

Review Article

Extra-pulmonary tuberculosis: towards an integrated diagnostic and management pathway: a narrative review

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ABSTRACT

Extrapulmonary tuberculosis (EPTB) accounts for a substantial and increasing share of global tuberculosis (TB) notifications, yet remains disproportionately difficult to diagnose because of its paucibacillary nature, heterogeneous organ involvement, and the fragmented way in which clinical, radiological, histopathological, and microbiological data are typically interpreted. To synthesize current evidence on EPTB diagnosis and management within a single pathway-based framework, with attention to organ specific diagnostic yield, special populations, and unresolved controversies. This narrative review synthesizes evidence from World Health Organization (WHO) consolidated guidelines, Cochrane systematic reviews, landmark randomized trials and recent diagnostic accuracy studies to provide an updated overview of the diagnosis and management of EPTB. Evidence suggests that no single test reliably excludes EPTB, diagnostic yield varies markedly by disease site and specimen type, with Xpert MTB/RIF Ultra outperforming Xpert MTB/RIF and smear microscopy across most extrapulmonary specimens but still leaving important gaps, particularly in cerebrospinal and pleural fluid. Children and people living with HIV are disproportionately affected and pose distinct diagnostic challenges. Management increasingly requires site-specific tailoring, especially for drug-resistant disease, where current WHO shorter regimens explicitly exclude central nervous system, osteoarticular, and disseminated forms. An integrated, multidisciplinary diagnostic pathway rather than test by test or organ by organ, evaluation offers the most practical framework for reducing diagnostic delay in EPTB.

Keywords: Tuberculosis, Extrapulmonary tuberculosis, Diagnosis, Xpert MTB/RIF Ultra, Drug-resistant tuberculosis, Multidisciplinary management

INTRODUCTION

Tuberculosis (TB) remains a leading cause of infectious morbidity and mortality worldwide. An estimated 10.7 million people developed TB globally in 2024, and 8.3

million new and recurrent cases were notified; of these, 16% were classified as extrapulmonary TB (EPTB), a proportion that exceeds 20% in several high-burden countries, including India.¹ Unlike pulmonary TB, which is diagnosed principally through sputum-based testing, EPTB can affect virtually any organ system and typically

presents with nonspecific, organ-localized symptoms that mimic malignancy, autoimmune disease, or pyogenic infection, resulting in frequent diagnostic delay and repeated invasive procedures before a diagnosis is reached. The risk of EPTB, and of disseminated disease in particular, is further increased by conditions that impair cell-mediated immunity, including HIV infection, diabetes mellitus, chronic kidney disease, malignancy, and biological immunosuppressive therapy, all of which are becoming more prevalent even in traditionally high-burden settings and are reshaping the epidemiology of EPTB toward more frequent atypical and multi-site presentations.²⁻⁴

The central diagnostic obstacle in EPTB is its paucibacillary biology and most extrapulmonary lesions contain far fewer organisms than cavitary pulmonary disease, which limits the sensitivity of smear microscopy, culture, and even molecular assays, with performance varying markedly by specimen type and disease site.^{5,6} As a result, no single investigation reliably excludes EPTB, and diagnosis usually depends on integrating clinical suspicion, imaging, histopathology, and microbiology rather than any one test in isolation - yet the existing literature tends to discuss these disciplines separately rather than as a single diagnostic pathway.^{7,8}

This review synthesizes current evidence on EPTB diagnosis and management using an integrated, pathway-based framework, with attention to organ-specific diagnostic yield, the distinct challenges posed by pediatric and HIV-associated disease, unresolved controversies in test and treatment selection, and the management of drug-resistant EPTB.

METHODS

We performed a structured literature through searches of Pubmed/Medline, Scopus, Cochrane library, and WHO tuberculosis guideline documents for articles relevant to EPTB diagnosis and management. Search terms included combinations of “tuberculosis”, “extrapulmonary tuberculosis”, “tuberculous lymphadenitis”, “tuberculous pleuritis”, “musculoskeletal tuberculosis”, “genitourinary tuberculosis”, “tuberculous meningitis”, “Xpert MTB/RIF”, “Xpert MTB/RIF Ultra”, “drug-resistant tuberculosis” and site-specific terms for organ based EPTB. We included systematic reviews, meta-analysis, randomized control trials, diagnostic accuracy studies, cohort studies, and major guideline documents.

Articles were selected for relevance to the diagnostic and management pathway of EPTB, with priority given to higher level evidence, recent guidelines and studies with direct clinical applicability. This review is based exclusively on previously published studies and did not involve human participants, animals, or identifiable patient data therefore ethical clearance was not required.

WHY EPTB IS DIFFICULT TO DIAGNOSE?

Effective cellular immune responses contain *M. tuberculosis* within organized granulomatous lesions at extrapulmonary sites, limiting bacillary replication and producing the low organism burden that defines paucibacillary disease.⁹ This has direct diagnostic consequences: smear microscopy is positive in only a small minority of extrapulmonary specimens, and even mycobacterial culture, the traditional reference standard, requires several weeks and still under detects a substantial proportion of true cases because specimen volumes are often small and bacillary density is low.^{3,10}

Pre-analytical factors compound this biological limitation. Many extrapulmonary specimens like cerebrospinal fluid (CSF), pleural or ascitic fluid, fine-needle aspirates are obtained in small volumes because of the invasiveness or risk of the procedure required to acquire them, leaving insufficient material to run histopathology, culture, and molecular testing in parallel without prioritizing one modality over another.

Inappropriate transport conditions, delayed processing, and formalin fixation of tissue intended for microbiological testing (which is required for histopathology but destroys viable organisms) further reduce diagnostic yield in routine practice, independent of the intrinsic sensitivity of the tests used.^{5,11} Nucleic acid amplification testing has narrowed, but not closed, this gap. A 2021 Cochrane review of Xpert MTB/RIF and Xpert MTB/RIF Ultra across extrapulmonary specimen types found pooled Xpert MTB/RIF sensitivity of 71.1% in CSF and only 49.5% in pleural fluid, whereas Xpert MTB/RIF Ultra improved sensitivity to 89.4% in CSF and 75.0% in pleural fluid, generally at some cost to specificity.⁵

An earlier meta-analysis of Xpert MTB/RIF in lymph node specimens reported a pooled sensitivity around 83% against a composite reference standard (CRS), reflecting the comparatively higher bacillary burden typical of tuberculous lymphadenitis.⁶

These site-specific differences mean that a negative molecular result carries very different implications depending on the specimen tested, and should never, by itself, be used to exclude EPTB in a patient with compatible clinical and radiological findings.

AN INTEGRATED DIAGNOSTIC PATHWAY

Rather than treating clinical evaluation, imaging, histopathology, microbiology, and molecular testing as sequential or independent steps, we propose that EPTB diagnosis is best conceptualized as a single, iterative pathway in which each discipline informs the interpretation of the others (Table 1).

Table 1: Integrated diagnostic pathway for suspected extrapulmonary tuberculosis.

Step	Key actions
1. Clinical suspicion	Assess risk factors (HIV, diabetes, chronic kidney disease, immunosuppressive therapy, TB contact); consider EPTB even with a normal chest radiograph, and in children and people living with HIV in particular
2. Risk stratification	Identify features warranting urgent evaluation (CNS signs, pericardial tamponade, disseminated disease)
3. Imaging	Localize disease and identify the safest, highest-yield site for specimen acquisition
4. Specimen acquisition	Prefer tissue over fluid wherever feasible; obtain adequate volume for parallel testing
5. Parallel testing	Send the same specimen for histopathology, mycobacterial culture, and Xpert MTB/RIF Ultra rather than sequential testing
6. Integrated interpretation	Reconcile clinical, radiological, histopathological, and microbiological findings; discordant results require multidisciplinary discussion, not automatic exclusion of TB
7. Treatment and follow-up	Initiate therapy (empirically if clinically justified); monitor response at defined intervals and reassess the diagnosis if improvement is inadequate

Abbreviations: CNS: central nervous system, EPTB: extrapulmonary tuberculosis, HIV: human immunodeficiency virus, TB: tuberculosis.

Clinical suspicion, guided by risk factors such as HIV infection, diabetes mellitus, chronic kidney disease, biological immunosuppressive therapy, and known TB contact, determines the intensity and urgency of subsequent investigation.¹²⁻¹⁴ Cross-sectional imaging (contrast-enhanced CT [computed tomography] or MRI [magnetic resonance imaging], and occasionally PET-CT [positron emission tomography-CT] for occult or multi-site disease) localizes disease and guides the choice of the least invasive specimen likely to yield a diagnosis. Wherever feasible, tissue rather than fluid should be obtained, since multiple studies have shown higher

diagnostic yield from tissue biopsies than from corresponding body fluids across several forms of EPTB.^{3,7} Every adequate specimen should, where resources allow, be sent simultaneously for histopathology, mycobacterial culture, and Xpert MTB/RIF Ultra, since these modalities are complementary rather than interchangeable: granulomatous inflammation without microbiological confirmation, or a positive molecular test without classical histological features, are both common and clinically significant patterns that require integrated interpretation rather than reliance on a single result (Figure 1)^{15,3}

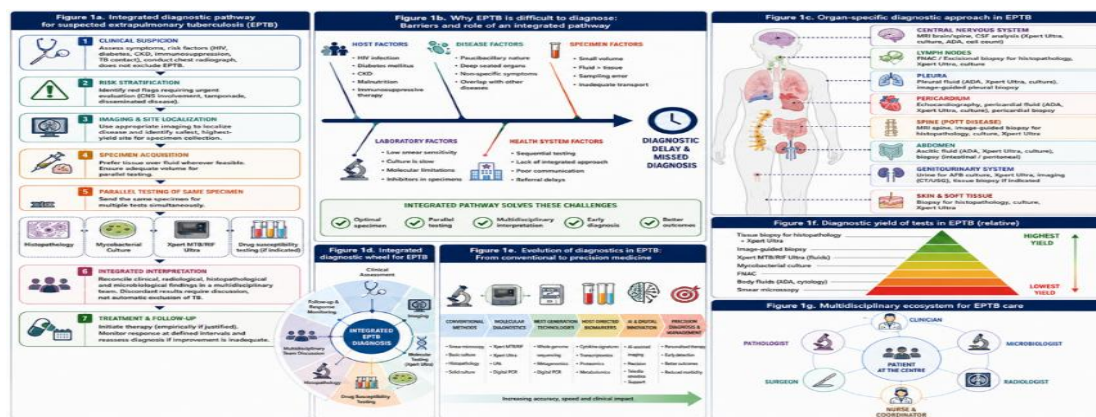


Figure 1: The figure illustrates a stepwise, multidisciplinary approach for EPTB diagnosis. It highlights host, disease, specimen, laboratory and health-system factors contributing to diagnostic delay, and emphasizes organ-specific sampling, optimized diagnostic tests, and multidisciplinary collaboration to improve diagnostic yield and patient outcomes.

AFB: acid fast bacilli, ADA: adenosine deaminase, CKD: Chronic Kidney Disease, CNS: central nervous system, COTS: collaborative ocular tuberculosis study, CSF: cerebrospinal fluid, CT: computed tomography, EPTB: extrapulmonary tuberculosis, FNAC: fine needle aspiration cytology, HIV: human immunodeficiency Virus, IGRA: interferon gamma release assay, MRI: magnetic resonance imaging, TB: tuberculosis, TST: tuberculin skin test

The World Health Organization's consolidated diagnostic guidance now recommends Xpert MTB/RIF Ultra as the initial molecular test for most extrapulmonary specimens, with mycobacterial culture and drug-susceptibility testing performed in parallel wherever feasible, reflecting exactly this principle of complementary rather than sequential testing.¹⁶

ORGAN-SPECIFIC DIAGNOSTIC YIELD

Diagnostic strategy must be tailored to the disease site, since both bacillary burden and the practicality of specimen acquisition vary considerably (Table 2).

Table 2: Organ-specific diagnostic yield in extrapulmonary tuberculosis (EPTB).

Extrapulmonary Sites	Preferred specimen	Approx. sensitivity (smear microscopy / culture / Xpert MTB/RIF Ultra)	Key adjunct	References
Lymph node	FNAC or excisional biopsy	Low / moderate / 67.0-89.7%	Histopathology (granuloma +/- caseation)	5, 68, 70
Pleura	Pleural biopsy > fluid	Very low / moderate / variable (38-80%)	Pleural fluid ADA (pooled sensitivity 92%)	5, 58, 59
CNS	CSF	10-20% / moderate / 70-95%	MRI (basal enhancement, hydrocephalus); Marais criteria; adjunctive dexamethasone	5, 23, 67
Pericardium	Pericardial fluid or biopsy	0-42% / 50-65% / 32.4-82.4%	Pericardial fluid ADA; echocardiography	5
Spine/ joint	Image-guided biopsy	Low / moderate / variable	Contrast MRI; chemotherapy alone usually sufficient	5,26
Abdomen (intestinal/peritoneal)	Colonoscopic or laparoscopic biopsy (>=6-8 pieces)	Low / moderate / variable (42.0-76.2%)	Ascitic ADA; CT/MR enterography	5
Genitourinary	Urine culture (multiple specimens) or tissue	Very low / low-moderate / variable	CT urography/MRI	5
Eye	Rarely tissue; usually presumptive	Not applicable (fluid sampling impractical)	COTS consensus criteria; IGRA/TST + imaging	5,33
Skin	Skin biopsy	Low / variable / variable	Histopathology; clinical morphology	5, 34

ADA: adenosine deaminase, CNS: central nervous system, COTS: collaborative ocular tuberculosis study, CSF: cerebrospinal fluid, CT: computed tomography, EPTB: extrapulmonary tuberculosis, FNAC: fine needle aspiration cytology, IGRA: interferon gamma release assay, MRI: magnetic resonance imaging, TST: tuberculin skin test

Lymph node TB

Tuberculous lymphadenitis is the most common form of EPTB accounting for approximately 30 to 40% of all EPTB cases, particularly in high-burden countries like India. In order to diagnosing a lymph node TB, process must always begin with a strong clinical suspicion.¹⁸ Fine needle aspiration cytology (FNAC) typically shows epithelioid granulomas with or without caseous necrosis and is the reasonable first investigation given its low morbidity, but FNAC alone cannot reliably distinguish TB from non-tuberculous mycobacterial infection, sarcoidosis, or lymphoma; excisional biopsy is preferred

when cytology is discordant with clinical suspicion or when the patient fails to respond to empirical therapy.¹⁷

Pleural TB

Pleural TB is responsible for ranging from 3% to 5% of all TB cases in low burden settings while rising to nearly 30% in high TB burden settings. In India, a developing country with high burden, pleural TB constitutes about 30 to 80 % of cases of pleural effusion.¹⁸ Pleural TB remains paucibacillary even on pleural fluid analysis, with smear and culture yields well below those of pulmonary disease. Pleural fluid adenosine deaminase (ADA) is a well-

validated adjunct: a widely cited meta-analysis of 63 studies found pooled sensitivity of 92% and specificity of 90% for ADA in tuberculous pleurisy, though ADA is not entirely specific and can be elevated in empyema and some malignancies. Pleural biopsy retains a higher microbiological and histological yield than fluid-based testing alone and should be pursued when ADA and fluid analysis are inconclusive.^{19,20}

Central nervous system (CNS) TB

Although it represents just 1–2% of all TB cases, central nervous system TB (CNS-TB) remains among the most severe and life-threatening form of *M. tuberculosis* infection.²¹ CNS TB carries the highest mortality of any form of EPTB and is diagnosed through a combination of CSF lymphocytic pleocytosis, elevated protein, and low glucose, together with Xpert MTB/RIF Ultra testing and characteristic basal meningeal enhancement or hydrocephalus on contrast MRI. Because no single test is adequately sensitive, the Marais uniform case definition classifies cases as definite, probable, or possible tuberculous meningitis by integrating clinical, CSF, and imaging criteria, and empirical anti-tubercular therapy is often justified on strong clinical suspicion alone given the mortality associated with delayed treatment.²² A landmark randomized trial in Vietnamese adolescents and adults found that adjunctive dexamethasone improved overall survival in tuberculous meningitis, establishing corticosteroids as standard adjunctive therapy in this form of EPTB, although the mortality benefit has not been consistently replicated across all patient subgroups, including some HIV-positive cohorts.²³

Pericardial TB

Tuberculous pericarditis is a leading cause of pericardial effusion in TB-endemic, HIV-prevalent regions and can progress to cardiac tamponade acutely or constrictive pericarditis chronically if unrecognized.²⁴ Microbiological confirmation is difficult: smear sensitivity in pericardial fluid is approximately 5%, and even culture confirms only 50–60% of true cases. Pericardial fluid ADA is a useful adjunct, and the randomized IMPI trial found that adjunctive prednisolone reduced progression to constrictive pericarditis, although it did not improve the composite primary outcome of death, tamponade, or constriction, and was associated with increased risk of malignancy in HIV positive participants - a finding that continues to support the cautious, individualized use of corticosteroids in this condition.²⁵

Musculoskeletal TB

Musculoskeletal TB accounts for roughly 1–3% of all TB cases and 10–12% of EPTB cases. Spinal TB (Pott's disease) represents about half of these, predominantly affecting the thoracolumbar spine. Diagnostic delay of four to six months is common because of insidious, nonspecific presentation, and contributes to neurological

complications and deformity.^{26–28} Contrast MRI is the imaging modality of choice, showing disc and paravertebral involvement well before plain radiography, and should guide image-directed biopsy for histological and microbiological confirmation; with early diagnosis and treatment, cure rates approaching 95% are achievable.²⁹

Abdominal TB

Abdominal TB (intestinal and peritoneal disease) accounts for roughly 11–16% of EPTB and commonly mimics Crohn's disease, malignancy, or other inflammatory conditions. Colonoscopy with at least six to eight biopsies improves microbiological yield, and characteristic findings include transverse ulcers, pseudo polyps, and short strictures around the ileocaecal valve; ascitic fluid ADA supports a diagnosis of peritoneal TB, though, as with pleural disease, it is an adjunct rather than a stand-alone diagnostic test.³⁰

Genitourinary TB

Genitourinary TB is one of the most common forms of EPTB globally constituting approximately 27% of cases worldwide, with reported rates ranging from 14% to 41%.³¹ The disease arises from hematogenous seeding of the kidneys with an insidious course that can span decades before clinical presentation; sterile pyuria and microscopic hematuria are common but nonspecific clues, and up to three-quarters of renal TB is unilateral at presentation. Urine culture has notoriously low sensitivity, and imaging (CT urography or MRI) combined with multiple culture specimens and, where available, Xpert testing on urine, is required for diagnosis; classification and management continue to evolve as reflected in dedicated urological consensus reviews.³²

Ocular TB

Ocular TB most often presents as tubercular uveitis and poses a distinctive diagnostic challenge because intraocular fluid sampling is rarely feasible; diagnosis therefore usually rests on a compatible ocular phenotype together with systemic evidence of TB exposure or infection (tuberculin skin testing [TST], interferon-gamma release assays [IGRA], chest imaging).

The Collaborative Ocular TB Study consensus guidelines provide structured, evidence and expert-based criteria for initiating anti-tubercular therapy in tubercular choroiditis and other uveitis phenotypes in the absence of microbiological confirmation.³³

Cutaneous TB

Cutaneous TB is diagnosed primarily on histopathology showing granulomatous dermal inflammation, with the specific morphological pattern - lupus vulgaris, scrofuloderma, TB verrucosa cutis, tuberculous chancre,

or orificial TB - determined largely by the route of inoculation and host immune status; culture and molecular testing add confirmatory value but have limited sensitivity given the paucibacillary nature of skin lesions.³⁴

SPECIAL POPULATIONS: CHILDREN AND PEOPLE LIVING WITH HIV

Children are disproportionately affected by EPTB because primary infection is more likely to disseminate hematogenously before adaptive immunity has fully matured.³⁵ A multicenter Spanish study found that EPTB accounted for 17.7% of pediatric TB cases and was independently associated with the child's foreign-born origin, underlying immune disorders, and drug-resistant disease; despite the challenges of pediatric specimen acquisition, bacteriological confirmation was actually more frequent in EPTB than in pulmonary disease in this cohort, though complications were present in 40% of extrapulmonary cases.³⁶

Tuberculous lymphadenitis and CNS disease predominate in young children, and diagnostic algorithms validated primarily in adults - including some imaging and CSF-based scoring criteria - may not transfer directly to pediatric populations, where smaller specimen volumes and age-specific normal ranges further complicate interpretation.³⁵ In people living with HIV, impaired granuloma formation increases the likelihood of disseminated and atypical presentations, reduces the sensitivity of smear microscopy and histopathology (since classical caseating granulomas may be poorly formed or absent) and increases reliance on molecular and culture-based confirmation even as bacillary burden in blood and tissue can paradoxically be higher in advanced immunosuppression.³⁷ Both populations warrant a lower threshold for empirical therapy alongside continued diagnostic effort, given the excess mortality associated with diagnostic delay in each group.³⁸

UNRESOLVED QUESTIONS AND CONTROVERSIES

Several practical questions remain genuinely unsettled. First, should Xpert MTB/RIF Ultra replace culture in extrapulmonary specimens? Ultra's higher sensitivity comes with a lower specificity than Xpert MTB/RIF in some specimen types, because it detects fewer bacilli, including in some cases non-viable organisms; consequently, current guidance retains culture in parallel wherever feasible, both to confirm diagnosis and to obtain drug-susceptibility data that Xpert-class assays cannot fully provide.^{5,16} Second, is FNAC alone adequate for tuberculous lymphadenitis, or should excisional biopsy be routine? In practice, FNAC remains the reasonable first step given its lower morbidity, reserving biopsy for diagnostic uncertainty or failure to respond to treatment.^{17,39}

Third, is surgery ever necessary in musculoskeletal TB, or does chemotherapy alone suffice? Decades-old but still-influential controlled trials by the Medical Research Council in Rhodesia and Hong Kong established that ambulatory chemotherapy alone achieves outcomes comparable to radical surgical debridement and spinal fusion in most patients with spinal TB, reserving surgery for neurological deficit, spinal instability, large abscesses, or failure of medical therapy - a principle that still broadly guides practice despite substantial advances in surgical technique since these trials were conducted.⁴⁰

Fourth, when is empirical anti-tubercular therapy justified before microbiological confirmation? This is most defensible in CNS and pericardial disease, where the mortality cost of delay is high and the sensitivity of available tests is intrinsically limited, but empirical therapy should not substitute for continued diagnostic effort, since alternative diagnoses (malignancy, fungal infection, sarcoidosis) can mimic EPTB closely at these sites.⁴¹⁻⁴³

Finally, emerging technologies like metagenomic and targeted next-generation sequencing, host-derived transcriptomic signatures, and artificial-intelligence-assisted image analysis - show promise for paucibacillary specimens but currently lack the validation, cost-effectiveness data, and infrastructure needed for routine use in most TB-endemic settings. A pooled meta-analysis of metagenomic next-generation sequencing across clinical specimen types reported sensitivity of only 69% (with even lower sensitivity of 58% in CSF specifically) despite near-perfect specificity, underscoring that these tools currently supplement rather than replace conventional testing.⁴⁴

IGRAs occupy a similar adjunctive role: a meta-analysis of IGRAs for EPTB found pooled sensitivities of 72% (QuantiferON) and 90% (T-SPOT.TB) but specificities as low as 68-82%, with sensitivity substantially lower in low- and middle-income, high-burden settings than in high-income countries - reflecting the inability of IGRAs to distinguish active disease from prior latent infection, which limits their diagnostic utility precisely where EPTB is most prevalent.⁴⁵ These emerging and adjunctive technologies should be regarded as tools to strengthen the integrated pathway described above, not as a substitute for it, pending further validation.

MANAGEMENT PRINCIPLES, INCLUDING DRUG-RESISTANT EPTB

Most drug-susceptible EPTB is treated with the standard six-month regimen (two-months of isoniazid [INH], rifampicin [RMP], pyrazinamide [PZA], and ethambutol [EMB], followed by four-months of INH and RMP) with some forms - notably CNS, osteoarticular, and disseminated disease - conventionally treated for longer (9-12 months) because of slower clinical and radiological

resolution, although the optimal duration for these forms remains debated and is the subject of ongoing trials.^{41,46,47}

Drug-resistant EPTB adds further complexity. Reported rates of drug-resistance in EPTB vary considerably by setting: a Thai cohort found INH, RMP, and multidrug-resistance in 7.8%, 0.5%, and 0.5% of EPTB isolates respectively (lower than corresponding pulmonary rates), whereas a systematic review from a high-burden Ethiopian setting reported pooled RMP-resistance of 6% and multidrug-resistance of 4%, with previous TB treatment and male sex as consistent risk factors across settings.^{48,49} Interestingly, a tertiary care center in the sub-Himalayan region of Uttarakhand observed a higher prevalence of INH-monoresistance among new TB cases (5.1%) than among previously treated, fully recovered TB cases (3.6%).⁵⁰

Because most extrapulmonary specimens are paucibacillary, phenotypic drug-susceptibility testing, which requires a positive culture, is frequently unattainable, making Xpert-class assays central to early detection of RMP-resistance as a surrogate for multidrug-resistance. The WHO's 2022 update to its drug-resistant TB treatment guidelines endorsed a six-month, all-oral bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) regimen for most patients with multidrug- or RMP-resistant TB, including many with EPTB.⁵¹ However, this and related shorter regimens explicitly exclude CNS TB, osteoarticular TB, and disseminated or miliary disease, reflecting both the exclusion of these presentations from the pivotal trials and concerns about adequate drug penetration into the CNS and bone.⁵¹ Patients with these forms of drug-resistant EPTB, as well as pregnant or breastfeeding women and young children, continue to require individualized, longer all oral regimens built from WHO-classified drug groups, guided by resistance testing and treatment history, together with adjunctive corticosteroids or surgical intervention (decompression, debridement, pericardiectomy) where structurally indicated.⁴⁷

Treatment monitoring and follow-up

Response to treatment should be assessed clinically and, where relevant, radiologically, at defined intervals rather than solely at treatment completion. Because many extrapulmonary sites resolve slowly, lymph nodes may show residual, non-progressive swelling for months after microbiological cure, and spinal or joint disease may show radiological lag well behind clinical improvement - imaging-based reassessment should be interpreted cautiously and in the context of clinical trajectory rather than used in isolation to diagnose treatment failure. Failure to improve after an adequate trial of therapy should prompt a structured reassessment: reconsideration of the underlying diagnosis (malignancy, sarcoidosis, fungal or non-tuberculous mycobacterial infection), assessment of treatment adherence and drug levels where feasible, and specific evaluation for drug-resistance, rather than simple

prolongation or empirical escalation of the same regimen. A minority of patients will develop a paradoxical reaction clinical or radiological worsening despite appropriate therapy and microbiological response which should be distinguished from true treatment failure before any regimen change is made.^{3,11,52-56}

RESOURCE AND IMPLEMENTATION CONSIDERATIONS

This diagnostic pathway assumed access to Xpert MTB/RIF Ultra, cross-sectional imaging, and histopathology resources unevenly distributed even within high-burden countries. Peripheral facilities in sub-Saharan Africa and South Asia often lack advanced molecular diagnostics and timely histopathology, necessitating referral to tertiary care centers and introducing delay.⁵⁷ Samples referral networks, accessible adjuncts such as pleural fluid ADA, and structured empirical treatment pathways for high mortality presentations (CNS, pericardial TB) therefore remain essential complements for molecular testing rather than their replacements.⁵⁸

Cost-effectiveness varies by setting: Ultra's incremental benefit over standard Xpert MTB/RIF is greatest for specimens with the lowest baseline sensitivity (CSF, pleural fluid), favoring prioritized rather than uniform rollout where resources are constrained.^{59,60} Despite a decade of diagnostic advances, gaps persist in timely EPTB diagnosis, particularly for paucibacillary disease in resource-limited settings. Progress will likely depend on strategic integration of complementary technologies rather than any single test.⁶¹

Among emerging tools, next-generation sequencing (NGS) is notable. Targeted NGS (tNGS) can simultaneously identify *M. tuberculosis* and resistance mutations directly from specimens, shortening the delay inherent to culture-based DST.⁶² Metagenomics NGS (mNGS) extends this to unbiased pathogen detection in undifferentiated disease, useful when TB mimics malignancy, fungal infection, or autoimmune disease, though sensitivity remains suboptimal for paucibacillary CSF and pleural fluid and cost, infrastructure, bioinformatics needs and contamination risk limit its routine use.^{63,64}

Host-derived biomarkers are another promising avenue: blood transcriptomic signatures, cytokine profiles and microRNA patterns have shown encouraging performance distinguishing active from latent TB. Validation in diverse EPTB populations could position these as adjuncts when tissue sampling fails, while proteomics, metabolomics and multi-omic approaches may enable composite diagnostic algorithms with improved sensitivity.^{65,66}

These technologies nonetheless face affordability and access barriers greatest where EPTB burden is highest with high capital and consumable costs, infrastructure connectivity and bioinformatics expertise. mNGS, tNGS

and AI-assited imaging are thus unlikely to be widely accessible in high TB burden settings soon, reinforcing that the integrated pathway proposed here specimen prioritization, parallel conventional testing, multidisciplinary interpretation should remain the diagnostic backbone.¹⁶

Expanding point of care (POC) access remains a global priority: portable NAAT platforms, simplified sample processing and decentralized referral networks could meaningfully reduce delay.⁶⁷ Future research should address implementation science, cost-effectiveness and equitable access, alongside diagnostic accuracy. Until then, an integrated pathway combining clinical, imaging, histopathological, microbiological and molecular assessment should remain the cornerstone of EPTB management

CONCLUSION

EPTB remains disproportionately difficult to diagnose because of its paucibacillary biology and heterogeneous organ involvement, and no single test however, advanced, is likely to close this gap alone. Reframing EPTB diagnosis as a single integrated pathway, in which clinical suspicion, imaging, tissue-based histopathology, and parallel microbiological and molecular testing inform one another rather than being interpreted in isolation, offers a practical way to reduce diagnostic delay with the tools already available in most settings. Particular attention to children and people living with HIV, in whom both disease burden and diagnostic difficulty are amplified, should be built into this pathway rather than treated as an afterthought. Management increasingly requires similar site-specific tailoring, particularly for drug-resistant disease, where shorter regimens now benefit most patients but explicitly do not extend to CNS, osteoarticular, and disseminated forms. Closing the remaining gaps in paucibacillary specimens, in resource-limited settings, and in special populations will depend on continued validation of emerging molecular and sequencing-based technologies rather than their premature substitution for the multidisciplinary pathway described here.

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