Diagnosis

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The first steps in diagnosing drug-resistant TB are to recognize that the patient is at risk and to expedite the laboratory diagnosis.

Introduction

The diagnosis of tuberculosis (TB) frequently requires a high index of suspicion, especially in low-prevalence areas. The index of suspicion should be based on consideration of clinical and epidemiological risk factors, symptoms, physical examination findings (e.g., enlarged lymph nodes or other findings suggestive of possible extra-pulmonary involvement), and radiographic findings. Once TB is considered, sputum or other specimens are collected for TB nucleic acid amplification test (NAAT), acid-fast bacilli (AFB) smear, growth detection, and drug-susceptibility testing (DST). The possibility of drug-resistant TB should be considered simultaneously with specimen collection and selection of the initial treatment regimen. Failure to consider the possibility of drug-resistant TB until conventional DST results return weeks to months later can result in inadequate drug regimens, amplification of drug resistance, and additional disease transmission.

Rapid identification of drug resistance in a patient with TB is critical in order to:

- Treat the patient with the most appropriate regimen
- Minimize transmission
- Prevent acquisition of further drug resistance
- Offer appropriate care to contacts
- Provide the best chance of cure

Predicting who is at risk prior to the return of conventional DST results is the first step in early detection of drug resistance.
Risk assessment for drug resistance

The most important predictors of drug-resistant TB are:

- Previous episode(s) of TB treatment
- Worsening clinical and/or radiographic findings while on TB therapy
- Origin from, history of residence in, or frequent travel to a region or country with a high prevalence of drug-resistant TB
- Exposure to an individual with known (or highly suspected) infectious drug-resistant TB, or exposure to individuals in congregate settings where drug resistance has been documented

Risk factors in persons with a history of prior TB

Suspicion for drug-resistant TB should be high and rapid molecular testing for drug resistance should be performed if the patient has 1 or more of the following characteristics on current or prior treatment:

- Lack of conversion of cultures to negative during the first 3 months of therapy
- Lack of improvement or only partial improvement in TB symptoms
- Worsening of TB symptoms or radiograph findings despite TB treatment
- Non-adherence or intermittent or erratic ingestion of prescribed anti-TB regimen
- Lack of directly observed therapy (DOT) or poorly supervised therapy
- Documented treatment failure or relapse: the risk for suspected acquired resistance in relapse cases is significantly lower if use of high-quality DOT with an appropriate regimen can be verified, but a rapid molecular test should still be obtained
- History of an inappropriate treatment regimen, including:
  - Administration of single-drug therapy
  - Too few effective drugs
  - Inadequate drug dosing

Risk factors in persons without prior TB history

Clinical suspicion of drug resistance should occur and rapid molecular testing for drug resistance should be considered when a patient with TB signs and symptoms has a history of 1 or more of the following:

- Exposure to a person with documented drug-resistant TB
- Exposure to an individual highly suspected of having drug-resistant TB, including those who have received more than one course of TB treatment, prolonged treatment or who had a delayed response to treatment
- Residence in or travel to a region with a high prevalence of drug-resistant TB (See Chapter 1, Epidemiology, for a list of the top 15 countries of origin for multidrug-resistant [MDR] TB patients in the United States, and Resources at the end of this chapter)
• Among foreign-born persons with TB, arrival in the United States within the previous two years (per 2010-2013 U.S. national surveillance data)
• Residence or work in an institution or setting in which drug-resistant TB is documented
• Treatment of pulmonary problems with a prolonged course of multiple medicines or an injectable agent for more than a few weeks in a foreign country; i.e., the patient may not realize that he/she was treated for TB

Questions to ask your patient

Soliciting a history of previous TB treatment requires a great deal of patience and attention to detail. In a confidential setting, allow plenty of time, use an accurate and unbiased medical interpreter (if necessary), and be willing to repeat or rephrase a question to obtain the information. Give the patient encouragement to reveal accurate information by asking and responding in a nonjudgmental manner. Ask the patient if he/she has any written information regarding his/her treatment, any old radiographs, etc.

• Have you been told you had TB before?
• Have you been treated for TB?
• Have you received injections or antibiotics for many months for a lung problem?

If your patient answers “yes” to any question(s) that indicate he or she may have been treated previously for TB, the following types of questions should be asked to obtain more information regarding previous treatment:

• Where were you treated?
• What medicines did you receive?
• How many different medicines? How many pills each day? What sizes and colors were the pills/capsules?
• Did you receive injections?
• How long were you on treatment?
• Were you told you were cured? Did your TB ever come back?
• How many times were you treated for TB?
• When did you start?
• When did you stop? Why did you stop (completed treatment, bad reaction to the medicine)?
• It’s hard to remember to take medicine every day. Did you take medications daily? Every pill?
• TB medicine can be expensive. Were you ever without medication?
• Did you miss medication sometimes? How often?
• Did healthcare workers watch you taking your medications?
• Did your urine turn orange?
• Did you feel better?
• Did you ever have a sputum collected for testing? What was the result?
• If positive, did your sputum test get better on treatment (change from positive to negative)?
• Did your doctor ever tell you: That you had to be treated for TB longer? That you had a return of TB? That you had to repeat treatment for TB? That you had TB that was drug resistant?

• Did your TB symptoms return after finishing treatment?

**TB treatment outside of the United States:** If the patient was previously treated for TB in the United States, records detailing his/her treatment should be obtained directly from the appropriate state and/or local jurisdiction. Past treatment outside the United States may be available through CureTB (Mexico/Latin America) or TB Net (see Appendix 2, Selected Organizations Working to Control and Prevent TB in the International Arena). If the patient was treated in Western Europe, Canada, or by a private provider in a high-resource country, records should be available and can be sought directly through the appropriate national/regional program. Immigration health records (e.g., class B1 records) may also be informative and should be obtained.

Many resource-limited countries, particularly those documented as among the highest TB burden countries, use standardized World Health Organization (WHO) TB regimens and diagnostic algorithms that may differ from recommended U.S.-based practices. Appendix 3, International Resources for TB Treatment and Policies, lists key WHO reference documents and other websites that may be helpful in understanding and identifying TB policies in selected countries.

If your patient answers “no” to the questions that indicate he or she may have been treated previously for TB, the following types of questions should be asked to evaluate if the patient has been exposed to drug-resistant TB:

• Have you been exposed to or had contact with anyone with TB (or who may be sick with a chronic cough)?

• If yes, when was that? Where were you exposed? For how long you were exposed?

• What is that patient’s name and age? Where was he/she treated? How long was he/she treated? Was he/she cured?

• Did you have a skin or blood test for TB? Do you know the results?

• Did you have a chest X-ray? Do you know the results?

• Did you receive medications to prevent TB? If so, what drugs and for how long? Did you come to a clinic for the medications where a healthcare worker observed you take the pills, or did a healthcare worker meet you and provide medications?

• Did you have cough, fever, weight loss, or other symptoms?

• If yes, when did those symptoms start?

• Have you ever given sputum specimens to check for TB?

*Whenever possible, obtain records regarding treatment of a presumed source case.*
Testing for TB infection

Suspicion of or evaluation for TB sometimes begins with the use of an interferon gamma release assay (IGRA) such as QuantIFERON-TB Gold (QFT-G) or T-SPOT.TB, or the tuberculin skin test (TST). None of these tests have perfect accuracy for diagnosis of TB infection or TB disease.

Studies suggest that the IGRA and TST may be negative in up to 40% of newly diagnosed, culture-positive TB cases. A negative IGRA test or TST does not rule out TB disease, and a positive IGRA test or TST does not distinguish between TB infection and TB disease. When a clinical suspicion for active TB disease exists, further testing for TB disease should continue regardless of IGRA or TST result.

For more information about testing for TB infection, see Chapter 10, Contacts.

Testing for TB disease

- All patients in whom a clinical suspicion for active pulmonary TB disease exists should at a minimum have one sputum specimen examined by NAAT and three sputum specimens, collected at least 8 hours apart, examined by AFB smear microscopy and mycobacterial culture.
- Culture remains the gold standard for the diagnosis of TB—it is the most sensitive test and enables comprehensive drug susceptibility testing. Sputum specimens should be submitted for culture regardless of whether or not NAAT is ordered.
- All patients in whom a clinical suspicion for active drug-resistant pulmonary TB disease exists should have a sputum specimen submitted for rapid molecular testing for drug resistance. For more information, see section: Testing for drug resistance, and Chapter 3, Laboratory.
- Patients in whom extrapulmonary disease is suspected should also have specimens from the site of disease examined by AFB smear, culture, and histopathology (when applicable). Rapid molecular tests may be performed on some non-respiratory specimens in laboratories capable of validating the assay. Specialized reference laboratories have the capacity to attempt molecular diagnosis through DNA extraction when formalin-fixed tissue is the only available specimen. For more information regarding molecular tests for extrapulmonary specimens, refer to Chapter 3, Laboratory.
- Patients in whom suspicion of active TB disease is high should be started on an appropriate treatment regimen empirically because culture often takes up to 2-6 weeks before a positive result is obtained. For more information on choosing an appropriate treatment regimen, refer to Chapter 4, Treatment.

Molecular assays for identification of Mycobacterium (M.) tuberculosis complex

NAATs are molecular assays that have been available since 1995, but initially had limited uptake due to cost and availability. Fortunately, with improved access, molecular assays are having a significant impact on TB care. The Centers for Disease Control and Prevention (CDC) 2009 recommendations promote the use of NAATs in all patients for whom a diagnosis of TB is being considered if the results would influence clinical or public health decision-making. When feasible, NAATs should also be considered for all
patients being evaluated for TB to prevent delays in diagnosis and treatment initiation. The type of NAAT used will vary based on local availability, but most commonly it will be a polymerase chain reaction (PCR)-based method.

- NAATs are more sensitive than sputum smear microscopy but a negative NAAT does not rule out active TB disease. If clinical suspicion for TB is high, NAAT testing should be repeated on a second specimen to increase sensitivity for diagnosing TB. When NAAT results are negative, decisions regarding empiric anti-TB treatment should be based on clinical suspicion of TB, risk of adverse outcomes, and public health considerations.

- NAATs have high specificity and positive predictive value for identifying TB.

Although different NAATs are available, increased implementation of the semi-automated Xpert MTB/RIF assay is anticipated and is worth mentioning within its global context.

- The Xpert MTB/RIF assay was approved by the U.S. Food and Drug Administration (FDA) in 2013 and can rapidly identify the presence of M. tuberculosis complex. The assay also rapidly identifies mutations in the rpoB gene that confer rifampin (RIF) resistance. See section: Molecular assays for identification of drug resistance.

- The Xpert MTB/RIF assay can be performed on raw sputum specimens, requires minimal sample preparation, provides results within 2 hours and is highly accurate for detecting M. tuberculosis complex.

- However, false-negative results do occur, particularly when sputum smears are negative or scanty-positive. False-positive results for identifying M. tuberculosis complex are less common, but do occur particularly when a patient has had a previous episode of TB disease.

Since Xpert MTB/RIF was first endorsed by WHO in 2010, there has been rapid uptake in many high-burden countries. In 2013, WHO updated its prior endorsement to recommend the use of Xpert MTB/RIF as the initial diagnostic test, when feasible, for all patients being evaluated for pulmonary TB and for some forms of extrapulmonary TB.

**Testing for drug resistance**

Definitive diagnosis of drug-resistant TB requires that M. tuberculosis complex be isolated and drug-susceptibility results be completed and conveyed to the clinician. State and/or local TB control officials should be notified promptly when drug resistance is either strongly suspected or confirmed.

Different techniques of conventional, growth-based DST may be used and are outlined in more detail in Chapter 3, Laboratory. With all techniques, growth detection and identification of M. tuberculosis complex may take a few weeks, and DST requires an additional 1 to 3 weeks. Slow growth of some mycobacterial strains (a common characteristic noted in many MDR-TB strains) further lengthens the time to identification and DST. Delays in reporting of culture confirmation and/or drug-susceptibility results to the treating provider can further delay the diagnosis of drug-resistant TB and initiation of appropriate treatment, resulting in ongoing transmission risk.

- In interpretation of M. tuberculosis complex drug-susceptibility results, clinical trials have ascertained that when tested on solid media, if more than 1% of organisms within a population are resistant to a given drug, clinical success with that drug is less likely.
• The interpretation of growth-based DST results for mycobacteria is somewhat different than that for most other pathogens. In the latter case, the clinician compares the minimum inhibitory concentration (MIC) of the pathogen with the achievable serum level. If a safe dose of the antibiotic will kill the bacteria in the patient, the drug can be successfully used. The interpretation of susceptibility testing for mycobacteria is not as straightforward; several variables complicate the process: 1) mycobacteria may reside within or outside of human cells; 2) mycobacteria have a long replication time and may exist in a continuum between dormant and active states; and 3) mycobacteria can live in a variety of tissue types for which drugs may have different penetration levels.

• The concentration that constitutes the breakpoint between a resistant and susceptible strain is called the “critical concentration.” The critical concentration is the level of drug that inhibits a wild-type (a strain that has not been exposed to TB drugs) M. tuberculosis complex strain, but does not appreciably suppress the growth of a resistant strain. The critical concentration may be different depending on the medium used for the assay.

• If, on solid media, more than 1% of the strain’s population grows at the critical concentration of the drug for that particular medium, the isolate is considered to be resistant to that drug and other drugs must be used in the regimen. Be aware that isoniazid [INH], streptomycin [SM], and fluoroquinolones may be tested at both low and high concentrations and it may be possible to still consider use of drugs that display low-level resistance only.

More detailed discussions regarding critical concentrations, use of high- and low-level testing of selected drugs, and interpretation of MICs can be found in Chapter 3, Laboratory.

Molecular assays for identification of drug resistance

Molecular assays for identification of drug resistance can hasten the time from weeks to 1-2 days to identify the presence of drug resistance. All molecular assays detect mutations in mycobacterial DNA that are known to cause resistance to a specific anti-TB drug. Because resistance mechanisms at the molecular level are not fully understood, current molecular assays cannot detect all drug resistance. Growth-based DST should be performed when isolates are available.

Current assays include:

• Xpert MTB/RIF assay: In addition to detecting M. tuberculosis complex, Xpert MTB/RIF also detects mutations in the rpoB gene that confer RIF resistance and is currently the only non-sequencing molecular test for drug resistance approved by the FDA. The detection of RIF resistance is predictive of MDR-TB because RIF mono-resistance is relatively uncommon. Although accuracy is high, false-positive results can occur. Positive results that are unexpected for the clinical circumstance (e.g., positive result for RIF resistance in a patient without risk factors for drug resistance) need closer review; consider consultation with experts. Further consultation with the laboratory can help determine whether the result is likely to be false-positive; e.g., if cycle threshold values are high and end-point fluorescence values are low, or when RIF resistance is detected by multiple probes suggesting the presence of nontuberculous mycobacteria (NTM). In this situation, confirmation using a sequence-based test should be done. For more details regarding test performance of the Xpert MTB/RIF assay, refer to Chapter 3, Laboratory.
• **Line-probe assays (LPAs):** LPAs are currently performed primarily outside of the United States, but are available at some U.S. reference laboratories for rapid identification of INH and RIF (MTBDRplus, Hain Lifesciences) or fluoroquinolones, ethambutol (EMB), and injectable agents (MTBDRs, Hain Lifesciences).

• **Sequencing-based assays:** Molecular assays that use a sequencing technique (e.g., Sanger sequencing, pyrosequencing or testing through the CDC Molecular Detection of Drug Resistance [MDDR] service) have the advantage of reporting on the actual mutations, which can be useful in interpretation.

When drug resistance has been identified by non-sequencing molecular assays (e.g., Xpert MTB/RIF or others) in low-incidence settings, confirmation by a sequence-based method is recommended because non-sequencing assays can report silent mutations as drug resistant.

For more details regarding different types of molecular assays for drug resistance identification and the genes and mutations associated with drug resistance, see Chapter 3, *Laboratory.*

**When to use rapid molecular tests for drug resistance**

Rapid molecular tests for drug resistance should be requested in all cases identified as at risk for drug-resistant TB (Table 1). Rapid identification of drug resistance is also indicated in circumstances where earlier identification of resistance confers a significant medical or public health advantage or in specific situations where molecular methods may have an advantage over conventional laboratory testing.
### TABLE 1.

#### Indications for molecular resistance testing

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<th>Indications for molecular resistance testing</th>
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| **Increased risk for drug resistance**      | • Patients born in or who have spent significant time (e.g., more than 1 month) in countries with high prevalence of drug resistance  
• Known contact to a drug-resistant TB case (or case with features highly suspicious for drug resistance)  
• Patients not responding to the current regimen  
• Patients who were treated previously and have relapsed |
| **Increased consequences of drug resistance** | • Case in a congregate or other setting with large numbers of contacts (e.g., correctional facilities, healthcare facilities, schools)  
• Patients in whom unidentified drug resistance may have significant consequences because of young age (less than 5 years old) or immunocompromised status  
• Case has contacts with risks for rapid progression of TB disease and in whom effective preventive “window” treatment is needed (such as young children under age 5, or immunocompromised persons) |
| **Laboratory issues**                        | • Cultures are mixed with other bacteria (conventional DST would be delayed or not possible to perform at all)  
• AFB smear-positive but culture negative (molecular tests can provide drug-susceptibility results despite lack of growth)  
• Pathology specimens not initially sent to mycobacteriology lab |
| **Program priorities**                       | • Universal MDR-TB screening via rapid molecular testing for all NAAT- or smear-positive TB patients may be available in some jurisdictions to identify drug-resistant TB cases earlier |

Although there are significant advantages offered by the addition of rapid molecular assays, **growth-based susceptibility testing remains an integral diagnostic test to confirm molecular results** and to investigate susceptibility to drugs for which molecular detection of resistance is not yet possible.
Communication with the TB laboratory

If drug resistance is strongly suspected based on the patient’s prior treatment history or exposure to drug-resistant TB, discuss concerns immediately with your TB laboratory.

- Timely and frequent communication with the laboratory is essential.
- Some laboratories do not perform DST unless a specific and/or separate order for DST has been submitted. Clarify the process if the laboratory’s protocols are not well known to you.
- If the laboratory that provides mycobacterial culture services has limited capacity for DST, the provider should arrange for the isolate to be sent to a reference laboratory immediately. Consult with the laboratory about which second-line drug DSTs are performed and which reference laboratory is being used.
- If necessary, clinicians should contact their state or local TB programs or an expert in MDR-TB for assistance in identifying a qualified public health/reference laboratory. The CDC MDDR service offers molecular sequencing services for rapid detection of drug resistance, as do other reference laboratories. In some jurisdictions, molecular methods are also available locally.
- The clinician should know the name, telephone number, and contact person for each laboratory that will process and perform DST on isolates for patients with suspected drug resistance.
- The clinician should expect traditional DST results within 1-3 weeks of TB identification on culture and should contact the laboratory if reports are not received in this time period. For a list of expected turn-around times for mycobacteriology laboratory services, see Chapter 3, Laboratory, Table 1.

When to order second-line drug testing

- **When resistance to RIF or more than one first-line drug** (INH, RIF, pyrazinamide [PZA], or EMB) is found, **DST should be requested for the full spectrum of second-line agents.** Amikacin, capreomycin, a fluoroquinolone (levofloxacin or moxifloxacin), and ethionamide are the minimum second-line drugs for which to test. Fewer laboratories perform testing for cycloserine, para-aminosalicylic acid, rifabutin, linezolid, clofazimine, and other agents, but these too may be important in some clinical situations.
- **When co-morbidities warrant a non-standardized regimen.**
False-positive results

False-positive results for culture or DST may be suspected when:

- The patient’s clinical manifestations do not seem to be compatible with the laboratory findings, particularly when associated with the following:
  - *M. tuberculosis* is cultured from a sample processed together with another patient’s sample that is smear-positive.
  - Only one culture is positive among several specimens collected.
  - Unusual drug resistance patterns are found in unrelated patients suggesting possible errors in inoculation or mislabeling of specimens.

The suspicion of a false positive result is greater when more than one of these conditions is met.

Cross-contamination can cause false-positive results for isolation of *M. tuberculosis* complex or detection of drug resistance. Cross-contamination occurs when aerosols produced during the processing of specimens containing *M. tuberculosis* inoculate other specimens processed on the same day or reagents used for the decontamination of specimens. **When there is a question regarding laboratory results, it is important to discuss the situation with the laboratory.**

Other potential causes for false-positive results

- **Errors at the specimen collection site:**
  - Mislabeling of specimens or mistakes in entry of demographic data at the clinical site of collection
  - Contamination of medical devices used for collecting specimens, such as inadequate cleaning of bronchoscopy tubing

- **Errors in the laboratory:**
  - Mislabeling of specimens or media:
    - when transferring a specimen from the original container to a centrifuge tube
    - when inoculating media with specimen
    - when working up a positive culture for identification or DST
  - Malfunctioning biosafety cabinet
  - Malfunction of laboratory test systems (e.g., releasing results when controls failed)
  - Cross-contamination due to poor technique or using a common vessel to add reagents to all specimens
  - Failure to check for contamination with non-AFB microorganisms
  - Failure to check for mixed infection with NTM; if present, the NTM may be the source of the drug resistance pattern
  - Data entry errors or errors in electronic reporting

**Rapid molecular tests for drug resistance** may report RIF resistant results that are false-positive due to the presence of silent mutations. These are mutations identified within a gene associated with drug resistance that do not confer in vitro resistance. For example, rapid molecular testing with Xpert MTB/RIF may report RIF resistance for an isolate later found to be RIF sensitive by growth-based (phenotypic) DST. Further investi-
gation using DNA sequencing can help to identify the responsible mutation as a known silent mutation, and thus confirm that the molecular test result should be considered a false-positive. For more discussion on silent mutations and causes for discordant results, see Chapter 3, Laboratory.

When investigating results of questionable validity, check all possible sources of errors.

- If possible, collect another specimen or test another isolate from the same patient.
- Repeat testing from the original sample (if still available).
- Repeat DST by using another method or another laboratory.
- Request genotyping to help identify false positive culture results due to cross-contamination, such as when the strain under investigation matches the isolate from another case diagnosed in the same laboratory and there is no epidemiologic link between the two cases.
- Consult with laboratory experts. It may take a team effort, with candid communication between the healthcare provider and laboratory personnel, to find a solution.

While gathering additional information from the laboratory or waiting for repeat DST results, decisions regarding the prescribed drug regimen should be based on patient and public health factors. Empiric expansion of the drug regimen can be considered for patients who have not responded well to standard therapy, or who have extensive disease or risk factors for poor outcomes. When the risk of transmission is high (e.g., residence in a congregate setting), empiric expansion of the drug regimen may be considered to reduce the risk of extended isolation if the drug resistance is confirmed. On the other hand, when individual patient or public health risk is low, standard or current therapy can be continued.

Discordant results

Discordant test results can occur between different laboratories.

- Although new methods are validated against the standard method, perfect agreement cannot always be achieved. Discrepancies in results due to differences in methodology, medium, and critical concentrations are inevitable.
- Some strains of *M. tuberculosis* complex have MICs that are close to the critical concentration tested. Experience over time has shown that the reproducibility for testing of these strains can be suboptimal.
- Tests at the different laboratories may not have been performed using the same specimen.
- Errors can occur during DST, including:
  - Failure to use a standardized, well homogenized inoculum
  - Failure to add a drug to the broth medium
  - Adding the wrong drug or concentration
  - Inoculation errors
  - Failure to recognize a mixed infection (*M. tuberculosis* complex and an NTM) which is more difficult to detect in broth systems
  - Failure to recognize contamination with a non-AFB microrganism, which is more difficult to recognize in broth systems
• Changes in the performance of DST or support of mycobacterial metabolism can occur when a new lot of culture media is made or received, and when a new lot of drug solutions is prepared or a new drug kit is received. Laboratories should perform proper quality control to ensure that DST performs as expected.

• If a subculture has to be made for DST, the microbiologist must take growth from various parts of a slant or a plate to assure that the organisms tested are diverse enough to be representative of the initial population.

• In the case of possible emerging resistance, testing different populations may result in different resistance patterns. If emerging resistance is suspected due to known risks for acquired resistance or inadequate regimen, a change in regimen may be indicated. See Chapter 4, Treatment.

Discordant results may also be encountered when different methods for testing drug resistance are used. Early results from molecular tests for drug resistance may on occasion be discordant with results reported later from the conventional growth-based (phenotypic) DST, which is currently considered the gold standard.

• In a 2014 evaluation comparing results of isolates tested through the CDC MDDR molecular service with matching results using growth-based (phenotypic) DST from public health laboratories, overall concordance for resistance was 93.9% for RIF and 90% for INH.

• Current molecular methods for detecting INH resistance test primarily for inhA and katG mutations, which identify approximately 85% of resistant strains. Testing for less common mutations is not routinely performed, and the mutations associated with resistance are unknown in 10-15% of remaining cases.

• For RIF resistance, the discordance between molecular and growth-based DST can be complex. Emerging evidence suggests that sequence-based testing may prove to be a better reference standard for determining resistance. The identification and implications of silent and disputed mutations that may be the source of test discordance are areas of continued investigation. For more details, see Chapter 3, Laboratory.

What to do if discordant test results are found:

• Assess whether results fit the clinical and epidemiological picture.

• Talk to the laboratory director and discuss reasons for conflicting results.

• Ask how the laboratory ruled out mixed infection with NTM or contamination with non-AFB microorganisms.

• If in doubt, your public health laboratory or a reference laboratory should repeat the test using the most recent isolate available.

• Discordance between rapid molecular tests and the growth-based (phenotypic) DST results should be investigated further with a sequence-based method.

• When the clinical level of suspicion for resistance is strongly at odds with the initial rapid molecular test (Xpert MTB/RIF or line-probe assay) results, confirmation using a sequence-based method is recommended.

• For more detailed discussions, see sections: Molecular tests for drug resistance and Difficulties interpreting results from molecular tests in Chapter 3, Laboratory.
Use of strain typing

Genotyping of *M. tuberculosis* complex can be useful in:

- Detecting unrecognized outbreaks or confirming outbreaks under investigation
- Investigating or identifying false-positive results (i.e., laboratory cross-contamination)
- Distinguishing between relapse or reinfection (if a previous isolate was genotyped or is still available for genotyping)
- Documenting the progression of acquired drug-resistant TB versus reinfection with a drug-resistant strain

  - TB due to a specific strain may initially be susceptible to a panel of drugs, but with inappropriate or inadequate treatment, a sub-population of drug-resistant TB organisms will flourish. In such instances, the resistant and susceptible populations are part of the same strain and therefore, have the same genotype. However, the drug-resistant bacteria will have acquired mutations that confer drug resistance. Reinfection with a resistant strain is likely to demonstrate a different genotype.

Summary

- Patients at highest risk of drug-resistant TB are those who:
  - Previously have been treated for TB
  - Came from or traveled to regions/countries with high rates of drug resistance
  - Have been exposed to individuals with known or high risk for drug-resistant TB
  - Are failing TB treatment

- Each TB patient should be assessed for risk of drug resistance.

- Rapid molecular testing for drug resistance should be performed when risks for drug-resistant TB are identified.

- Communication to the laboratory that drug resistance is suspected is essential for rapid susceptibility testing and optimal patient care.

- Proper control of TB transmission requires timely performance of all required laboratory tests.

- Drug-resistant TB should be confirmed by a public health laboratory or reference laboratory.

- If a patient is suspected or confirmed to have MDR/XDR-TB, consultation with an expert in TB for further management and treatment is recommended.
Resources

**WHO map of global MDR-TB notification.**
http://www.who.int/tb/challenges/mdr/en/
Accessibility verified November 5, 2015.

**The Online TST/IGRA Interpreter.**
An online tool that estimates the risk of active TB for an individual with a TST reaction of $\geq 5$mm, based on his/her clinical profile.
http://www.tstin3d.com
Accessibility verified November 1, 2015.

**The BCG World Atlas.**
An interactive website providing detailed information on current and past BCG policies and practices for over 180 countries.
http://www.bcgatlas.org
Accessibility verified November 5, 2015.

References

- Centers for Disease Control and Prevention. Updated guidelines for the use of nucleic acid amplification tests in the diagnosis of tuberculosis. *MMWR.* 2009; 58 (01); 7-10.


