Geisinger

Geisinger Health Plan Policies and Procedure Manual

Policy: MPA G2063 – Testing for Diagnosis of Active or Latent Tuberculosis

Section: Medical Policy

Subject: Testing for Diagnosis of Active or Latent Tuberculosis

Applicable line of business:

Commercial	**x**	**Medicaid**	**x**
Medicare	**x**	**ACA**	**x**
CHIP	**x**		

I. Policy: Testing for Diagnosis of Active or Latent Tuberculosis

II. Purpose/Objective: To provide a policy of coverage regarding Testing for Diagnosis of Active or Latent Tuberculosis

III. Responsibility:

A. Medical Directors
B. Medical Management

IV. Required Definitions

1. Attachment – a supporting document that is developed and maintained by the policy writer or department requiring/authoring the policy.
2. Exhibit – a supporting document developed and maintained in a department other than the department requiring/authoring the policy.
3. Devised – the date the policy was implemented.
4. Revised – the date of every revision to the policy, including typographical and grammatical changes.
5. Reviewed – the date documenting the annual review if the policy has no revisions necessary.

Commercial

Geisinger Health Plan may refer collectively to health care coverage sponsors Geisinger Health Plan, Geisinger Quality Options, Inc., and Geisinger Indemnity Insurance Company, unless otherwise noted. Geisinger Health Plan is part of Geisinger, an integrated health care delivery and coverage organization.

Medicare

Geisinger Gold Medicare Advantage HMO, PPO, and HMO D-SNP plans are offered by Geisinger Health Plan/Geisinger Indemnity Insurance Company, health plans with a Medicare contract. Continued enrollment in Geisinger Gold depends on contract renewal. Geisinger Health Plan/Geisinger Indemnity Insurance Company are part of Geisinger, an integrated health care delivery and coverage organization.

CHIP

Geisinger Health Plan Kids (GHP Kids) is a Children's Health Insurance Program (CHIP) offered by Geisinger Health Plan in conjunction with the Pennsylvania Department of Human Services (DHS). Geisinger Health Plan is part of Geisinger, an integrated health care delivery and coverage organization.

Medicaid

Geisinger Health Plan Family (GHP Family) is a Medical Assistance (Medicaid) insurance program offered by Geisinger Health Plan in conjunction with the Pennsylvania Department of Human Services (DHS). Geisinger Health Plan is part of Geisinger, an integrated health care delivery and coverage organization.

V. Additional Definitions
Medical Necessity or Medically Necessary means Covered Services rendered by a Health Care Provider that the Plan determines are:

a. appropriate for the symptoms and diagnosis or treatment of the Member's condition, illness, disease or injury;
b. provided for the diagnosis, and the direct care and treatment of the Member's condition, illness disease or injury;
c. in accordance with current standards of good medical treatment practiced by the general medical community.
d. not primarily for the convenience of the Member, or the Member's Health Care Provider; and

the most appropriate source or level of service that can safely be provided to the Member. When applied to hospitalization, this further means that the Member requires acute care as an inpatient due to the nature of the services rendered or the Member's condition, and the Member cannot receive safe or adequate care as an outpatient

Medicaid Business Segment
Medically Necessary — A service, item, procedure, or level of care that is necessary for the proper treatment or management of an illness, injury, or disability is one that:

- Will, or is reasonably expected to, prevent the onset of an illness, condition, injury or disability.
- Will, or is reasonably expected to, reduce or ameliorate the physical, mental or developmental effects of an illness, condition, injury or disability.
- Will assist the Member to achieve or maintain maximum functional capacity in performing daily activities, taking into account both the functional capacity of the Member and those functional capacities that are appropriate for Members of the same age.

Policy Description

Infection by *Mycobacterium tuberculosis* (Mtb) results in a wide range of clinical presentations dependent upon the site of infection from classic signs and symptoms of pulmonary disease (cough greater than two to three weeks' duration, lymphadenopathy, fevers, night sweats, weight loss) to silent infection with a complete absence of signs or symptoms (Lewinsohn et al., 2017).

Culture of Mtb is the gold standard for diagnosis as it is the most sensitive and provides an isolate for drug susceptibility testing and species identification (Bernardo, 2024). Nucleic acid amplification tests (NAAT) use polymerase chain reactions (PCR) to enable sensitive detection and identification of low-density infections (Pai et al., 2004). Interferon-gamma release assays (IGRAs) are blood tests of cell-mediated immune response which measure T cell release of interferon (IFN)-gamma following stimulation by specific antigens such as *Mycobacterium tuberculosis* antigens (Lewinsohn et al., 2017; Menzies, 2024) used to detect a cellular immune response to *M. tuberculosis* which would indicate latent tuberculosis infection (LTBI) (Pai et al., 2014).

Related Policies

Policy Number	Policy Title
N/A	Not applicable

Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the "Applicable State and Federal Regulations" section of this policy document.

1) To diagnose or screen for latent tuberculosis (TB) infection, an interferon gamma release assay (IGRA) **MEETS COVERAGE CRITERIA** in:
   a) Individuals who are at risk for infection with *Mycobacterium tuberculosis* (Mtb).

b) Individuals who are unlikely to be infected with Mtb when screening is obliged by law.

2) For all suspected TB infections, the following tests **MEET COVERAGE CRITERIA**:
   a) Acid fast bacilli (AFB) smear/stain.
   b) Culture and culture-based drug susceptibility testing of *Mycobacteria* spp.

3) Direct probe or amplified probe nucleic acid-based testing, including PCR, **MEETS COVERAGE CRITERIA** for **any** of the following:
   a) *Mycobacteria* spp.
   b) *M. tuberculosis.*
   c) *M. avium intracellulare.*

4) For individuals whose sputum is AFB smear positive or Hologic Amplified MTD positive, molecular-based drug susceptibility testing **MEETS COVERAGE CRITERIA** when **one** of the following criteria is met:
   a) The individual has been treated for TB in the past.
   b) The individual was born in or has lived for at least 1 year in a foreign country with at least a moderate TB incidence (≥20 per 100, 000) or a high primary multi-drug resistant (MDR)-TB prevalence (≥2%).
   c) The individual is a contact of an individual with MDR-TB.
   d) The individual is HIV infected.

5) Repeat drug susceptibility testing **MEETS COVERAGE CRITERIA** in **any** of the following situations:
   a) For individuals whose sputum cultures remain positive after 3 months of treatment.
   b) When there is bacteriological reversion from negative to positive.

6) For individuals with pleural effusion, pericardial effusion, or ascites and suspected TB infection, cell counts, protein, glucose, and lactate dehydrogenase (LDH) concentrations of cerebrospinal, pleural, peritoneal, pericardial, and other fluids **MEETS COVERAGE CRITERIA**.

7) In HIV-infected individuals with CD4 cell counts ≤100 cells/microL who have signs and symptoms of tuberculosis, urine-based detection of mycobacterial cell wall glycolipid lipoarabinomannan (LAM) **MEETS COVERAGE CRITERIA**.

8) For individuals with active tuberculosis, IGRA **DOES NOT MEET COVERAGE CRITERIA**.

9) Simultaneous ordering of any combination of direct probe, amplified probe, and/or quantification for the same organism in a single encounter **DOES NOT MEET COVERAGE CRITERIA**.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual's illness.

10) Quantitative nucleic acid testing for *Mycobacterium* spp, *M. tuberculosis*, and *M. avium intracellulare* **DOES NOT MEET COVERAGE CRITERIA**.

11) Whole genome sequencing of *Mycobacterium* spp. for the detection of drug resistance **DOES NOT MEET COVERAGE CRITERIA**.

12) Genotyping of *Mycobacterium* spp. **DOES NOT MEET COVERAGE CRITERIA**.

13) Testing of adenosine deaminase (ADA) and interferon-gamma (IFN- γ) levels in cerebrospinal, pleural, peritoneal, pericardial, and other fluids for the diagnosis of extrapulmonary TB **DOES NOT MEET COVERAGE CRITERIA**.

14) Testing of serum protein biomarkers or panels of biomarkers for the detection and diagnosis of TB **DOES NOT MEET COVERAGE CRITERIA**.

Table of Terminology

Term	Definition
ADA	Adenosine deaminase
AFB	Acid fast bacilli
ASM	American Society of Microbiology
ATS	American Thoracic Society
BCG	Bacillus Calmette-Guérin
CCs	Critical concentrations
CD4	Cluster of differentiation 4
CDC	Centers for Disease Control and Prevention
CLIA '88	Clinical Laboratory Improvement Amendments of 1988
CMS	Centers for Medicare and Medicaid Services
CSF	Cerebrospinal fluid
DOR	Diagnostic odds ratio
DR-TB	Drug resistant tuberculosis
DST	Drug susceptibility testing
DSTs	Drug susceptibility tests
ECDC	European Centre for Disease Prevention and Control
ELISA	Enzyme-linked immunosorbent assay
ELISPOT	Enzyme-linked immunospot
ERS	European Respiratory Society
FDA	Food and Drug Administration
HIV	Human immunodeficiency virus
IDSA	Infectious Diseases Society of America
IFN	Interferon
IFN- γ	Interferon gamma
IGRA	Interferon gamma release assay
LAM	Lipoarabinomannan
LD/LDH	Lactate dehydrogenase
LDTs	Laboratory-developed tests
LF-LAM	Lipoarabinomannan assay
LPAs	Line probe assays
LTBI	Latent tuberculosis infection
MDR	Multi-drug resistant
MIC	Minimum inhibitory concentration
MMR	Measles-mumps-rubella
Mtb	*Mycobacterium tuberculosis*

MTBC	*Mycobacterium tuberculosis* complex
MTD	*Mycobacterium tuberculosis* direct
NAA	Nucleic acid amplification
NAAT	Nucleic acid amplification tests/techniques
NICE	National Institute for Health and Care Excellence
NIH	National Institute of Health
NLR	Negative likelihood ratio
NPF	National Psoriasis Foundation
NPV	Negative predictive value
NSTC	National Society of Tuberculosis Clinicians
NTCA	National Tuberculosis Controllers Association
NTM	Non-Tuberculosis Mycobacterium Species
OR	Odds ratio
PCR	Polymerase chain reactions
pDST	Phenotypic drug susceptibility testing
PLR	Positive likelihood ratio
PPV	Positive predictive value
QFT-G/QFT-GT	Quantiferon- Tuberculosis Gold
QFT-GIT	Quantiferon- Tuberculosis Gold In-Tube
RBS	Rapid biosensor
RIF	Rifampicin
RR-TB	Rifampicin-resistant tuberculosis
SL-LPA	Second-line line probe assays
TB	Tuberculosis
TBNET	Tuberculosis Network European Trials Group
TNF	Tumor necrosis factor
TNF- α	tumor necrosis factor–α
TNFi	Tumor necrosis alpha inhibitor
TST	Tuberculin skin tests
WGS	Whole-genome sequencing
WHO	World Health Organization

Scientific Background

Tuberculosis (TB) continues to be a major public health threat globally, causing an estimated 10.0 million new cases and 1.2 million deaths from TB among HIV-negative individuals and 208,000 deaths among HI-positive people in 2019 (WHO, 2020), with the emergence of multidrug resistant strains only adding to the threat (Dheda et al., 2014). The lungs are the primary site of infection by Mtb and subsequent TB disease. Onset of symptoms is usually gradual with a persistent cough being most frequently reported (95%) followed by the typical symptoms of fever (75%), night sweats (45%) and weight loss (55%) (Heemskerk et al., 2015). Clinical manifestations include primary TB, reactivation TB, laryngeal TB, endobronchial TB, lower lung field TB infection, and tuberculoma (Bernardo, 2024). Extrapulmonary infection represents approximately 20% of cases of active TB with an additional 7% having concurrent pulmonary and extrapulmonary infections (Peto et al., 2009).

In most individuals, initial *Mycobacterium tuberculosis* infection is eliminated, or contained by host defenses, while infection remains latent (Barry et al., 2009; Dheda et al., 2010). Persons with latent TB infection (LTBI)

are considered to be asymptomatic and not infectious; however, latent Mtb bacilli may remain viable and reactivate to cause active, contagious infection. Identification and treatment of LTBI are important TB control strategies, especially in settings with a low TB incidence, where reactivation of LTBI often accounts for the majority of nonimported TB disease (ATS, 2000; Landry & Menzies, 2008; Pai et al., 2014).

Latent TB Testing (LTBI)

The goal of testing for LTBI is to identify individuals who are at increased risk for the development of tuberculosis (TB) and therefore who would benefit from treatment of latent TB infection. Only those who would benefit from treatment should be tested so a decision to test presupposes a decision to treat if the test is positive (Menzies, 2024).

Proprietary Testing

The Bactec MGIT 960 System was approved by the FDA in 1998 for the detection of mycobacteria growth from clinical specimens (except blood). In 1994 the FDA approved the Ge-Probe Amplified Mycobacterium Tuberculosis Direct Test as a Nucleic acid-based in vitro diagnostic devices for the detection of *Mycobacterium tuberculosis* complex in respiratory specimens. These devices are non-multiplexed and intended to be used as an aid in the diagnosis of pulmonary tuberculosis when used in conjunction with clinical and other laboratory findings (Lewinsohn et al., 2017).

In 2015 the FDA approved the Xpert® MTB/RIF Assay, performed on the GeneXpert® Instrument Systems, as a qualitative, nested real-time polymerase chain reaction (PCR) in vitro diagnostic test for the detection of *Mycobacterium tuberculosis* complex DNA in raw sputum or concentrated sputum sediment prepared from induced or expectorated sputum. In specimens where *Mycobacterium tuberculosis* complex (MTB-complex) is detected, the Xpert MTB/RIF Assay also detects the rifampin-resistance associated mutations of the *rpoB* gene (Lewinsohn et al., 2017).

The QuantiFERON-TB® assay (CSL Biosciences, Australia) for detection of gamma interferon production is a blood test that has been used in humans in Australia. In November 2001, this test received approval from the U.S. Food and Drug Administration (FDA) in the United States for the following indication: "The QuantiFERON-TB test is intended as an aid in the detection of latent Mycobacterium tuberculosis infection" (FDA, 2001).

In December of 2004, QuantiFERON-TB® GOLD received FDA approval for the detection of latent TB. This test differs from the first-generation test in that instead of using PPD as the stimulus for interferon production, two antigens, ESAT-6 and CFP-10, are used. These antigens are present in mycobacterium tuberculosis but are not present in those exposed to BCG or non-tuberculous mycobacteria (Lewinsohn et al., 2017).

The QFT-GIT measures IFN-γ plasma concentration using an enzyme-linked immunosorbent assay (ELISA), has been approved by the US Food and Drug Administration (FDA) and has replaced the QuantiFERON-TB Gold (QFT-G) test (Lewinsohn et al., 2017).

The T-SPOT assay enumerates T cells releasing IFN-γ using an enzyme-linked immunospot (ELISPOT) assay. The T-SPOT.TB assay is currently available in Europe, Canada, and has been approved for use in the United States with revised criteria for test interpretation (Lewinsohn et al., 2017)

Analytical Validity

Mycobacterial infection results in a predominantly cell-mediated immune response (Daniel, 1980). Skin testing (TST) has long been a convenient, cost-effective method for assessing cell-mediated immune responses to a variety of antigens and has been the “gold standard” for diagnostic screening for *Mycobacterium tuberculosis* infections. However, multiple factors challenge the accuracy of the skin test, including skill requirements for and variability in placement and reading, cross-reactivity, and underlying illness or

immunosuppression (Daniel, 1980). The sensitivity of the TST is approximately 71%–82% (Francis et al., 1978; Katial et al., 2001; Lewinsohn et al., 2017).

The cell-mediated immune response to *M. tuberculosis* involves production of gamma interferon (IFN-γ) (Fenton et al., 1997). Interferon-gamma release assays (IGRAs), which are in-vitro culture assays measuring IFN-γ production in response to tuberculin antigen stimulation, have been developed as diagnostic screening tests (Katial et al., 2001; Lein & Von Reyn, 1997) IGRAs have specificity >95% for diagnosis of latent TB infection and a sensitivity of 80-90% (Menzies et al., 2007; Pai et al., 2014). The two commercially available IGRAs are the QuantiFERON-TB Gold In-Tube (QFT-GIT) assay and T-SPOT.TB assay. Both assays are FDA-approved and available worldwide. These tests are not used to diagnose an active infection (as active infections are microbiologic diagnoses), but they still provide use as a confirmatory test for the TST (Menzies, 2024).

Clinical Utility and Validity

LTBI Testing

Diel et al. (2012) performed a meta-analysis investigating the "positive and the negative predictive value (PPV and NPV, respectively) from a test-determined LTBI state for progression to active TB of interferon-γ release assays (IGRAs) and the tuberculin skin test (TST)." The authors found that the "pooled PPV for progression for all studies using commercial IGRAs was 2.7% compared with 1.5% for the TST." PPV was found to increase to 6.8% and 2.4% respectively when only high-risk groups were included. The authors concluded that "Commercial IGRAs have a higher PPV and NPV for progression to active TB compared with those of the TST"(Diel et al., 2012).

Ruan et al. (2016) further assessed the "diagnostic value of interferon-γ release assays (IGRAs) for latent tuberculosis infection (LTBI) in patients with rheumatic disease before receiving biologic agents." 11 studies (n = 1940) were included. The authors found that "compared with the tuberculin skin test (TST), the pooled agreements in QFT-G/GIT and T-SPOT.TB were 72% and 75%, respectively. BCG vaccination was positively correlated with positive rates of TST (pooled odds ratio [OR] 1.64). Compared with TST, IGRAs were better associated with the presentence of one or more tuberculosis (TB) risk factors." The authors concluded that "in rheumatic patients with previous BCG vaccination or currently on steroid therapy, IGRAs would be the better choice to identify LTBI by decreasing the false-positivity and false-negativity rate compared with conventional TST" (Ruan et al., 2016).

Auguste et al. (2017) compared IGRA and TST for identifying latent tuberculosis infection that progresses to active tuberculosis. A total of 17 studies were included. However, no significant differences were observed, and the authors concluded that "prospective studies comparing IGRA testing against TST on the progression from LTBI to TB were sparse, and these results should be interpreted with caution due to uncertainty, risk of bias, and unexplained heterogeneity. Population-based studies with adequate sample size and follow-up are required to adequately compare the performance of IGRA with TST in people at high risk of TB" (Auguste et al., 2017).

Nasiri et al. (2019) performed a meta-analysis focusing on the diagnostic accuracy of IGRA and TST for LTBI in transplant patients. A total of 16 articles were included, and the results are as follows: "pooled sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), negative likelihood ratio (NLR) and diagnostic odds ratio (DOR) for TST were 46%, 86%, 46.3%, 88.7%, 3.3, 0.63, and 5 respectively. For QFT-G (an IGRA), the pooled sensitivity, specificity, PPV, NPV, PLR, NLR, and DOR were 58%, 89%, 72.7%, 80.6%, 5.3, 0.47, and 11, respectively. Likewise, for T-SPOT.TB (another IGRA), the pooled sensitivity, specificity, PPV, NPV, PLR, NLR, and DOR were 55%, 92%, 60.4%, 90.2%, 6.7, 0.52, and 16, respectively." The authors concluded that "IGRAs were more sensitive and specific than the TST with regard to the diagnosis of LTBI in the transplant candidates. They have added value and can be complementary to TST" (Nasiri et al., 2019).

Khanna et al. (2021) performed a retrospective review of QuantiFERON TB test (QFT) results to evaluate the utility of serial LTBI screening in patients taking biologics and to identify risk factors in patients. They found that "Repeat LTBI testing in patients taking biologics revealed a low rate of conversion (1.17%)," and concluded that their "results suggest clinical utility and cost-effectiveness of repeat LTBI screening in patients on biologics may be more valuable if not performed routinely, but driven by a focused review of TB exposure risk factors in each patient" (Khanna et al., 2021).

In a prospective observational study conducted in a tertiary care center in India, Neema et al. (2021) found that "Treatment of LTBI prevents up to 60–70% patients from developing active tuberculosis; however, a patient may develop active tuberculosis despite prophylaxis especially with TNF inhibitors and patient should be followed up regularly." As such, "A thorough search for active tuberculosis should be performed. Timely detection of LTBI helps in the prevention of development of active tuberculosis in the patients on immunosuppressive treatment." However, it should be noted that the target study population for this study is the Indian population, which the authors acknowledged has a high prevalence of tuberculosis and latent tuberculosis infection already, and so it is unclear if the value may not be extrapolated to other populations.

Ren et al. (2024) studied the sensitivity of interferon-γ release assays (IGRAs) in identifying MTB-infected individuals. The study included 302 individuals, assigned into the following groups: healthy control, LTBI, IGRA-positive TB, and IGRA-negative TB. The Luminex xMAP assay was used to measure MTB antigen-specific blook plasma chemokine concentrations. "Levels of CXCL9, CXCL10, IL-2, and CCL8 biomarkers were predictive for active TB." The CXCL9-based enzyme-linked immunosorbent assay sensitivity rate was 95.9% and the specificity rate as 100%. CXCL9 and CXCL9-CXCL10 assays had statistically similar area under the curve values, "thus demonstrating that combined analysis of CXCL10 and CXCL9 levels did not improve active TB diagnostic performance." The authors concluded that "The MTB antigen stimulation-based CXCL9 assay may compensate for low IGRA diagnostic accuracy when used to diagnose IGRA-negative active TB cases and thus is an accurate and sensitive alternative to IGRAs for detecting MTB infection" (Ren et al., 2024).

Active TB Testing

The diagnosis of TB disease should be suspected in patients with relevant clinical manifestations and exposure history (Lewinsohn et al., 2017). Laboratory testing is an integral part of the rapid and accurate diagnosis of TB to facilitate timely initiation of treatment.

Microbiologic testing is used to evaluate an active TB infection. These tests may include the acid-fast bacilli smear (AFB), the mycobacterial culture, and molecular testing. Smears are the fastest and cheapest diagnostic tool, cultures are the most sensitive, and molecular testing is used for assessing drug resistance (Bernardo, 2024).

The detection of acid-fast bacilli (AFB) on microscopic examination of stained sputum smears is the most rapid and inexpensive technique (Bernardo, 2024); however, it is limited by its lack of sensitivity in certain situations, such as extrapulmonary infection or coinfection with HIV (Pai et al., 2016). The mycobacteria retain the stain in a mineral-acid or acid-alcohol solution, and microscopy identifies these strains. LED microscopy has seen more use recently than the traditional light microscopy (Bernardo, 2024).

Rapid and accurate diagnosis is critical for timely initiation of TB treatment (Pai et al., 2016). Although sensitive, culture can take over two weeks to return results (Lewinsohn et al., 2017). Three specimens should be examined to assure a sensitivity of approximately 70%. The first specimen has a sensitivity of approximately 53.8%, increasing by 11.1% with a second specimen, and another 2-5% with a third (Mase et al., 2007). A first morning specimen increases sensitivity by 12%, and concentrating specimens can increase sensitivity by 18% (Steingart, Ng, et al., 2006). Use of fluorescence microscopy also increases sensitivity 10% over conventional microscopy (Lewinsohn et al., 2017; Steingart, Henry, et al., 2006). The positive predictive value has been reported to be 97.9-100% (Gordin & Slutkin, 1990), but it is impacted by non-tuberculosis *Mycobacterium* species (NTM) (Yajko et al., 1994).

Nucleic acid amplification techniques (NAAT) have been developed for rapid diagnosis of TB. Two major tests are available, the Amplified Mycobacterium tuberculosis Direct (MTD) test and the Xpert MTB/RIF test. NAAT-based assays are more sensitive than smear, but less sensitive than culture, with a reported sensitivity of 96% and specificity of 99% (Greco et al., 2006; Lewinsohn et al., 2017). NAAT testing has >95% positive predictive value in the setting of AFB smear-positive specimens for distinguishing tuberculous from nontuberculous mycobacteria, and it can establish the presence of tuberculosis in 50 to 80% of AFB smear-negative specimens (Cheng et al., 2005). NAAT does not replace the roles of AFB smear and culture (Ling et al., 2008) in the diagnostic algorithm for tuberculosis and results must be interpreted in conjunction with AFB smear results while mycobacterial culture is pending (CDC, 2009; Lewinsohn et al., 2017).

Sequence-based assays provide the genetic identity of a particular mutation and, therefore, can predict drug resistance with greater accuracy than probe-based assays. The testing identifies genetic mutations associated with rifampin and isoniazid resistance as well as resistance to second-line drugs including fluoroquinolones and the injectables amikacin, kanamycin, and capreomycin. Molecular testing results are generally available within days and can be used to guide initial treatment decisions and inform design of prevention regimens for contacts (Bernardo, 2024; Taylor et al., 2005).

More proprietary tests exist for the assessment of TB. Rapid Biosensor (RBS) offers a breath test "TB Breathalyzer" for TB. The test proposes that it can detect actively infectious bacilli instead of relying on sputum (which some patients do not produce). The test estimates its limit of detection at 25-75 bacilli and notes that it can be used easily in rural communities. When a patient coughs in the collection tube, any TB bacilli will react with the biochemical formulation at the bottom of the tube, which is then detected by the diode laser in the reader unit (RBS, 2015).

The reference standard for diagnosis of any TB infection is isolation of *M. tuberculosis* (Pai et al., 2016). The isolate recovered should be identified according to the Clinical and Laboratory Standards Institute guidelines (Institute, 2018) and the American Society for Microbiology Manual of Clinical Microbiology (Lewinsohn et al., 2017; Woods et al., 2015), and all United States jurisdictions require submission of culture isolates identified as *M. tuberculosis* for confirmation of identification and drug susceptibility testing (Taylor et al., 2005). Positive cultures are also reported to public health authorities for oversight and case management (Bernardo, 2024).

Cruciani et al. (2004) performed a meta-analysis of 10 studies (1381 strains from 14745 clinical specimens) which found that both liquid and solid culture media methods are highly specific (99%). Liquid culture methods are more sensitive (81.5-85.8%) and have a shorter time to detection (13.2-15.2 day) than solid media but are more prone to contamination (4-9%). Solid media has a sensitivity of 76% and averages 25.8 days for detection. The use of both culture methods increases the overall sensitivity to 87.7-89.7%.

Bourgi et al. (2017) "aimed to evaluate the reliability and projected impact of nucleic acid amplification (NAA) testing in patients with acid-fast bacilli (AFB) smear-positive respiratory samples." The authors identified a retrospective cohort of AFB smear-positive patients and evaluated the projected change in "duration of airborne isolation and unnecessary Mycobacterium tuberculosis (MTB) treatment with introducing NAA testing into clinical decision making for AFB smear-positive patients." A total of 130 patients were found to be AFB positive, of which 80 tested positive on NAA. 82 patients grew MTB on culture. NAA testing was found to have a sensitivity of 97.6% and specificity of 100%. Integrating NAA testing into clinical decision making led to shortened time in airborne isolation (6.0 ± 7.6 vs 23.1 ± 38.0) and 9.5 ± 11.32 fewer days of "unnecessary MTB treatment in patients with negative NAA test." The authors concluded, "Nucleic acid amplification testing provided a rapid and accurate test in the diagnosis of MTB while significantly reducing the duration of isolation and unnecessary medications in patients with negative NAA test" (Bourgi et al., 2017).

Urine testing for mycobacterial cell wall glycolipid (Shah et al., 2010) has been investigated as a point of care assay for diagnosis of TB in HIV infected patients (Nakiyingi et al., 2014). The test was 97.6% specific and 67.9% sensitive in patients with CD4<100. It is useful in addition to routine diagnostic tests for HIV-infected patients with signs and symptoms of TB and CD4 ≤100 cells/microL and for all HIV-infected patients who are

seriously ill (Shah et al., 2016; WHO, 2015a). Gupta-Wright et al. (2018) evaluated the sputum Xpert MTB/RIF with or without urine lipoarabinomannan (LAM) testing. There was no difference in overall mortality over 2574 patients, but they found that urine Lam testing might benefit some high-risk subgroups (CD4 <100, severe anaemia, and patients with clinically suspected tuberculosis) (Gupta-Wright et al., 2018).

Adenosine deaminase (ADA) and interferon-gamma (IFN- γ) levels in cerebrospinal, pleural, peritoneal, and pericardial fluids have been studied in the diagnosis of extrapulmonary TB. In 2017, a joint review by the ATS, IDSA, and CDC found the sensitivity of ADA in these fluids to be 79% and the specificity to be 83% for TB. The sensitivity of IFN- γ in these fluids was 89% and the specificity was 97%. However, the authors remarked that neither the ADA level nor the IFN-γ level provide a definitive diagnosis of TB disease (Lewinsohn et al., 2017).

De Groote et al. (2017) developed a panel based on proteomic analysis. A total of 1470 serum samples were collected from patients "with symptoms and signs suggestive of active pulmonary TB that were systematically confirmed or ruled out for TB by culture and clinical follow-up." Six protein biomarkers were identified: "SYWC, kallistatin, complement C9, gelsolin, testican-2, and aldolase C," which performed well in a training set (area under curve = 0.92) to distinguish between TB and non-TB. It was also found to have 90% sensitivity and 80 % specificity. The authors concluded that their panel "warrants diagnostic development on a patient-near platform" (De Groote et al., 2017).

Heyckendorf et al. (2018) compared the utility of genotypic and phenotypic assays for evaluation of tuberculosis (TB) drug resistance. The authors used the results from the assays to develop treatment regimens for the 25 multi- and extensively drug-resistant tuberculosis patients in the study. Compared to phenotypic assay-developed regimens, whole genome sequencing (WGS) yielded a regimen of drugs at 93% agreement with the phenotypic assay's regimen. Further, the whole genome sequencing-derived regimen did not contain any drugs identified as resistant by the phenotypic assay. However, the authors commented that "MIC [minimum inhibitory concentration] testing revealed that pDST [phenotypic drug susceptibility testing] likely underestimated the true rate of resistance for key drugs (rifampin, levofloxacin, moxifloxacin, and kanamycin) because critical concentrations (CCs) were too high." Results derived from other genotypic assays (Xpert, line probe assays) had lower agreement with the phenotypic assay (49% and 63% respectively). The authors concluded that "WGS can be used to rule in resistance even in M/XDR strains with complex resistance patterns, but pDST for some drugs is still needed to confirm susceptibility and construct the final regimens. Some CCs for pDST need to be reexamined to avoid systematic false-susceptible results in low-level resistant isolates" (Heyckendorf et al., 2018).

Ustinova et al. (2019) investigated an assay's ability to identify and distinguish between nontuberculous mycobacteria (NTM) and *Mycobacterium tuberculosis* complex (MTBC) in culture and sputum. A total of 301 NTM cultures with mycobacteriosis were measured, and sputum samples were contributed by "104 patients with mycobacteriosis, 3627 patients with tuberculosis and 118 patients with other lung diseases." The authors results were as follows: "Specificity and sensitivity of the assay for MTBC was found to be 100% both in culture and sputum samples; for NTM, the specificity was 100% in culture and sputum, the sensitivity reached 100% in culture and 73.1% in sputum samples. Positive predictive value (PPV) and negative predictive value (NPV) of the assay for culture were both 100%, for clinical material 100% and 80.8%, respectively" (Ustinova et al., 2019).

Adams et al. (2019) compared the performances of the tuberculin skin test (TST) and two interferon-gamma-release assays (IGRAs). Five hundred and five health care workers (HCWs) in Cape Town, South Africa, were screened for latent tuberculosis infection (LTBI) using the three assays. The authors identified LTBI prevalence to be 81%. TST at a cut off of 10 mm had the highest sensitivity at 93% and the lowest specificity at 57%. The QFT-GIT IGRA sensitivity was 80% and specificity was 96%; the TSPOT.TB IGRA sensitivity was 74% and specificity was 96%. Positive predictive values for IGRAs was 90% and 96% for TST and the highest negative predictive value was 66%. However, a composite rule using both TST and QFT-GIT improved negative

predictive value to 90%. The authors concluded that "in an endemic setting a positive TST or IGRA was highly predictive of LTBI, while a combination of TST and IGRA had high rule-out value (Adams et al., 2019).

Zürcher et al. (2019) evaluated the "mortality in patients with tuberculosis from high-burden countries, according to concordance or discordance of results from drug susceptibility testing done locally and in a reference laboratory." A total of 634 patients were included, 272 of which were HIV-positive. The authors identified 394 strains (62%) to be "pan-susceptible," 45 (7%) to be monoresistant, 163 (27%) to be multi-drug resistant, and 30 (5%) to be "extensively" resistant. The laboratory results were concordant for 513 (81%) patients and discordant for 121 (19%) patients, resulting in a 90.8% sensitivity and 84.3% specificity. The authors identified a 7.33 odds ratio of death for patients with discordant results, which potentially led to under-treatment. The authors concluded "inaccurate drug susceptibility testing by comparison with a reference standard leads to under-treatment of drug-resistant tuberculosis and increased mortality" (Zürcher et al., 2019).

Jain et al. (2021) conducted a cross-sectional study in India to "compare the performance of GeneXpert MTB/RIF (GXpert) assay with [the] composite reference standard in diagnosing cases of tubercular pleural effusion (TPE) and to evaluate the reliability of rifampicin resistance." In diagnosing TPE, the sensitivity of the assay was 16.6% among 158 study participants, with a specificity of 100%, diagnostic accuracy of 52.5%, positive predictive value of 100%, and negative predictive value of 47.5%. Because of these findings, the researchers concluded that this GXpert assay would need to be combined with "routine pleural fluid analysis" to accurately diagnose TPE in suspected patients (Jain et al., 2021).

Karthek et al. (2021) evaluated the usage of the same GeneXpert MTB/RIF assay in the context of spinal tuberculosis. In conducting a retrospective review from 136 patients that underwent spinal biopsy for spondylodiscitis, 86 final patients met the criteria for spinal tuberculosis (61.6% demonstrated Mtb positivity in tissue samples and 38.4% were positive through pus samples). From this data, the researchers found a 65.1% sensitivity, 100% specificity, 100% PPV, and 56.5% NPV for this assay. It was also accurate in detecting drug resistance among patient specimen (Karthek et al., 2021).

Medina-Marino et al. (2024) conducted a randomized study in South Africa to assess the acceptability and feasibility of in-home TB testing of household contacts. The study included 84 households with at least one eligible symptomatic contact, for a total of 98 household contacts. The household contacts were all randomized, with 51 receiving in-home testing and 47 receiving standard-of-care. In-home testing included GeneXpert MTB/RIF molecular testing, and referrals for clinic-based treatment for positive cases. Standard-of-care testing included clinic-based sputum collection and testing. The median number of days between screening and receiving testing results was zero for the in-home testing group, and 16.5 for the standard-of-care testing group. The authors concluded that "in-home testing for TB was acceptable, feasible, and increased HHCs with a molecular test result" and that "in-home testing mitigates a major limitation of household contact investigations (dependency on clinic-based referral), revealing new strategies for enhancing early case detection" (Medina-Marino et al., 2024).

Guidelines and Recommendations

World Health Organization (WHO)

The WHO published recommendations for the diagnosis of TB, stating that:

- "Mycobacteria can be visually distinguished from other microorganisms by their thick lipid containing cell walls, which retain biochemical stains despite decolourization by acid-containing reagents (known as 'acid fastness'). Given that the examination of two sputum specimens is adequate to identify the majority (95-98%) of smear-positive TB patients, WHO's current policy on case-finding using microscopy recommends that in settings with appropriate external quality assessment and documented good-quality microscopy two specimens should be examined" (WHO, 2015b).

- "Direct Ziehl–Neelsen staining of sputum specimens and examination using light microscopy is suitable for use at all levels of laboratory, including peripheral laboratories at primary health-care centres or district hospitals. There is insufficient evidence that processed sputum specimens (for example, those that are concentrated or chemically treated) give better results than direct smear microscopy. Therefore, the use of such methods is not recommended" (WHO, 2015b).
- "Evidence shows that the diagnostic accuracy of LED microscopy is comparable to that of conventional fluorescence microscopy and it surpasses that of conventional Ziehl–Neelsen microscopy (by an average of 10%). Therefore, WHO recommends replacing conventional fluorescence microscopy with LED microscopy, and that LED microscopy should be phased in as an alternative to conventional Ziehl–Neelsen light microscopy in all settings, prioritizing high-volume laboratories" (WHO, 2015b).
- "Mycobacteria can be cultured in specific solid or liquid media. Bacterial growth can be identified visually (that is, by identifying specific characteristics) or by automated detection of its metabolism. All positive mycobacterial cultures must be tested to confirm the identification of *M. tuberculosis* complex (MTBC)" (WHO, 2015b).
- "Differentiation of the members of the MTBC is necessary for the treatment of individual patients and for epidemiological purposes, especially in areas of the world where tuberculosis has reached epidemic proportions or wherever the transmission of M. bovis between animals or animal products and humans is a problem. In addition, it can be important to rapidly identify isolates of M. bovis bacillus Calmette-Guérin (BCG) recovered from immunocompromised patients. Differentiation of species with the MTBC can be achieved using either phenotypic26 and/ or genotypic methods" (WHO, 2015b).
- "The use of rapid immunochromatographic assays (or strip tests for speciation) to identify cultured isolates is recommended because they provide definitive identification of all members of the MTBC (including M. bovis) in 15 minutes" (WHO, 2015b).
- "WHO recommends that either TST or IGRA can be used to test for LTBI in high-income and upper middle-income countries with estimated TB incidence less than 100 per 100000 population" (WHO, 2015a).
- "It is strongly recommended that commercial serodiagnostic tests not be used for the diagnosis of pulmonary and extra-pulmonary TB. Currently available commercial serodiagnostic tests (also referred to as serological tests) provide inconsistent and imprecise findings. There is no evidence that existing commercial serological assays improve patient outcomes, and high proportions of false positive and false-negative results may have an adverse impact on the health of patients" (WHO, 2015b).
- "There is no consistent evidence that IGRAs are more sensitive than TST for diagnosis of active TB disease. Studies evaluating the incremental value of IGRAs to conventional microbiological tests show no meaningful contribution of IGRAs to the diagnosis of active TB. IGRAs are considered inadequate as rule-out or rule-in tests for active TB, especially in the context of HIV infection. IGRAs should not be used for the diagnosis of active TB disease" (WHO, 2015b).

The following recommendations involve LTBI (WHO, 2018).

- "Either a tuberculin skin test (TST) or interferon-gamma release assay (IGRA) can be used to test for LTBI."
- "LTBI testing by TST or IGRA is not a requirement for initiating preventive treatment in people living with HIV or child household contacts aged < 5 years. (Strong recommendation, moderate-quality evidence. Updated recommendation)"
- "Adults and adolescents living with HIV should be screened for TB according to a clinical algorithm. Those who do not report any of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have active TB and should be offered preventive treatment, regardless of their ART status."
- "People living with HIV who have a positive test for LTBI benefit more from preventive treatment than those who have a negative LTBI test; LTBI testing can be used, where feasible, to identify such individuals."

- "Patients initiating anti-TNF treatment, patients receiving dialysis, patients preparing for an organ or haematological transplant and patients with silicosis should be systematically tested and treated for LTBI. (Strong recommendation, low–very low-quality evidence. Updated recommendation)"
- "In countries with a low TB incidence, systematic testing for and treatment of LTBI may be considered for prisoners, health workers, immigrants from countries with a high TB burden, homeless people and people who use illicit drugs. (Conditional recommendation, low–very low-quality evidence. Existing recommendation)"
- "Systematic testing for LTBI is not recommended for people with diabetes, people with harmful alcohol use, tobacco smokers and underweight people unless they are already included in the above recommendations. (Conditional recommendation, very low-quality evidence. Existing recommendation)"
- "There is no gold standard method for diagnosing LTBI. TST and IGRA require a competent immune response in order to identify people infected with TB and are imperfect tests for measuring progression to active disease" (WHO, 2018).

The WHO also published an additional guideline in 2020, which discusses preventive treatment. Some relevant recommendations and comments are listed below:

- "Either a tuberculin skin test (TST) or interferon-gamma release assay (IGRA) can be used to test for LTBI."
- "There is no strong evidence that one test should be preferred over the other in terms of predicting progression from TB infection to TB disease. Neither TSTs nor IGRAs should be used in persons having a low risk of TB infection and disease."
- A testing algorithm was also published in the guideline, which discusses latent TB testing and subsequent treatment in individuals at risk. The guideline writes that both asymptomatic household contacts (of patients with TB), as well as members of non-HIV risk groups (such as patients with "silicosis, dialysis, anti-TNF agent treatment, preparation for transplantation or other risks in national guidelines" should be tested with TST or IGRA.
- "There is no gold standard method for diagnosing LTBI. TST and IGRA require a competent immune response in order to identify people infected with TB and are imperfect tests for measuring progression to active disease."

Finally, the WHO published an extensive guideline on the diagnosis of tuberculosis. Some relevant recommendations and comments are listed below:

- "Recommendations on Xpert MTB/RIF [Mycobacterium tuberculosis/rifampicin] and Xpert Ultra as initial tests in adults and children with signs and symptoms of pulmonary TB:

    1. In adults with signs and symptoms of pulmonary TB, Xpert MTB/RIF should be used as an initial diagnostic test for TB and rifampicin-resistance detection in sputum rather than smear microscopy/culture and phenotypic DST [drug susceptibility testing].
    (Strong recommendation, high certainty of evidence for test accuracy; moderate certainty of evidence for patient-important outcomes)
    2. In children with signs and symptoms of pulmonary TB, Xpert MTB/RIF should be used as an initial diagnostic test for TB and rifampicin-resistance detection in sputum, gastric aspirate, nasopharyngeal aspirate and stool rather than smear microscopy/culture and phenotypic DST.
    (Strong recommendation, moderate certainty for accuracy in sputum; low certainty of evidence for test accuracy in gastric aspirate, nasopharyngeal aspirate and stool)
    3. In adults with signs and symptoms of pulmonary TB and without a prior history of TB (≤5 years) or with a remote history of TB treatment (>5 years since end of treatment), Xpert Ultra should be used as an initial diagnostic test for TB and for rifampicin-resistance detection in sputum, rather than smear microscopy/culture and phenotypic DST.
    (Strong recommendation, high certainty of evidence for test accuracy)

4. In adults with signs and symptoms of pulmonary TB and with a prior history of TB and an end of treatment within the last 5 years, Xpert Ultra may be used as an initial diagnostic test for TB and for rifampicin-resistance detection in sputum, rather than smear microscopy/culture and phenotypic DST. *(Conditional recommendation, low certainty of evidence for test accuracy)*
5. In children with signs and symptoms of pulmonary TB, Xpert Ultra should be used as the initial diagnostic test for TB and detection of rifampicin resistance in sputum or nasopharyngeal aspirate, rather than smear microscopy/culture and phenotypic DST.
   (Strong recommendation, low certainty of evidence for test accuracy in sputum; very low certainty of evidence for test accuracy in nasopharyngeal aspirate)"

- "Recommendations on Xpert MTB/RIF and Xpert Ultra as initial tests in adults and children with signs and symptoms of extrapulmonary TB:

6. In adults and children with signs and symptoms of TB meningitis, Xpert MTB/RIF or Xpert Ultra should be used in cerebrospinal fluid (CSF) as an initial diagnostic test for TB meningitis rather than smear microscopy/culture.
   (Strong recommendation, moderate certainty of evidence for test accuracy for Xpert MTB/RIF; low certainty of evidence for test accuracy for Xpert Ultra)
7. In adults and children with signs and symptoms of extrapulmonary TB, Xpert MTB/RIF may be used in lymph node aspirate, lymph node biopsy, pleural fluid, peritoneal fluid, pericardial fluid, synovial fluid or urine specimens as the initial diagnostic test rather than smear microscopy/culture.
   (Conditional recommendation, moderate certainty of evidence for test accuracy for pleural fluid; low certainty for lymph node aspirate, peritoneal fluid, synovial fluid, urine; very low certainty for pericardial fluid, lymph nodes biopsy)
8. In adults and children with signs and symptoms of extrapulmonary TB, Xpert Ultra may be used in lymph node aspirate and lymph node biopsy as the initial diagnostic test rather than smear microscopy/culture.
   (Conditional recommendation, low certainty of evidence)
9. In adults and children with signs and symptoms of extrapulmonary TB, Xpert MTB/RIF or Xpert Ultra should be used for rifampicin-resistance detection rather than culture and phenotypic DST.
   (Strong recommendation, high certainty of evidence for test accuracy for Xpert MTB/RIF; low certainty of evidence for Xpert Ultra)
10. In HIV-positive adults and children with signs and symptoms of disseminated TB, Xpert MTB/RIF may be used in blood, as an initial diagnostic test for disseminated TB.
    (Conditional recommendation, very low certainty of evidence for test accuracy)"

It should be noted that recommendation 10 (above) "applies only to a particular population (HIV-positive adults with signs and symptoms of disseminated TB). The GDG did not feel comfortable extrapolating this recommendation to other patient populations."

- "Recommendations on Xpert MTB/RIF and Xpert Ultra repeated testing in adults and children with signs and symptoms of pulmonary TB:

11. In adults with signs and symptoms of pulmonary TB who have an Xpert Ultra trace positive result on the initial test, repeated testing with Xpert Ultra may not be used. (Conditional recommendation, very low certainty of evidence for test accuracy)
12. In children with signs and symptoms of pulmonary TB in settings with pretest probability below 5% and an Xpert MTB/RIF negative result on the initial test, repeated testing with Xpert MTB/RIF in sputum, gastric fluid, nasopharyngeal aspirate or stool specimens may not be used.
    (Conditional recommendation, low certainty of evidence for test accuracy for sputum and very low for other specimen types)

13. In children with signs and symptoms of pulmonary TB in settings with pretest probability 5% or more and an Xpert MTB/RIF negative result on the initial test, repeated testing with Xpert MTB/RIF (for total of two tests) in sputum, gastric fluid, nasopharyngeal aspirate and stool specimens may be used.
    (Conditional recommendation, low certainty of evidence for test accuracy for sputum and very low for other specimen types)
14. In children with signs and symptoms of pulmonary TB in settings with pretest probability below 5% and an Xpert Ultra negative result on the initial test, repeated testing with Xpert Ultra in sputum or nasopharyngeal aspirate specimens may not be used.
    (Conditional recommendation, very low certainty of evidence for test accuracy)
15. In children with signs and symptoms of pulmonary TB in settings with pretest probability 5% or more and an Xpert Ultra negative result on the first initial test, repeated one Xpert Ultra test (for a total of two tests) in sputum and nasopharyngeal aspirate specimens may be used.
    (Conditional recommendation, very low certainty of evidence for test accuracy)"

- "Recommendations on Xpert MTB/RIF and Xpert Ultra as initial tests for pulmonary TB in adults in the general population either with signs and symptoms of TB or chest radiograph with lung abnormalities or both:

16. In adults in the general population who had either signs or symptoms of TB or chest radiograph with lung abnormalities or both, the Xpert MTB/RIF or Xpert Ultra may replace culture as the initial test for pulmonary TB.
    (Conditional recommendation, low certainty of the evidence in test accuracy for Xpert)

17. In adults in the general population who had either a positive TB symptom screen or chest radiograph with lung abnormalities or both, one Xpert Ultra test may be used rather than two Xpert Ultra tests as the initial test for pulmonary TB.
    (Conditional recommendation, very low certainty of evidence for test accuracy)"

It should be noted that recommendation 16 (above) "applies only to the use of Xpert MTB/RIF or Xpert Ultra for clinical case management in situations where an immediate decision on patient treatment needs to be made and recourse to supplementary tests is not available or would incur delays." Moreover, recommendation 17 (above) "applies only to the use of Xpert Ultra for clinical case management."

- "Recommendations on Truenat MTB, MTB Plus, and Truenat MTB-RIF Dx in adults and children with signs and symptoms of pulmonary TB:
  1. In adults and children with signs and symptoms of pulmonary TB, the Truenat MTB or MTB Plus may be used as an initial diagnostic test for TB rather than smear microscopy/culture.
     (Conditional recommendation, moderate certainty of evidence for test accuracy)
  2. In adults and children with signs and symptoms of pulmonary TB and a Truenat MTB or MTB Plus positive result, Truenat MTB-RIF Dx may be used as an initial test for rifampicin resistance rather than culture and phenotypic DST.
     (Conditional recommendation, very low certainty of evidence for test accuracy)"

Recommendation 1 is "is extrapolated to children for sputum, although the tests are expected to be less sensitive in children."

- Regarding first-line LPAs [line probe assays]:

  - "For persons with a sputum smear-positive specimen or a cultured isolate of MTBC, commercial molecular LPAs may be used as the initial test instead of phenotypic culture-based DST to detect resistance to rifampicin and isoniazid."
    (Conditional recommendation, moderate certainty in the evidence for the test's accuracy)

The WHO clarifies the above recommendation with the following remarks:

1. These recommendations apply to the use of LPAs for testing sputum smear-positive specimens (direct testing) and cultured isolates of MTBC (indirect testing) from both pulmonary and extrapulmonary sites.
2. LPAs are not recommended for the direct testing of sputum smear-negative specimens.
3. These recommendations apply to the detection of MTBC and the diagnosis of MDR-TB, but acknowledge that the accuracy of detecting resistance to rifampicin and isoniazid differs and, hence, that the accuracy of a diagnosis of MDR-TB is reduced overall.
4. These recommendations do not eliminate the need for conventional culture-based DST, which will be necessary to determine resistance to other anti-TB agents and to monitor the emergence of additional drug resistance.
5. Conventional culture-based DST for isoniazid may still be used to evaluate patients when the LPA result does not detect isoniazid resistance. This is particularly important for populations with a high pretest probability of resistance to isoniazid.
6. These recommendations apply to the use of LPA in children based on the generalization of data from adults. (WHO, 2021)

- Regarding second-line LPAs (SL-LPA):

1. "For patients with confirmed MDR/RR-TB [multi-drug resistant/rifampicin-resistant tuberculosis], SL-LPA may be used as the initial test, instead of phenotypic culture-based DST, to detect resistance to fluoroquinolones.
2. For patients with confirmed MDR/RR-TB, SL-LPA may be used as the initial test, instead of phenotypic culture-based DST, to detect resistance to the SLIDs [second-line injectable drug]."

- Regarding Lateral flow urine lipoarabinomannan assay [LF-LAM]:

"**In inpatient settings**

1. WHO strongly recommends LF-LAM to assist in the diagnosis of active TB in HIV-positive adults, adolescents and children:

   1.1 with signs and symptoms of TB (pulmonary and/or extrapulmonary) or seriously ill (**strong** recommendation, moderate certainty in the evidence about the intervention effects); or

   1.2 with advanced HIV disease or who are seriously ill (**strong** recommendation, moderate certainty in the evidence about the intervention effects); or

   1.3 irrespective of signs and symptoms of TB and with a CD4 cell count of less than 200 cells/mm^3 (**strong** recommendation, moderate certainty in the evidence about intervention effects)

In outpatient settings

2. WHO suggests using LF-LAM to assist in the diagnosis of active TB in HIV-positive adults, adolescents and children:

   2.1 with signs and symptoms of TB (pulmonary and/or extrapulmonary) or seriously ill (**conditional** recommendation, low certainty in the evidence about test accuracy);

   2.2 irrespective of signs and symptoms of TB and with a CD4 cell count of less than 100 cells/mm^3 (**conditional** recommendation, very low certainty in the evidence about test accuracy)

In outpatient settings

3. WHO recommends **against** using LF-LAM to assist in the diagnosis of active TB in HIV-positive adults, adolescents, and children:

    3.1 without assessing TB symptoms (**strong** recommendation, very low certainty in the evidence about test accuracy);
    3.2 without TB symptoms and unknown CD4 cell count or without TB symptoms and CD4 cell count greater than or equal to 200 cells/mm^3 (**strong** recommendation, very low certainty in the evidence about test accuracy); and
    3.3 without TB symptoms and with a CD4 cell count of 100-200 cells/mm^3 (**conditional** recommendation, very low certainty in the evidence about test accuracy)."

Finally, WHO did not discuss whole genome sequencing of clinical isolates in the context of assessing drug resistance susceptibility for TB (WHO, 2021).

American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention

The ATS/IDSA/CDC published clinical practice guidelines for diagnosis of TB in 2017 that stated the following:

LTBI:

- "We recommend performing an interferon-γ release assay (IGRA) rather than a tuberculin skin test (TST) in individuals 5 years or older who meet the following criteria: (1) are likely to be infected with *Mtb*, (2) have a low or intermediate risk of disease progression, (3) it has been decided that testing for LTBI is warranted, and (4) either have a history of BCG vaccination or are unlikely to return to have their TST read (*strong recommendation, moderate-quality evidence*)."
- "We suggest performing an IGRA rather than a TST in all other individuals 5 years or older who are likely to be infected with *Mtb*, who have a low or intermediate risk of disease progression, and in whom it has been decided that testing for LTBI is warranted (*conditional recommendation, moderate-quality evidence*)."
- "There are insufficient data to recommend a preference for either a TST or an IGRA as the first-line diagnostic test in individuals 5 years or older who are likely to be infected with *Mtb*, who have a high risk of progression to disease, and in whom it has been determined that diagnostic testing for LTBI is warranted."
- "Guidelines recommend that persons at low risk for *Mtb* infection and disease progression NOT be tested for *Mtb* infection. We concur with this recommendation. However, we also recognize that such testing may be obliged by law or credentialing bodies. If diagnostic testing for LTBI is performed in individuals who are unlikely to be infected with *Mtb* despite guidelines to the contrary:"
    - "We suggest performing an IGRA instead of a TST in individuals 5 years or older (*conditional recommendation, low-quality evidence*). Remarks: A TST is an acceptable alternative in settings where an IGRA is unavailable, too costly, or too burdensome."
    - "We suggest a second diagnostic test if the initial test is positive in individuals 5 years or older (*conditional recommendation, very low-quality evidence*). Remarks: The confirmatory test may be either an IGRA or a TST. When such testing is performed, the person is considered infected only if both tests are positive."
- "We suggest performing a TST rather than an IGRA in healthy children <5 years of age for whom it has been decided that diagnostic testing for LTBI is warranted (*conditional recommendation, very low-quality evidence*)."
- "While both IGRA and TST testing provide evidence for infection with Mtb, they cannot distinguish active from latent TB. Therefore, the diagnosis of active TB must be excluded prior to embarking on treatment for LTBI. This is typically done by determining whether or not symptoms suggestive of TB disease are present, performing a chest radiograph and, if radiographic signs of active TB (eg, airspace

opacities, pleural effusions, cavities, or changes on serial radiographs) are seen, then sampling is performed, and the patient managed accordingly."

TB Disease:

- "We recommend that acid-fast bacilli (AFB) smear microscopy be performed, rather than no AFB smear microscopy, in all patients suspected of having pulmonary TB."
- "We suggest that both liquid and solid mycobacterial cultures be performed, rather than either culture method alone, for every specimen obtained from an individual with suspected TB disease."
- "We suggest performing a diagnostic nucleic acid amplification test (NAAT), rather than not performing a NAAT, on the initial respiratory specimen from patients suspected of having pulmonary TB."
- "We recommend performing rapid molecular drug susceptibility testing for rifampin with or without isoniazid using the respiratory specimens of persons who are either AFB smear positive or Hologic Amplified MTD positive and who meet one of the following criteria: (1) have been treated for tuberculosis in the past, (2) were born in or have lived for at least 1 year in a foreign country with at least a moderate tuberculosis incidence (≥20 per 100000) or a high primary multidrug-resistant tuberculosis prevalence (≥2%), (3) are contacts of patients with multidrug-resistant tuberculosis, or (4) are HIV infected."
- "We suggest mycobacterial culture of respiratory specimens for all children suspected of having pulmonary TB."
- "We suggest that cell counts, and chemistries be performed on amenable fluid specimens collected from sites of suspected extrapulmonary TB.
- "We suggest that adenosine deaminase levels be measured, rather than not measured, on fluid collected from patients with suspected pleural TB, TB meningitis, peritoneal TB, or pericardial TB."
- "We suggest that free IFN-γ levels be measured, rather than not measured, on fluid collected from patients with suspected pleural TB or peritoneal TB."
- "We suggest that AFB smear microscopy be performed, rather than not performed, on specimens collected from sites of suspected extrapulmonary TB.
- "We recommend that mycobacterial cultures be performed, rather than not performed, on specimens collected from sites of suspected extrapulmonary TB."
- "We suggest that NAAT be performed, rather than not performed, on specimens collected from sites of suspected extrapulmonary TB."
- "We suggest that histological examination be performed, rather than not performed, on specimens collected from sites of suspected extrapulmonary TB."
- "Recently, whole-genome sequencing (WGS) has been applied to investigation of tuberculosis outbreaks. This technique may add discriminatory power to strain identification, but the role of WGS in outbreak investigation is still being determined."
- "We recommend one culture isolate from each mycobacterial culture-positive patient be submitted to a regional genotyping laboratory for genotyping" (Lewinsohn et al., 2017).

National Institute of Health (NIH)

The NIH published a set of guidelines regarding opportunistic infections in HIV-positive patients. The NIH writes that "All persons with HIV should be tested for LTBI [latent TB infection] at the time of HIV diagnosis, regardless of their epidemiological risk of TB exposure."

The NIH also comments on diagnostic testing, stating that "sputum acid-fast bacilli (AFB) smear, nucleic acid amplification (NAA) testing, and AFB culture should be performed in people with HIV with symptoms of TB disease who have a normal chest radiograph, as well as in those with no pulmonary symptoms but evidence of TB disease elsewhere in the body." The NIH remarks that "pleural fluid, pericardial fluid, ascites, and cerebrospinal fluid should be sampled if clinical evidence of involvement exists."

The NIH also discusses drug resistance testing, recommending that "Drug resistance should be considered in all people with HIV, especially those who meet any of the following criteria:

- Known exposure to a person with drug-resistant TB,
- Residence in a setting with high rates of primary drug-resistant TB,
- Persistently positive smear or culture results at or after four months of treatment, or
- Previous TB treatment, particularly if it was not directly observed or was interrupted for any reason."

The NIH recommends "Rapid molecular DST for rifampin (and isoniazid, if available) should be performed on the initial isolates from all patients suspected of having TB, because resistance to rifampin is associated with an increased risk of treatment failure, recurrent TB, and amplification of resistance to additional TB medications."

Overall, the NIH recommends that "For all patients with TB disease, phenotypic DST to first-line TB drugs (isoniazid, rifampin, ethambutol, and pyrazinamide) should be performed, regardless of the source of the specimen. Given the alternative of a shorter drug-susceptible TB regimen containing moxifloxacin, public health laboratories in the U.S. may add routine moxifloxacin susceptibility testing as well. Molecular resistance testing should be performed, and resistance testing should be repeated if sputum cultures remain positive for M. tuberculosis at or after 4 months of treatment or become positive again 1 month or longer after culture conversion to negative. Resistance testing for second-line TB medications (including bedaquiline, linezolid, clofazimine, pretomanid, cycloserine, ethionamide, and others) should be limited to specimens with resistance to first-line TB medications and should be performed in reference laboratories with substantial experience in these techniques." The NIH makes a further stipulation that "isolates with an initial reading of rifampin by commercial NAA test should undergo confirmatory testing (rpoB gene sequencing and phenotypic DST). Clinicians who suspect drug-resistant TB in a patient with HIV should make every effort to expedite a diagnosis and consult with their state TB program and then the CDC as needed" (NIH, 2024).

American Thoracic Society, U.S. Centers for Disease Control and Prevention, European Respiratory Society, and Infectious Diseases Society of America (ATS/CDC/ERS/IDSA)

This joint guideline was published to discuss the treatment of drug-resistant tuberculosis. The guideline notes that "molecular DSTs [drug susceptibility tests] should be obtained for rapid detection of mutations associated with resistance. When rifampin resistance is detected, additional DST should be performed immediately for first-line drugs, fluoroquinolones, and aminoglycosides." The guideline further stated that "A rapid test for a [sic] least rifampin resistance should ideally be done for every patient, but especially for those at risk of drug resistance." Individuals who "have or recently had close contact with a patient with infectious DR-TB [drug resistant tuberculosis] especially when the contact is a young child or has HIV infection, are at risk of developing DR-TB."

The guideline also remarks that if "sputum cultures remain positive after 3 months of treatment, or if there is bacteriological reversion from negative to positive at any time, DST [drug susceptibility testing] should be repeated" and that monthly cultures help to "identify early evidence of failure." Finally, this guideline refers to the above 2017 Lewinsohn guideline as providing "additional details on the optimal use of diagnostic tools and algorithms" (Nahid et al., 2019).

United State Preventative Service Task Force (USPSTF)

A 2023 recommendation from USPSTF found adequate evidence that accurate screening tests for LTBI are available, that the treatment of LTBI provides a moderate health benefit in preventing progression to active disease, and that the harms of screening and treatment are small. The USPSTF has moderate certainty that screening for LTBI in persons at increased risk for infection provides a moderate net benefit. "This recommendation applies to asymptomatic adults 18 years or older at increased risk for tuberculosis (TB). It does not apply to adults with symptoms of TB or to children and adolescents" (USPSTF et al., 2023).

The USPSTF also notes that to achieve the benefit of this screening, it is important that persons who screen positive for LTBI receive follow-up and treatment. While the USPSTF found no evidence on the optimal frequency of screening for LTBI, in the absence of evidence, they recommend that "a reasonable approach is to repeat screening based on specific risk factors; screening frequency could range from 1-time-only screening

among persons at low risk for future TB exposure to annual screening among those who are at continued risk of exposure (USPSTF et al., 2023).

The USPSTF provides additional information on how to implement their recommendation:

- "Populations at increased risk for LTBI, based on increased prevalence of active disease and increased risk of exposure, include persons who were born in, or are former residents of, countries with high TB prevalence and persons who live in, or have lived in, high-risk congregate settings (e.g., homeless shelters or correctional facilities).
- Clinicians can consult their local or state health departments for more information about populations at increased risk in their community, since local demographic patterns may vary across the US.
- Two types of screening tests for LTBI are currently available in the US: the tuberculin skin test (TST) and the interferon-gamma release assay (IGRA).
    - The TST requires trained personnel to administer intradermal purified protein derivative and interpret the response 48 to 72 hours later.
    - The IGRA requires a single venous blood sample that measures the CD4 T-cell response to specific Mycobacterium tuberculosis antigens and laboratory processing within 8 to 30 hours after collection.
    - Testing with IGRA may have advantages over TST for persons who have received a BCG vaccination, as IGRA does not cross-react with the vaccine, and for persons who may be unlikely to return for TST interpretation" (USPSTF et al., 2023).

The USPSTF provides the following additional information for clinicians to know pertaining to their recommendation:

- "TB disproportionately affects Asian, Black, Hispanic/Latino, Native American/Alaska Native, and Native Hawaiian/Pacific Islander persons. Incidence of TB varies by geography and living accommodations, suggesting an association with social determinants of health.
- LTBI is an infection with M tuberculosis in which the bacteria are alive but contained by the immune system. Persons with LTBI have no apparent symptoms, do not feel sick, cannot spread TB to others, and usually have a positive TB skin test or positive TB blood test reaction.
- Active TB or TB disease is an illness in which TB bacteria are multiplying and attacking a part of the body, usually the lungs. TB disease may be symptomatic (including weakness, weight loss, fever, no appetite, chills, sweating at night, bad cough, pain in the chest, or coughing up blood). A person with TB disease may be infectious and spread TB bacteria to others" (USPSTF et al., 2023).

Infectious Diseases Society of America (IDSA)/American Society of Microbiology (ASM)

In the 2024 update to the IDSA/ASM joint guideline, A Guide to Utilization of the Microbiology Laboratory for Diagnosis of Infectious Diseases, concerning Mycobacterium tuberculosis, they recommend AFB smear or AFB culture when performing laboratory diagnosis. They do allow for the use of NAAT for diagnosing M. tuberculosis; however, they state, "A negative result does not rule out Mycobacterium tuberculosis." They also state "although most molecular tests have excellent sensitivity, a *Mycobacterium tuberculosis NAAT* test should be an adjunct to a culture and never ordered alone. No current commercial methods are FDA-cleared for these specimens, so laboratories must have validated the test they use."

In cases of laboratory diagnosis of pulmonary infections in cystic fibrosis due to suspected *Mycobacterium* spp, they recommend performing a mycobacterial culture from the expectorated sputum, bronchoscopically obtained cultures, or other respiratory cultures (Miller et al., 2024).

Committee on Infectious Diseases, American Academy of Pediatrics, 32nd Edition (2021-2024, Red Book)

Highlights from the updated Red Book include the following:

- The AAP notes that there are NAATs cleared by the FDA for detection of *M. tuberculosis* from smear-positive and smear-negative sputum specimens.
- For children younger than two years, the TST [tuberculin skin test] is the preferred method for detection of infection.
- "For children 2 years and older, either TST or IGRA [interferon gamma release assay] can be used, but in people previously vaccinated with BCG, IGRA is preferred to avoid a false-positive TST result caused by a previous vaccination with BCG."
- Universal testing with either TST or IGRA is discouraged "because it results in either a low yield of positive results or a large proportion of false-positive results, leading to an inefficient use of health care resources."
- All organ transplant candidates should be given a TST or IGRA before starting immunosuppressive therapy.
- The AAP recommends the following for an "immediate" TST or IGRA:
  - children who are contacts of people with confirmed or suspected contagious tuberculosis (contact investigation)
  - children with clinical or radiographic findings suggesting TB
  - children immigrating from countries with endemic infection (e.g., Asia, Middle East, Africa, Latin America, countries of the former Soviet Union), including international adoptees
  - children with history of significant travel to countries with endemic infection who have substantial contact with the resident population
- The AAP also recommends an annual TST/IGRA for children with HIV (AAP, 2021).

Tuberculosis Network European Trials Group (TBNET)/RESIST-TB

This consensus statement encompasses molecular drug resistance testing for *Mycobacterium tuberculosis*.

- "Although they do not cover all mutations involved in RMP resistance, molecular methods for RMP could be considered a standard for the diagnostic evaluation of patients with presumptive MDR-TB. In low MDR-TB prevalence countries, physicians should be aware of possible false-positive resistance results of molecular tests, and RMP resistance should be confirmed by a second molecular test on a different sample or by phenotypic tests."
- "Although >90% of RMP-resistant strains are also resistant to INH, molecular testing for INH drug resistance is important."
- "In all patients with evidence of M. tuberculosis with an rpoB mutation in a direct specimen or when DST indicates MDR-TB, molecular testing for second-line resistance should be undertaken to guide treatment and to reduce the time to diagnose XDR-TB."
- "WGS [whole genome sequencing] provides the complete sequence information of the bacterial genome. However, due to the lack of correlation with in vitro (phenotypic DST) and in vivo (treatment outcome) data at present, it is not possible to interpret the clinical value of the vast majority of mutations or polymorphisms detected."
- "The level of discordance between molecular and culture-based DST depends on the drug and the genomic region evaluated. Despite the fact that results of phenotypic methods do not always correspond to response to clinical treatment, culture-based methods are still regarded by most experts involved in this document as the gold standard for DST" (Domínguez et al., 2016).

National Institute for Health and Care Excellence (NICE)

NICE has published guidelines for assessment of TB, which include the following recommendations:

- "If the Mantoux test is positive but a diagnosis of active TB is excluded, consider an interferon gamma release assay if more evidence of infection is needed to decide on treatment."

- "For adults who are severely immunocompromised, such as those with HIV and CD4 counts of fewer than 200 cells/mm^3, or after solid organ or allogeneic stem cell transplant, offer an interferon-gamma release assay and a concurrent Mantoux test."
- "For other adults who are immunocompromised, consider an interferon-gamma release assay alone or an interferon-gamma release assay with a concurrent Mantoux test. If either test is positive (for Mantoux, this is an induration of 5 mm or larger, regardless of BCG history), assess for active TB."
- "Only consider using interferon-gamma release assays alone in children and young people if Mantoux testing is not available or is impractical."
- "If TB is a possibility, microbiology staff should consider carrying out TB culture on samples, even if it is not requested."
- "Request rapid diagnostic nucleic acid amplification tests for the *M. tuberculosis* complex (*M. tuberculosis, M. bovis, M. africanum*) on primary specimens if there is clinical suspicion of TB disease, and:
  - the person has HIV or
  - rapid information about mycobacterial species would alter the person's care or
  - the need for a large contact-tracing initiative is being explored."
- "For people with clinically suspected TB, a TB specialist should request rapid diagnostic nucleic acid amplification tests for rifampicin resistance on primary specimens if a risk assessment for multidrug resistance identifies any of the following risk factors:
  - "history of previous TB drug treatment, particularly if there was known to be poor adherence to that treatment"
  - "contact with a known case of multidrug-resistant TB"
  - "birth or residence in a country in which the World Health Organization reports that a high proportion (5% or more) of new TB cases are multidrug-resistant."
- If the rapid diagnostic nucleic acid amplification test for the *M. tuberculosis* complex is negative in a person at high risk of multidrug-resistant TB:
  - "obtain further specimens for nucleic acid amplification testing and culture, if possible"
  - "use rapid rifampicin resistance detection on cultures that become positive for the *M. tuberculosis* complex"
- "If the rapid diagnostic nucleic acid amplification test for rifampicin resistance is positive:
  - "test for resistance to second-line drugs" (NICE, 2024).

European Respiratory Society (ERS) and the European Centre for Disease Prevention and Control (ECDC) Statement: European Union Standards for Tuberculosis Care

This joint guideline was intended to "define the essential level of care for managing patients who have or are presumed to have TB, or are at increased risk of developing the disease."

- "All patients (adults, adolescents and children who are capable of producing sputum) thought to have pulmonary tuberculosis should have at least two sputum specimens submitted for microscopic examination and one for rapid testing for the identification of tuberculosis and drug resistance using an internationally recommended (rapid) molecular test. The sample should be sent for liquid culture and, if positive, for culture-based drug susceptibility testing (DST) in a quality-assured laboratory."
- "For all patients (adults, adolescents and children) presumed to have extrapulmonary tuberculosis, appropriate specimens from the suspected sites of involvement should be obtained for microbiological testing (microscopy, rapid molecular tests, culture, species identification, DST with rapid molecular tests and culture-based techniques) and histopathological examination in quality-assured laboratories."
- "All persons with chest radiographic findings suggestive of pulmonary tuberculosis should have sputum specimens submitted for microscopic examination, rapid molecular tests, culture, species identification and DST with rapid molecular tests and culture-based techniques in a quality-assured laboratory" (ERS/ECDC, 2017).

National Society of Tuberculosis Clinicians (NSTC) of the National Tuberculosis Controllers Association (NTCA)

In 2023, the NSTC of the NTCA jointly released a set of clinical recommendations for "Testing and Treatment of Latent Tuberculosis Infection in the United States." In relation to testing, the NTSC/NTCA states that "IGRAs are generally preferred, but the TST is acceptable… In choosing which test to use, consider the patient's history of BCG, age, and ability to return for a second appointment. IGRAs offer greater specificity than a TST in persons who were BCG vaccinated or who have non-tuberculous mycobacterial infections. For this reason, IGRAs are preferred for most non-US-born patients who received, or may have received, BCG vaccination. For other persons, either a TST or IGRA can be used depending on test availability and cost."

When discussing immunocompromised patients, the organizations stated that "dual testing with TST and an IGRA simultaneously increases the overall specificity for infection." However, "Dual testing should not be routine, but it may be considered for patients when there is concern about their ability to mount a strong immune response to a test, for persons who are at risk of severe forms of TB disease, or for persons in whom TB infection is strongly suspected because of exposure risks or symptomatology. Children aged <2 years old can be included in a dual testing strategy if one of the above circumstances is present."

In regard to serial testing, "When serial or periodic testing is required, as with some health care personnel at ongoing risk for TB exposure, either an IGRA or the TST may be used. For TST testing, the initial test should be a two-step TST. Because IGRAs do not cause boosting, serial testing with IGRAs does not require two-step testing to establish a baseline."

For persons who are "at low risk for TB infection or active TB disease are required to be tested by law for other reasons, use either an IGRA or TST. If the result is positive, perform a second test with the same or a different method to confirm the test result."

When an MMR vaccine and TB test are both indicated, the Advisory Committee on Immunization Practices recommends:

- "Administer the TST or IGRA simultaneously with the live vaccine (preferred scenario).
- If a TST or IGRA has already been administered, a live vaccine can be administered at any time >1 day after the administration of the TB test.
- If a live vaccine has already been administered, wait at least 28 days before administering a TST or IGRA.
- In two-step testing, wait at least 28 days after the live vaccine is administered before administering the first TST. Continue from there to complete the two-step testing. Wait to administer any additional doses of live vaccine until after the second TST is measured."

In terms of officially diagnosing latent tuberculosis infection, the NSTC states, "At the completion of pretreatment clinical evaluation, if a patient with a positive test result for TB infection does not have any symptoms of TB, and the CXRs and other diagnostic tests results are normal, then active TB disease is excluded and LTBI is diagnosed" (NSTC, 2023).

National Psoriasis Foundation (NPF)

In reviewing the literature surrounding immunosuppressive therapies and the risk of tuberculosis, the National Psoriasis Foundation found that "The biologic TNF–α inhibitors are very promising in the treatment of psoriasis. However, because TNF–α is also an important cytokine in preventing TB infection and in keeping latent TB infection from becoming active disease, the use of TNF–α inhibitors has been associated with an increased risk of developing active TB. A higher incidence of TB has also been reported with other immunosuppressive/immunomodulatory treatments for psoriasis. It is, therefore, of utmost importance to appropriately screen all patients for latent TB infection prior to initiating any immunologic therapy. Delaying immunologic therapy until latent TB infection prophylaxis is completed is preferable. However, if the patient is

adhering to his prophylactic regimen and is appropriately tolerating the regimen, therapy may be started after one to two months if the clinical condition requires" (Doherty et al., 2008). This screening "for latent TB infection before commencement of treatment is of utmost importance when beginning treatment with the tumor necrosis factor–α inhibitors, T-cell blockers, cyclosporine, or methotrexate" and the "currently recommended method for screening is the tuberculin skin test." However, the authors also acknowledge that "There are few evidence-based studies on screening for latent TB infection in psoriasis patients treated with systemic and biologic agents," and so the power of the results may be limited (Doherty et al., 2008).

Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: https://www.cms.gov/medicare-coverage-database/search.aspx. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
81099	Unlisted urinalysis procedure
81425	Genome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis
81426	Genome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator genome (eg, parents, siblings) (list separately in addition to code for primary procedure)
81479	Unlisted molecular pathology procedure
82945	Glucose, body fluid, other than blood
83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified
83615	Lactate dehydrogenase (LD), (LDH)
84157	Protein, total, except by refractometry; other source (eg, synovial fluid, cerebrospinal fluid)
84311	Spectrophotometry, analyte not elsewhere specified
86480	Tuberculosis test, cell mediated immunity antigen response measurement; gamma interferon
86481	Tuberculosis test, cell mediated immunity antigen response measurement; enumeration of gamma interferon-producing T-cells in cell suspension
87070	Culture, bacterial; any other source except urine, blood or stool, aerobic, with isolation and presumptive identification of isolates
87077	Culture, bacterial; aerobic isolate, additional methods required for definitive identification, each isolate

87116	Culture, tubercle or other acid-fast bacilli (eg, TB, AFB, mycobacteria) any source, with isolation and presumptive identification of isolates
87149	Culture, typing; identification by nucleic acid (DNA or RNA) probe, direct probe technique, per culture or isolate, each organism probed
87150	Culture, typing; identification by nucleic acid (DNA or RNA) probe, amplified probe technique, per culture or isolate, each organism probed
87153	Culture, typing; identification by nucleic acid sequencing method, each isolate (eg, sequencing of the 16S rRNA gene)
87181	Susceptibility studies, antimicrobial agent; agar dilution method, per agent (eg, antibiotic gradient strip)
87184	Susceptibility studies, antimicrobial agent; disk method, per plate (12 or fewer agents)
87185	Susceptibility studies, antimicrobial agent; enzyme detection (eg, beta lactamase), per enzyme
87186	Susceptibility studies, antimicrobial agent; microdilution or agar dilution (minimum inhibitory concentration [MIC] or breakpoint), each multi-antimicrobial, per plate
87187	Susceptibility studies, antimicrobial agent; microdilution or agar dilution, minimum lethal concentration (MLC), each plate (list separately in addition to code for primary procedure)
87188	Susceptibility studies, antimicrobial agent; macrobroth dilution method, each agent
87190	Susceptibility studies, antimicrobial agent; mycobacteria, proportion method, each agent
87206	Smear, primary source with interpretation; fluorescent and/or acid fast stain for bacteria, fungi, parasites, viruses or cell types
87550	Infectious agent detection by nucleic acid (DNA or RNA); Mycobacteria species, direct probe technique
87551	Infectious agent detection by nucleic acid (DNA or RNA); Mycobacteria species, amplified probe technique
87552	Infectious agent detection by nucleic acid (DNA or RNA); Mycobacteria species, quantification
87555	Infectious agent detection by nucleic acid (DNA or RNA); Mycobacteria tuberculosis, direct probe technique
87556	Infectious agent detection by nucleic acid (DNA or RNA); Mycobacteria tuberculosis, amplified probe technique
87557	Infectious agent detection by nucleic acid (DNA or RNA); mycobacteria tuberculosis, quantification
87560	Infectious agent detection by nucleic acid (DNA or RNA); mycobacteria avium-intracellulare, direct probe technique
87561	Infectious agent detection by nucleic acid (DNA or RNA); mycobacteria avium-intracellulare, amplified probe technique
87562	Infectious agent detection by nucleic acid (DNA or RNA); mycobacteria avium-intracellulare, quantification

Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

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Revision History

Effective Date	Summary
01/01/2025	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria. The following edits were made for clarity and consistency: Verb tense in CC13 and CC14 fixed from “testing DO not meet” to “testing DOES not meet”.
12/01/2023	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria. The following edits were made for clarity: CC3-8 edited for clarity and consistency, including changing “patient” to “individual”
06/01/2022	Initial Policy Implementation

EXCLUSIONS:
Note: A complete description of the process by which a given technology or service is evaluated and determined to be experimental, investigational or unproven is outlined in MP 15 - Experimental Investigational or Unproven Services or Treatment.

Medicaid Business Segment:

Any requests for services, that do not meet criteria set in the PARP, may be evaluated on a case by case basis.

LINE OF BUSINESS:
Eligibility and contract specific benefits, limitations and/or exclusions will apply. Coverage statements found in the line of business specific benefit document will supersede this policy. For Medicare, applicable LCD’s and NCD’s will supercede this policy. For PA Medicaid Business segment, this policy applies as written.

Geisinger Health Plan may refer collectively to health care coverage sponsors Geisinger Health Plan, Geisinger Quality Options, Inc., and Geisinger Indemnity Insurance Company, unless otherwise noted. Geisinger Health Plan is part of Geisinger, an integrated health care delivery and coverage organization.

Coverage for experimental or investigational treatments, services and procedures is specifically excluded under the member's certificate with Geisinger Health Plan. Unproven services outside of an approved clinical trial are also specifically excluded under the member's certificate with Geisinger Health Plan. This policy does not expand coverage to services or items specifically excluded from coverage in the member’s certificate with Geisinger Health Plan. Additional information can be found in MP015 Experimental, Investigational or Unproven Services.

Prior authorization and/or pre-certification requirements for services or items may apply. Pre-certification lists may be found in the member's contract specific benefit document. Prior authorization requirements can be found at https://www.geisinger.org/health-plan/providers/ghp-clinical-policies