an appropriate regimen could improve treatment outcomes, while also acknowledging the need for more comprehensive evaluation of final treatment results and adverse drug reactions.

Differences in treatment success have also been reported across geographical settings. For example, a study conducted in Ethiopia documented a treatment success rate exceeding 65%, while the proportion of patients lost to follow-up reached 16.8%. The authors identified loss to follow-up, advanced age, and the presence of comorbid conditions as important challenges that may hinder the achievement of favorable treatment outcomes.

The importance of pretreatment DST is further supported by evidence indicating that treatment initiated without prior assessment of drug susceptibility may be associated with an increased risk of acquired resistance, particularly among patients whose infections are already resistant to one or more anti-tuberculosis agents. These findings emphasize the need to establish an accurate resistance profile before selecting an appropriate therapeutic regimen whenever feasible.

Despite these observations, the available evidence does not establish that molecular testing alone directly improves treatment outcomes. Its potential clinical benefit is more appropriately understood as part of a broader diagnostic and therapeutic pathway involving early resistance detection, appropriate regimen selection, timely treatment initiation, adherence support, and continuous monitoring.

Factors Influencing the Relationship Between Molecular Diagnosis and Treatment Outcomes

The association between molecular identification of drug resistance and subsequent treatment outcomes is influenced by several interrelated clinical, therapeutic, and socioeconomic factors. Early detection is particularly valuable when it leads to the prompt initiation of a regimen that is effective against the identified resistance pattern. Conversely, the clinical benefit of rapid diagnosis

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may be limited when appropriate medications, confirmatory testing, or specialist treatment services are unavailable. Available evidence suggests that timely recognition of resistance to second-line drugs, followed by access to an effective treatment regimen, may increase the probability of a favorable outcome. Nevertheless, more detailed investigations are required to establish the extent of this relationship.

A history of previous or ineffective anti-tuberculosis treatment represents another important consideration. Patients who have received unsuccessful or inadequate treatment may be more likely to harbor resistant bacterial populations, creating additional challenges for selecting an effective regimen. Previous treatment exposure should therefore be carefully considered when interpreting molecular findings and planning subsequent therapeutic interventions.

The composition of the treatment regimen and the availability of anti-tuberculosis medications may also influence clinical outcomes. Treatment recommendations and drug combinations have evolved over time in response to updated international guidelines and emerging evidence. Consequently, patients treated during different study periods may have received substantially different therapeutic regimens. Furthermore, variations in access to specific medications and drug-susceptibility testing facilities may contribute to differences in treatment effectiveness between healthcare settings.

Patient adherence is another major determinant of treatment success. The prolonged duration and complexity of some drug-resistant tuberculosis regimens, together with potential adverse drug reactions, may make consistent medication use difficult. Socioeconomic circumstances, limited access to healthcare services, insufficient treatment education, and inadequate social support can further complicate adherence. Patient-centered interventions, including structured case management, appropriate counseling, treatment education, and additional support measures, may help overcome these barriers and improve continuity of care.

Comorbid conditions and individual clinical or psychosocial circumstances should also be incorporated into treatment planning. The presence of additional diseases may complicate medication selection, increase the risk of adverse reactions, and affect a patient's ability to complete the prescribed regimen.

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Therefore, individualized management and regular clinical monitoring are important components of comprehensive care for patients with drug-resistant tuberculosis.

The interpretation of treatment outcomes also depends on the classification criteria applied in individual studies. According to World Health Organization (WHO) definitions, treatment success is a combined outcome comprising patients classified as cured and those who have completed treatment. Conversely, unfavorable outcomes may include death, treatment failure, loss to follow-up, or changes in the treatment regimen under specified circumstances. These categories should be clearly distinguished because loss to follow-up does not necessarily indicate microbiological treatment failure. Combining loss to follow-up with other unfavorable outcomes may obscure important differences between patients who discontinue treatment and those who experience confirmed therapeutic failure.

Practical Considerations for Implementing Molecular Drug-Resistance Testing

The successful implementation of molecular diagnostic methods for drug-resistant tuberculosis depends on several interconnected factors, including laboratory infrastructure, technical capacity, financial resources, and the availability of trained personnel. Although modern molecular platforms offer substantial advantages in terms of diagnostic speed and accuracy, their integration into routine clinical practice may be challenging, particularly in healthcare settings with limited resources. Certain systems, such as the Abbott m2000 platform, require considerable laboratory infrastructure, specialized equipment, and designated areas for molecular sample preparation and amplification.

The introduction of point-of-care molecular testing in high-burden regions may also be restricted by financial constraints, logistical challenges, and insufficient laboratory facilities. The cost of equipment, maintenance, consumables, and staff training can limit the widespread adoption of these technologies. In contrast, diagnostic platforms with simplified procedures and fewer technical requirements may facilitate the decentralization of testing and improve access to molecular diagnostics across different levels of the healthcare system.

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Ensuring the reliability and reproducibility of molecular test results requires appropriate specimen collection, transportation, processing, and quality-control procedures. Laboratories should establish standardized protocols for specimen handling and implement quality-assurance systems capable of identifying and addressing potential technical errors. Continuous staff training is equally important, particularly regarding accurate patient identification, specimen labeling, data recording, and documentation of other essential diagnostic information.

For line-probe assays, quality control may involve the inclusion of both positive and negative controls in every testing batch. If either control produces an unacceptable result, the testing procedure should be repeated, beginning with the DNA extraction stage. Such measures help identify potential procedural errors and reduce the likelihood of reporting inaccurate results.

Effective communication between clinicians and laboratory personnel is another essential component of the diagnostic process. Clinicians should be familiar with the available testing methods, specimen requirements, and appropriate procedures for requesting molecular and phenotypic DST. Where clinically indicated, collecting specimens from multiple potentially affected anatomical sites may increase the likelihood of obtaining adequate material for microbiological investigation and subsequent drug-susceptibility assessment.

Conclusion

Drug-resistant tuberculosis remains a major global health challenge, requiring accurate and timely diagnostic approaches to support effective treatment and limit further transmission. Molecular diagnostic techniques, including Xpert MTB/RIF, line-probe assays, targeted sequencing, and next-generation sequencing, have substantially improved the speed of resistance detection compared with conventional culture-based methods. By identifying genetic mutations associated with resistance to first- and second-line anti-tuberculosis drugs, these technologies enable earlier treatment decisions and may reduce delays in initiating appropriate therapeutic regimens.

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Nevertheless, molecular testing has important limitations. Its diagnostic accuracy depends on the genetic regions targeted by individual assays, and uncommon or newly recognized mutations may remain undetected. Differences between genotypic and phenotypic susceptibility results, together with the presence of heteroresistant bacterial populations, further complicate the interpretation of resistance profiles. Therefore, molecular findings should be evaluated alongside phenotypic drug-susceptibility testing, clinical characteristics, and treatment history whenever necessary.

The potential benefits of rapid molecular diagnosis extend beyond the identification of drug resistance. Earlier recognition of resistant tuberculosis can facilitate appropriate regimen selection, support timely treatment initiation, and potentially reduce the risk of ineffective therapy and ongoing transmission. However, favorable treatment outcomes also depend on several additional factors, including medication availability, treatment adherence, comorbidities, socioeconomic circumstances, and continuous clinical monitoring. Consequently, improved diagnostic speed alone cannot guarantee treatment success.

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