Recommendations to Reduce the Risk of Transmission of *Mycobacterium tuberculosis* (Mtb) by Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)

Guidance for Industry

This guidance is for immediate implementation.

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(3) without initially seeking prior comment because the agency has determined that prior public participation is not feasible or appropriate.

FDA invites comments on this guidance. Submit one set of either electronic or written comments on this guidance at any time. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

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U.S. Department of Health and Human Services
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Contains Nonbinding Recommendations

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This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

We, FDA, are issuing this guidance to assist you, establishments making donor eligibility (DE) determinations,[1] in understanding the requirements in 21 CFR part 1271, subpart C (21 CFR part 1271, subpart C). The regulations under 21 CFR part 1271, subpart C, set out requirements for determining donor eligibility, including donor screening and testing, for donors of human cells, tissues, and cellular and tissue-based products (HCT/Ps).[2] This guidance provides recommendations for screening donors for evidence of, and risk factors for, infection with *Mycobacterium tuberculosis* (Mtb), the organism that causes tuberculosis. The guidance also recommends additional steps that HCT/P establishments should take to reduce risk of transmission of Mtb until such time as appropriate FDA-licensed, approved, or cleared donor screening tests are available for use to test donors for Mtb infection.

This guidance identifies Mtb as a relevant communicable disease agent or disease (RCDAD) as defined in 21 CFR 1271.3(r)(2) and supplements the recommendations contained in other DE guidance documents for donors of HCT/Ps.[3]

FDA is implementing this guidance without prior public comment because the Agency has determined that prior public participation is not feasible or appropriate (see 21 CFR 10.115(g)(2)). FDA made this determination because there is an urgent public health need to reduce the risk of transmission of Mtb by HCT/Ps. FDA identified a safety concern when investigating reports of Mtb infections in recipients of allograft bone products.[4] These multi-

[1] See 21 CFR 1271.50.
[2] HCT/Ps are defined in 21 CFR 1271.3(d) as "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient."
[3] See generally https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/tissue-guidances.
[4] Centers for Disease Control and Prevention. Second Nationwide Tuberculosis Outbreak Caused by Bone Allografts Containing Live Cells — United States, 2023, MMWR Morb Mortal Wkly Rep. Jan 5, 2024; 72(5253);1385–1389.

state outbreaks indicated that there is a risk of transmission of Mtb infection by HCT/Ps. This guidance document is being implemented immediately, but it remains subject to comment in accordance with the Agency's good guidance practices (see 21 CFR 10.115(g)(3)).

In general, FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. *Mycobacterium tuberculosis* Epidemiology and Public Health Impact

Tuberculosis (TB) is a communicable disease caused by a group of genetically related *Mycobacteria* species collectively referred to as *Mycobacterium tuberculosis* complex. *Mycobacterium tuberculosis* (Mtb) is the most common organism within the Mtb complex to cause TB (Ref. 1). TB is a global health problem with a significant disease burden that can lead to chronic disability, and it is one of the top 10 causes of death worldwide (Refs. 1-7). Although the United States (U.S.) has one of the lowest TB rates in the world and has seen a substantial decline in the rate of TB over the last several decades, TB continues to remain a problem causing significant morbidity and mortality. During 2022, 8,300 new cases of TB disease were reported in the U.S., compared with 7,874 cases during 2021 (Refs. 8-10). Latent tuberculosis infection (LTBI) is estimated to affect a quarter of the world's population and approximately 13.2 million persons, or 4% to 5%, of the U.S. population (Refs. 7-8, 11). People with LTBI do not feel sick and do not have any symptoms. They are infected with Mtb, but do not have TB disease (Refs. 2, 11).

The majority of TB cases in the U.S. are due to reactivation of LTBI in persons who were born in or lived in countries where TB is endemic and the disease burden is moderate to high (e.g., Mexico, the Philippines, Vietnam, India, China, Haiti, Guatemala and other countries) (Refs. 16-19). One study estimated the prevalence of LTBI in the U.S. among this group to be 15.9% overall and ranged from 2.6% in persons aged 6-14 years to 32.1% in ages ≥ 65 years (Refs. 19-20).

Mtb transmission occurs primarily through inhalation of aerosol droplet nuclei containing the bacteria. Individuals who have infectious TB can expel droplet nuclei containing the bacteria through coughing, sneezing, speaking, and singing (Refs. 2, 21-24). Whether or not an individual develops TB infection or disease following an exposure is a function of their immune response to the inoculum of Mtb bacilli, and might lead to latent infection, a state in which Mtb bacteria survive in the body in a dormant state and there is no evidence of clinical disease (i.e., LTBI) (Refs. 1-2, 25).

Occupationally acquired TB infections have been reported among individuals exposed to

Mtb through aerosol generating procedures (e.g., irrigation of tuberculous infected wounds or abscesses, laboratory processing of infected tissues or other specimens, use of a bone saw on Mtb-infected bone). Healthcare workers acquired TB infections following direct inoculation of nonintact skin (Refs. 44-60), and from exposure to not only contaminated bone allograft products, but also to recipients of these products, during their wound and routine patient care, and to surgical instruments and medical waste associated with use of the bone allograft products (Ref. 61). Cutaneous TB from direct inoculation of skin has also been reported with tattoos, body piercings, acupuncture, autopsies, and surgical procedures that used unsterile equipment (Refs. 48-60, 62).

Risk factors for TB infection and disease include common conditions associated with impaired immunity (e.g., chronic kidney disease, diabetes mellitus, malignancy, immunosuppressive therapy, etc.), behavioral factors including substance abuse, tobacco use, and malnutrition, and environmental factors leading to increased exposure to individuals with infectious tuberculosis (e.g., living or working in crowded facilities such as homeless shelters, long-term care facilities and nursing homes, incarceration in jails, prisons, correctional facilities, and other congregate settings) (Refs. 11, 26-30).

TB may be underdiagnosed due to the need for a high index of clinical suspicion, inherent diagnostic difficulty, and/or attribution of the clinical syndrome to alternate causes. Persons with LTBI are, by definition, asymptomatic; and a person with TB disease might have symptoms or signs that can mimic or overlap with other medical conditions. Sepsis due to Mtb in hospitalized patients might not be identified during their admission and blood cultures and other specimen cultures may be negative (Refs. 31-36).

III. DISCUSSION

FDA has identified Mtb as an RCDAD under 21 CFR 1271.3(r)(2). This determination was based on the risk of transmission by HCT/Ps, severity of effect, and availability of appropriate screening and testing measures.

A. Risk of Transmission

There is a risk of transmission of Mtb by HCT/Ps. This is supported by evidence that Mtb can disseminate to organs and tissues via hematogenous, lymphatic, or contiguous spread which may result in infection of bone, ocular tissues, skin, and connected networks such as the central nervous system, and genitourinary tract (Refs. 1-2, 37), and congenital (perinatal) TB is transmitted in utero (Refs. 38-43).

In addition, because Mtb can be transmitted through inhalation of aerosol droplet nuclei containing the bacteria, there is a risk of transmission to those who may handle or otherwise come in contact with a contaminated HCT/P, such as medical personnel who may be exposed to such products or recipients of those HCT/Ps, or to medical waste or surgical instruments (Refs. 44-61).

1. Potential for Transmission of Mtb by Blood Products and Solid Organs

To date, there have been no documented cases of Mtb in humans transmitted through transfusion of blood or blood components and Mtb is not a relevant transfusion-transmitted infection (RTTI).[5]

Mtb has been transmitted through solid organ transplantation (including lung, liver, kidney, and heart) and has been associated with high morbidity and mortality (Refs. 63-75). All potential transmissions of Mtb reported to the Organ Procurement and Transplantation Network (OPTN) Ad Hoc Disease Transmission Advisory Committee between 2008 and 2018 were analyzed and, among 51 total reports, nine (17%) (9 donors/35 recipients) had 1 or more recipients with proven/probable donor-derived TB transmission, and all of these donors had one or more TB risk factors (i.e., born in a TB-endemic country, travel to a TB-endemic country, incarceration), or had a history of LTBI (Refs. 76-77).

2. Potential for Transmission of Mtb by HCT/Ps

Mtb has been transmitted by transplantation of allograft bone, heart valves, and dura mater (Refs. 31, 78-85). In 2021, a national outbreak of Mtb infection occurred in the U.S. associated with transplantation of a bone allograft product that resulted in significant morbidity and mortality (Ref. 31). A similar outbreak of donor-derived TB transmitted by a bone allograft product occurred in 2023 (Refs. 84-85).

Transmission of Mtb by HCT/Ps derived from gestational cells and tissues (e.g., amniotic membrane, umbilical cord tissue, umbilical cord blood), and cells and tissues for reproductive use, has not been reported. However, Mtb transmission between sexual partners has been reported (Refs. 86-90). Mtb has been detected in ovaries and semen (Refs. 86, 88, 89), and from related anatomical areas (e.g., cervix, fallopian tubes) (Refs. 88, 90). Mtb has also been identified in placenta in cases of chorioamnionitis and congenital TB (Refs. 38-43, 91-92).

Mtb DNA has been identified in hematopoietic progenitor/stem cells (HPCs) derived from peripheral blood and bone marrow of donors with LTBI, and viable Mtb has been cultured from mesenchymal stem cells in bone marrow of individuals previously considered to be successfully treated for pulmonary TB. Although transmission of Mtb via HPCs used in hematopoietic stem cell transplantation (HSCT) has not been previously reported, there remains a potential risk of transmission (Refs. 93-97). Additionally, typical HSCT recipients are severely immunocompromised which may increase their risk for TB and the severity of an infection.

Mtb infects dermal fibroblasts and can be detected in the skin of individuals with cutaneous TB using mycobacterial cultures or a polymerase chain reaction (PCR)

[5] 21 CFR 630.3(h).

assay for the detection of Mtb DNA (Refs. 48-60, 62). However, Mtb transmission to the recipients of skin or dermal allografts has not been reported.

Mtb transmission via ocular tissue has not been reported; however, Mtb has been detected in ocular tissues (i.e., cornea, sclera, and conjunctival tissues), and in fluids that have contact with ocular tissues, using mycobacterial cultures and/or PCR for Mtb DNA from individuals with systemic TB, LTBI, primary ocular TB, and retinal vasculitis due to Mtb (Refs. 98-101). Surgical procedures used during the recovery of corneas and sclera can potentially lead to cross contamination if Mtb organisms are present in the donor's blood or ocular fluids, particularly when whole globes are enucleated (Ref. 100).

HCT/Ps that are known to have transmitted Mtb are bone, heart valves, and dura mater. Because Mtb organisms have been detected in other HCT/P types, there remains a potential risk of Mtb transmission from HPCs, gestational cells and tissues, reproductive cells and tissues, skin, and corneas or sclera. In addition, TB has sufficient incidence and/or prevalence to affect the potential HCT/P donor population.

B. Severity of Effect

As described earlier, TB is one of the top 10 causes of death worldwide (Refs. 1-7). TB disease is associated with a risk for development of several complications including, but not limited to, neurological diseases, pulmonary disease, renal failure, heart failure, adrenal failure, thyroid dysfunction, osteomyelitis, sepsis, infertility, miscarriage, and complications in newborns from perinatal transmission (Refs. 102-126).

Infection with Mtb can be fatal or life-threatening, could result in permanent impairment of a body function or permanent damage to body structure, or could necessitate medical or surgical intervention to preclude permanent impairment of body function or permanent damage to a body structure.

C. Availability of Appropriate Screening and/or Testing Measures

Appropriate donor screening measures have been developed for reducing the risk of transmission of Mtb (discussed in section IV. A., B., and C. of this document), and screening measures are in place for evaluating evidence of infection in HCT/P donors to reduce the risk of transmission due to disease agents associated with sepsis,[6] which may be caused by Mtb.

There are currently no FDA-licensed, cleared, or approved donor screening tests for use in testing HCT/P donors for evidence of Mtb infection. However, a donor's medical record or medical history may include results of other tests for detection of immune response to or presence of Mtb, which are discussed below.

[6] Guidance for Industry, *Recommendations to Reduce the Risk of Transmission of Disease Agents Associated with Sepsis by Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)*, January 2025.

There are FDA-approved diagnostic products that can detect an immune response to TB antigens; examples include FDA-approved purified protein derivative (PPD) of tuberculin antigens injected intradermally for the tuberculin skin test (TST), and interferon-gamma release assay (IGRA) blood tests (e.g., T-SPOT.TB test and Quantiferon-TB Gold Plus test). Both types of tests measure immune sensitization to mycobacterial protein antigens that occurs following exposure to mycobacteria, and these tests should be used in conjunction with clinical risk assessment, radiography, and other medical and diagnostic evaluations to aid in the diagnosis of Mtb infection. These additional medical and diagnostic evaluations are essential to diagnosing TB disease and LTBI. When using the TST and IGRA tests, the person tested must have viable intact immune cells to produce an accurate result, which makes them impractical for evaluating TB risk for a cadaveric (non-heart beating) donor. A variety of factors can affect TST and/or IGRA test performance, including recent infection (i.e., testing before a cell-mediated immune response has developed), age, receipt of Bacillus Calmette-Guerin (BCG) vaccine, and impaired immunity, specifically, T-lymphocyte mediated cellular immunity (Refs. 130-136). Negative tests results do not exclude LTBI or TB disease.

FDA-cleared diagnostic tests, such as nucleic acid amplification tests (NAAT), including PCR tests, for the detection of Mtb in respiratory specimens (e.g., sputum) are also available. The results of such tests are not intended to be used in isolation and are to be used as an adjunct to other laboratory tests and clinical findings.[7] A negative result does not exclude Mtb infection (Refs. 17, 31, 127-130). We note that PCR testing of a bone product from an infected donor has not consistently provided the level of sensitivity necessary to identify presence of TB (Refs. 31, 85), and FDA has not authorized a PCR test for the detection of Mtb using a bone specimen.

Detection of acid-fast bacilli (AFB) in stained and acid-washed smears examined microscopically may provide initial bacteriologic evidence of the presence of mycobacteria in clinical specimens. However, AFB smears should be collected on three consecutive days to increase sensitivity, AFB smears may produce false negative results due to a variety of reasons (e.g., low levels of Mtb in the specimen, microscope and technologist issues, etc.), and negative results from smears do not exclude LTBI or TB disease (Refs. 127-130).

Mycobacterial cultures to detect AFB require specific growth media and may take 4 to 8 weeks to grow the bacilli organism (Ref. 128). CDC considers a positive culture for Mtb to confirm the diagnosis of TB disease (Ref. 130), and clinical practice guidelines for diagnosis of TB 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 (Ref. 130). Although 20% of U.S. TB cases were not culture confirmed (Ref. 127), AFB cultures showed growth when bone product specimens were tested during the investigations of both outbreaks in the U.S.,

[7] See, e.g., 21 CFR 866.3372 and Class II Special Controls Guideline: Nucleic Acid-Based In Vitro Diagnostic Devices for the Detection of *Mycobacterium tuberculosis* Complex in Respiratory Specimens.

including when PCR testing was negative (Refs. 31, 85).

IV. RECOMMENDATIONS

As noted in sections I. and III. of this document, FDA has identified Mtb as an RCDAD as defined in 21 CFR 1271.3(r)(2). The following recommendations and policies are intended to reduce the risk of transmission of Mtb by HCT/Ps.

A. Screening a Donor for Risk Factors and Conditions for Mtb Infection

Unless an exception identified in 21 CFR 1271.90(a) applies, you must review relevant medical records and ask questions about the donor's medical history and relevant social behavior, including risk factors for RCDADs (21 CFR 1271.3(s), 21 CFR 1271.75(a)). You should also screen the birth mother when an infant donor is less than 1 month of age. In accordance with 21 CFR 1271.75(d), you must determine to be ineligible any potential HCT/P donor who is identified as having a risk factor for Mtb infection. The following should be considered risk factors:

1. A positive test for TB infection or a medical diagnosis of TB disease, TB infection, or LTBI (Refs. 31-36, 38-43, 62, 78-86, 91-97).

During review of relevant medical records, including the donor medical history interview, the following information should also be obtained and considered, in light of other information about the donor (Refs. 11, 16-20, 23, 26-31):

- Persons who were born in, have ever lived in, or ever traveled to areas of the world where TB is common (e.g., most countries in Latin America, the Caribbean, Africa, Asia, Eastern Europe, and Russia);
- Persons who have ever lived in or worked in high-risk congregate settings (e.g., jails, prisons, correctional facilities, long-term care facilities, homeless shelters);
- Persons who ever lived with, or have been a close contact with, another person who has TB; or
- Persons who have certain medical conditions (e.g., diabetes, chronic kidney disease/end stage renal disease with or without dialysis), or are on medication, that can impair immune function.

A donor who falls into any of the categories described in the bullets above might be eligible provided there is no clinical or physical evidence, or suspicion, of LTBI or TB disease, and no communicable disease risks have been identified (discussed in section IV. B. and C. of this guidance).

B. Screening a Donor for Clinical Evidence of Mtb Infection

Unless an exception identified in 21 CFR 1271.90(a) applies, you must review relevant medical records for clinical evidence of RCDADs (21 CFR 1271.75).

For cadaveric (non-heart beating) donors, establishments should:

- Determine whether an autopsy was not performed due to a perceived risk of transmission of a communicable disease, including TB, or,
- If an autopsy was performed, whether any special precautions were taken that would suggest there was special concern regarding the risk of transmission of TB from the donor.

If an autopsy was performed, you should wait for the final autopsy report unless it would compromise the utility of the tissue, for example, because your HCT/P (e.g., cornea) needs to be released within a limited timeframe.

In accordance with 21 CFR 1271.75(d), you must determine to be ineligible any potential HCT/P donor who exhibits clinical evidence of Mtb infection (Refs. 17, 31-36, 38-43, 48-62, 78-101, 127-136). Examples of clinical evidence of Mtb infection:

1. Persons who have ever had a medical diagnosis of TB disease or LTBI; or

2. Persons who have ever had a positive test for TB infection or TB disease. For example, a positive blood test such as Interferon Gamma Release Assay (IGRA) (e.g., T-SPOT.TB, QuantiFERON-TB Gold Plus, QuantiFERON-TB Gold In-Tube), a positive tuberculin skin test (TST) (also known as PPD, Mantoux, or tine test), or a positive test for TB infection on any specimen (i.e., mycobacterial culture, NAAT or PCR for Mtb DNA).

A person with TB disease may have a number of symptoms or signs that can mimic or overlap with other medical conditions. A person with symptoms of TB disease may have one or more of the following types of clinical evidence of Mtb infection that should be considered when making a donor eligibility determination (Refs. 2-3, 43-46, 98-127):

- cough lasting 3 weeks or longer;
- chest pain;
- coughing up blood (hemoptysis) or sputum (pulmonary TB);
- weakness or fatigue;
- unexplained weight loss or muscle wasting (cachexia or consumption);
- loss of appetite;
- fever, chills, night sweats;
- generalized or localized lymphadenopathy or lymphadenitis;
- blood in the urine (renal TB);
- headache or confusion (TB meningitis);
- back pain (TB of the spine);
- hoarseness (TB of the larynx); or
- radiographic imaging (e.g., x-ray or CT scan) suggestive of TB disease.

When a potential donor has one or more symptoms or signs above, you should document your communication with their primary treating physician to obtain additional information regarding their patient's potential for TB infection or LTBI, unless TB has already been ruled out by the patient's primary treating physician.

C. Screening a Donor for Physical Evidence of Mtb Infection

Relevant medical records (21 CFR 1271.3(s)) include the report of the physical assessment of a cadaveric (non-heart beating) donor (21 CFR 1271.3(o)) or the physical examination of a living donor. Unless an exception identified in 21 CFR 1271.90(a) applies, in accordance with 21 CFR 1271.75(d)(1), you must determine to be ineligible any potential HCT/P donor who has risk factors for or clinical evidence of TB infection. The following are examples of physical evidence associated with TB infection:

1. Generalized lymphadenopathy (Refs. 111-112).

2. Unexplained cutaneous lesions that may be consistent with tuberculosis (Refs. 44-52).

D. Testing a Donor for Evidence of Mtb infection

Under 21 CFR 1271.80(c), establishments must use appropriate FDA-licensed, approved, or cleared donor screening tests in accordance with the manufacturer's instructions to adequately and appropriately reduce the risk of transmission of RCDADs, such as Mtb. As discussed above, FDA-approved and -cleared products for the detection of immune response to or presence of Mtb are available. However, there are currently no FDA-licensed, cleared, or approved donor screening tests for use in testing HCT/P donors for evidence of Mtb infection.

Following investigations of TB outbreaks linked to HCT/Ps, FDA recognizes the public health need to reduce risk of Mtb transmission by HCT/Ps, given the morbidity and mortality experienced after recent, multistate outbreaks. We also recognize that, with the current absence of FDA-licensed, cleared, or approved donor screening tests for Mtb, HCT/P establishments may wish to use products described in section III.C, such as FDA-cleared diagnostic tests, to test HCT/P donors to help reduce risk of transmission. In light of these considerations, FDA does not intend to object if an establishment chooses to collect a specimen from a living donor of HCT/Ps (or while the donor's heart is still beating) and test for evidence of Mtb infection using a test discussed in section III.C, even though such tests are not FDA-licensed, cleared, or approved as donor screening tests.[8] FDA would not consider a negative or nonreactive

[8] FDA also generally does not intend to take action against a manufacturer of a test described in section III.C. where the manufacturer offers such a test to an HCT/P establishment to test donors for evidence of Mtb infection while there are no FDA-licensed, approved, or cleared donor screening tests available. This policy does not otherwise change FDA's expectations regarding these manufacturer's compliance with applicable device requirements, such as submission of medical device reports in accordance with 21 CFR part 803.

test result obtained from such testing to override other clinical and physical evidence of, and risk factors for, Mtb infection discussed in section IV. A., B., and C. of this guidance. In addition, when making a donor eligibility determination, you should consider any negative or nonreactive test result obtained using the tests described above along with such clinical and physical evidence, and risk factors.

FDA expects establishments to use appropriate licensed, approved, or cleared Mtb donor screening tests once such tests are available.

E. Additional Risk Reduction Measures

During the investigation of both Mtb outbreaks in the U.S., mycobacterial cultures of bone product specimens showed growth, including when PCR testing was negative (Refs. 31, 85). Based on this information and considering the type of HCT/Ps that are known to have transmitted Mtb, performing AFB cultures for bone, heart valves, and dura mater can help mitigate the risk of Mtb transmission. Therefore, as an interim measure, until appropriate FDA-licensed, approved, or cleared donor screening tests for Mtb are available, we recommend:

1. Manufacturers that process bone[9], heart valves, or dura mater should select appropriate liquid and solid mycobacterial cultures (AFB cultures) to test for presence of Mtb using appropriate pre-processing donor specimens when the disinfection or sterilization process used has not been validated to demonstrate the capability to eliminate contamination with Mtb. Both liquid and solid mycobacterial cultures should be performed, rather than either culture method alone (Refs. 127-130).

   The specimen selected for testing should be representative of the HCT/P to be evaluated. FDA recommends manufacturers evaluate the suitability of both AFB culture methods regarding use of adequate controls to detect inhibition and to use voluntary standards from a Standards Development Organization (Ref. 128).

2. If a donor specimen selected for testing, as described above, has a positive AFB culture (shows growth), you should discard not only the bone, heart valves, or dura mater from that donor that has a positive AFB culture, but also all HCT/P types recovered from that donor. If growth is a mixed culture, an assessment for contamination is recommended (Ref. 128). If the donor specimen has a negative AFB culture (no growth), you should consider the potential for false negative culture results (Refs. 127-129).

While we do not consider these additional steps to be part of the donor testing required under 21 CFR 1271.80, FDA believes that performing AFB culture, as recommended

[9] For clarity, this does not include minimally manipulated bone marrow for homologous use and not combined with another article, which is excepted from the definition of an HCT/P under 21 CFR 1271.3(d)(4).

above, is an important interim measure to address safety concerns regarding TB transmission from HCT/Ps.[10] You should follow your procedures for sharing with other establishments information pertaining to possible contamination or potential for transmission of communicable disease, and you are responsible for sharing this information with other establishments that recovered or received HCT/Ps from the same donor (21 CFR 1271.160(b)(2)(i)).

V. IMPLEMENTATION

FDA recommends that you implement the recommendations in this guidance as soon as feasible, but not later than 4 weeks after the guidance issue date.

[10] We also note that an establishment that processes HCT/Ps "must process each HCT/P in a way that does not cause contamination or cross-contamination during processing, and that prevents the introduction, transmission, or spread of communicable disease through the use of the HCT/P" (21 CFR 1271.220(a)). In addition, establishments "must recover, process, store, label, package, and distribute HCT/Ps, and screen and test cell and tissue donors, in a way that prevents the introduction, transmission, or spread of communicable diseases" (21 CFR 1271.145).

VI. REFERENCES

1. Forellad, M.A., et al., Virulence factors of the Mycobacterium tuberculosis complex. Virulence. 2013 Jan 1; 4(1):3-66.
2. Dhedra, K., et al., Tuberculosis. Lancet. 2016 Mar 19; 387(10024):1211-1226. doi: 10.1016/S0140-6736(15)00151-00158.
3. Tiemersma, E.W., et al., Natural history of tuberculosis: duration and fatality of untreated pulmonary tuberculosis in HIV negative patients: a systematic review. PLoS One 2011; 6: e17601.6/S0140-6736(15)00151-00158. Epub 2015 Sep 13.
4. Houben, R.M.and Dodd, P.J., The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling. *PLoS Med*. 2016; 13(10):e1002152. Epub 2016 Oct 25.
5. Floyd, K., et al., Global tuberculosis targets and milestones set for 2016–2035: definition and rationale. Int J Tuberc Lung Dis. 2018; 22(7):723–730.
6. World Health Organization. Global Tuberculosis Report 2022. https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022 (Accessed on August 23, 2023).
7. Cohen, A., Mathiasen, et al., The global prevalence of latent tuberculosis: a systematic review and meta-analysis. Eur Respir J 2019; 54: 1900655.
8. Miramontes, R., et al., Tuberculosis Infection in the United States: Prevalence Estimates from the National Health and Nutrition Examination Survey, 2011-2012. 2015; 10(11): e0140881.
9. Filardo, T.D., et al., Tuberculosis — United States, 2021. MMWR Morb Mortal Wkly Rep. 2022 Mar 25; 71(12):441-446.
10. Schildknecht, K.R., et al., Tuberculosis – United States, 2022. MMWR Morb Mortal Wkly Rep. 2023 Mar 24; 72 (12):297-303.
11. US Preventive Services Task Force; Mangione CM, et al. Screening for Latent Tuberculosis Infection in Adults US Preventive Services Task Force Recommendation Statement. JAMA. 2023 May 2; 329(17):1487-1494.
12. Hofmeister, M.G., et al., Estimating prevalence of hepatitis C Virus Infection in the United States, 2013-2016. Hepatology. 2019 Mar; 69(3):1020-1031.
13. Edlin, B., et al., Toward a more accurate estimate of the prevalence of hepatitis C in the United States. Hepatology. 2015 Nov; 62(5):1353-1363.
14. Centers for Disease Control and Prevention. Estimated HIV incidence and prevalence in the United States 2017–2021. HIV Surveillance Supplemental Report 2023; 28(4).
15. Centers for Disease Control and Prevention. Viral Hepatitis Surveillance—United States, 2021. Atlanta: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2021. https://www.cdc.gov/hepatitis/statistics/2021surveillance/hepatitis-c.htm.
16. Deutsch-Feldman, M., et al., Tuberculosis - United States, 2020. Morb Mortal Wkly Rep. 2021; 70(12):409. Epub 2021 Mar 26.
17. Centers for Disease Control and Prevention. Reported TB in the United States, 2019 surveillance report. Atlanta, GA: US Department of Health and Human Services, CDC; 2020. https://www.cdc.gov/tb/statistics/reports/2019/default.htm.

18. Collins, J.M., et al., Prevalence of Latent Tuberculosis Infection Among Non-US-Born Persons by Country of Birth—United States, 2012–2017. Clin Infect Dis. 2020 Nov 2; ciaa1662.
19. Tsang, C.A., et al., US Tuberculosis Rates among Persons Born Outside the United States Compared with Rates in Their Countries of Birth, 2012–2016. Emerg Infect Dis. 2020 March; 26(3):533-540.
20. World Health Organization. Use of high burden country lists for TB by WHO in the post-2015 era: Summary: World Health Organization. https://cdn.who.int/media/docs/default-source/hq-tuberculosis/who_globalhbcliststb_2021-2025_backgrounddocument.pdf?sfvrsn=f6b854c2_9.
21. Sepkowitz, K.A., How contagious is tuberculosis? Clin Infect Dis. 1996; 23(5):954.
22. Loudon, R.G. and Spohn, S.K., Cough frequency and infectivity in patients with pulmonary tuberculosis. Am Rev Respir Dis. 1969; 99(1):109.
23. Loudon, R.G. and Roberts, R.M., Droplet expulsion from the respiratory tract. Am Rev Respir Dis. 1967; 95(3):435.
24. Loudon, R.G. and Roberts R.M., Singing and the dissemination of tuberculosis. Am Rev Respir Dis. 1968; 98(2):297.
25. Jacobs, A.J. et al., Antibodies and Tuberculosis. Tuberculosis (Edinb). 2016 Dec; 101:102–113.
26. Segall, L. and Covic, A., Diagnosis of tuberculosis in dialysis patients: current strategy. Clin J Am Soc Nephrol; 2010 Jun; 5(6):1114-1122.
27. Dobler, C.C., et al., Risk of tuberculosis in dialysis patients: a nationwide cohort study. PLoS One. 2011; 6(12):e29563. doi: 10.1371/journal.pone.0029563.
28. Christopoulos, A.I., et al., Risk factors for tuberculosis in dialysis patients: a prospective multi-center clinical trial. BMC Nephrol 10, 36 (2009). https://doi.org/10.1186/1471-2369-10-36.
29. Centers for Disease Control and Prevention. Who Should Be Tested for TB Infection? https://www.cdc.gov/tb/risk-factors/?CDC_AAref_Val=https://www.cdc.gov/tb/topic/testing/whobetested.htm.
30. NGUMC | Tuberculosis Outbreak Warning Issued for Those Who Work or Volunteer in Homeless Shelters in Downtown Atlanta, August 4, 2014. https://www.ngumc.org/newsdetail/195121.
31. Schwartz, N.G., et al., Nationwide tuberculosis outbreak in the USA linked to a bone graft product: an outbreak report. Lancet Infect Dis. 2022 Nov; 22(11): 1617–1625.
32. Mishra, R., Patel, H.K., Singasani, R., Vakde, T. Tuberculosis septic shock, an elusive pathophysiology and hurdles in management: a case report and review of literature. World J Crit Care Med. 2019; 8:72–81.
33. Kethireddy, S., Light, R.B., Mirzanejad, Y., et al. Mycobacterium tuberculosis septic shock. Chest. 2013; 144:474–482.
34. Arya, V., et al. Tuberculosis-Associated Septic Shock: A Case Series. Cureus. 2022 Mar; 14(3): e23259.
35. Jog, S., Pawar, B., Patel, D. Mycobacterial Sepsis and Multiorgan Failure

Syndrome. Annual Update in Intensive Care and Emergency Medicine 2011; 1: 531–542.
36. Adegbite, B.R., et al., Clinical features, treatment outcomes and mortality risk of tuberculosis sepsis in HIV-negative patients: a systematic review and meta-analysis of case reports. Infection. 2023; 51(3): 609–621.
37. Wu, I.L., Chitnis, A.S., Jaganath, D. A narrative review of tuberculosis in the United States among persons aged 65 years and older. J Clin Tuberc Other Mycobact Dis. 2022 Jun 13; 28:100321.
38. El-Messidi, A., Czuzoj-Shulman, N., Spence A., Abenhaim H. Medical and obstetric outcomes among pregnant women with tuberculosis: a population-based study of 7.8 million births. Am J Obstet Gynecol. 2016; 215:797.e1–797.e6.
39. Peng, W., Yang, J., Liu, E. Analysis of 170 cases of congenital TB reported in the literature between 1946 and 2009. Pediatr Pulmonol. 2011; 46:1215–1224.
40. Schaaf, H.S., Collins, A., Bekker, A., Davies, P.D.O. Tuberculosis at extremes of age. Respirology. 2010; 15:747–763.
41. Smith, K.C. Congenital tuberculosis: a rare manifestation of a common infection. Curr Opin Infect Dis. 2002; 15:269–274.
42. Miele K, Rock RB, LaCourse SM, et al. Notes from the Field: Undiagnosed Tuberculosis During Pregnancy Resulting in a Neonatal Death — United States, 2021. MMWR Morb Mortal Wkly Rep 2023; 72:1331–1332. DOI: http://dx.doi.org/10.15585/mmwr.mm7249a4 .
43. Mony, V.K., Polin, J., Adler, E., et al., Congenital tuberculosis: a missed opportunity. J Pediatric Infect Dis Soc. 2014; 3:e45–e47.
44. MacGregor, R.R. Cutaneous tuberculosis. Clin Dermatol. 1995; 13(3):245.
45. Tapias, L., et al. Primary cutaneous inoculation tuberculosis in a healthcare worker as a result of a surgical accident. Int J Dermatol. 2008; 47:833–835.
46. Minkowitz, S., et al., "Prosector's wart" (cutaneous tuberculosis) in a medical student. Am J Clin Pathol. 1969 Feb; 51(2):260-263.
47. Soto-Febre, F., et al., Cutaneous inoculation tuberculosis in a healthcare worker: Case report and literature review. ID Cases. 2020 May 7; 20:e00788.
48. Hutton, M.D., et al. Nosocomial transmission of tuberculosis associated with a draining abscess. J Infect Dis. 1990 Feb; 161(2):286-295.
49. Kim, J.K. Three cases of primary inoculation tuberculosis as a result of illegal acupuncture. Ann Dermatol. 2010; 22(3):341. Epub 2010 Aug 5.
50. Rutala, W.A., Weber DJ. Disinfection and Sterilization in Health Care Facilities: What Clinicians Need to Know. Clin Infect Dis. 2004 Sep 1; 39(5):702-709.
51. Kluger, N. Cutaneous infections related to permanent tattooing. Med Mal Infect. 2011 Mar; 41(3):115-122. Epub 2010 Dec 8.
52. Kaur, C., et al., How safe is nose-piercing? Inoculation cutaneous tuberculosis revisited. Int J Dermatol. 2003 Aug; 42(8):645-646.
53. Gao, W., Zeng, Y., Chen, W. Multiple subcutaneous tuberculous abscesses in a dermatomyositis patient without pulmonary tuberculosis: a case report and literature review. BMC Infect Dis. 2020 Jun 12; 20(1):409. doi: 10.1186/s12879-020-05137-w.
54. Pike, R.M. Laboratory-associated infections: summary and analysis of 3,921 cases. Hlth Lab Sci 1976; 13:105-114.

55. Miller, C.D., Songer, J.R., Sullivan, J.F. A twenty-five-year review of laboratory-acquired human infections at the National Animal Disease Center. Am Ind Hyg Assoc J. 1987; 48:271-275.
56. Grist, N.R., Emslie JA. Infections in British clinical laboratories, 1982-1983. J ClinPathol. 1985; 38:721-725.
57. Muller, H.E. Laboratory-acquired mycobacterial infection. Lancet. 1988; 2:331.
58. Pike, R.M., et al., Continuing importance of laboratory-acquired infections. Am J Public Health Nations Health. 1965; 55:190-199.
59. Bates, J.H., et al. Epidemiology of Primary tuberculosis in an industrial school. N Engl J Med. 1965; 272:714.
60. Wenner, L., et al., Aerosol Generation During Bone-Sawing Procedures in Veterinary Autopsies. Vet Pathol. 2017; Vol. 54(3) 425-436.
61. Li, R., et al., Transmission of Mycobacterium Tuberculosis to Healthcare Personnel Resulting From Contaminated Bone Graft Material, United States, June 2021–August 2022. Clin Infect Dis. 2023 May 24; 76(10):1847-1849.
62. Keijman, J., et al., Unusual nosocomial transmission of Mycobacterium tuberculosis. Eur J Clin Microbiol Infect Dis. 2001 Nov; 20(11):808-809.
63. Mourad, G. Transmission of Mycobacterium tuberculosis with renal allografts. Nephron. 1985; 41(1):82-85.
64. Graham, J.C., et al., Tuberculosis transmitted through transplantation. J Infect. 2001 Nov; 43(4):251-254.
65. Centers for Disease Control and Prevention. Transplantation-transmitted tuberculosis—Oklahoma and Texas, 2007. MMWR Morb Mortal Wkly Rep. 2008 Apr 4; 57(13):333-336.
66. Mortensen, E., et al., Three cases of donor-derived pulmonary tuberculosis in lung transplant recipients and review of 12 previously reported cases: opportunities for early diagnosis and prevention. Transpl Infect Dis. 2014 February; 16(1): 67–75.
67. Coll, E., et al., Three cases of donor-derived pulmonary tuberculosis in lung transplant recipients and review of 12 previously reported cases: opportunities for early diagnosis and prevention. Transpl Infect Dis. 2014 Feb; 16(1):67-75.
68. Ruijter, B.N., et al., Donor-derived tuberculosis via orthotopic liver transplantation. Neth J Med. 2017 Nov; 75(9):415-417.
69. Kay, A., et al., Solid Organ Transplant–Transmitted Tuberculosis Linked to a Community Outbreak — California, 2015. MMWR Morb Mortal Wkly Rep. 2017 Aug 4; 66(30):801-805.
70. Morris, M.I., et al., Diagnosis and Management of Tuberculosis in Transplant Donors: A Donor-Derived Infections Consensus Conference Report. Am J Transplant. 2012 Sep; 12(9):2288-2300. Epub 2012 Aug 6.
71. Weile, J., et al. First case of Mycobacterium tuberculosis transmission by heart transplantation from donor to recipient. Int J Med Microbiol. 2013 Dec; 303(8):449-451.
72. Abad, C.L.R., Razonable, R.R. Donor derived Mycobacterium tuberculosis infection after solid-organ transplantation: A comprehensive review. Transplant infectious disease: an official journal of the Transplantation Society. 2018;

20(5):e12971.
73. Jones, J.M., Vikram, H.R., Lauzardo, M., Hill, A., Jones J., Haley, C., et al. Tuberculosis transmission across three states: The story of a solid organ donor born in an endemic country, 2018. Transplant Infectious Disease. 2020; 22(6).
74. Edathodu, J., Alrajhi, A., Halim, M., Althawadi, S. Multi-recipient donor-transmitted tuberculosis. The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease. 2010; 14(11):1493-1495.
75. Shingde, R., Habachou, L.I., Calisa, V., Craig, J.C., Tong, A., Chen, S.C., et al. Unexpected donor-derived infectious transmissions by kidney transplantation: A systematic review. Transplant infectious disease: an official journal of the Transplantation Society. 2018; 20(2):e12851.
76. Malinis, M., La Hoz, R.M., Vece, G., Annambhotla, P., et al. Donor-derived tuberculosis among solid organ transplant recipients in the United States—2008 to 2018. Transplant Infectious Disease, 13982273, Apr 2022, Vol. 24, Issue 2. DOI: 10.1111/tid.13800.
77. Organ Procurement and Transplantation Network. Guidance for Identifying Risk Factors for Mycobacterium tuberculosis (MTB) During Evaluation of Potential Living Kidney Donors. 11-13-2022. https://optn.transplant.hrsa.gov/professionals/by-topic/guidance/guidance-for-identifying-risk-factors-for-mycobacterium-tuberculosis-mtb-during-evaluation-of-potential-living-kidney-donors/
78. James, J.I. Tuberculosis transmitted by banked bone. J Bone Joint Surg Br 1953; 35-B: 578.
79. Sanus, G.Z., Tanriverdi, T., Tutunculer, B., Ulu, M.O., Ozyurt, E. Central nervous system tuberculosis subsequent to dural grafting. Can J Neurol Sci 2008; 35: 531–534.
80. Warwick, R.M., et al. Mycobacteria and allograft heart valve banking: an international survey. J Hosp Infect 2008; 68:255–261.
81. Khanna, S.K., Munro, J.L. Homograft aortic valve replacement: Seven years' experience with antibiotic treated valves . Thorax 1981; 36:330–337.
82. Anyanwu, C.H., Nassau, E., Yacoub, M. Miliary tuberculosis following homograft valve replacement. Thorax 1976; 31: 101–106.
83. Eastlund, T., Warwick, R.M. Diseases Transmitted by Transplantation of Tissue and Cell Allografts. Chapter 4 in Tissue & Cell Clinical Use: An Essential Guide, Blackwell Publishing Ltd., 2012.
84. CDC: Tuberculosis (TB) Disease Associated with Suspected Contaminated Viable Bone Matrix Material Used in Surgical and Dental Procedures | HAI | CDC. https://archive.cdc.gov/#/details?url=https://www.cdc.gov/hai/outbreaks/TB-bone-allograft.html.
85. Centers for Disease Control and Prevention. Second Nationwide Tuberculosis Outbreak Caused by Bone Allografts Containing Live Cells — United States, 2023, MMWR Morb Mortal Wkly Rep. Jan 5, 2024; 72(5253);1385–1389.
86. Angus, B.J., et al., Cutaneous Tuberculosis of the Penis and Sexual Transmission of Tuberculosis Confirmed by Molecular Typing. Clin Infect Dis. 2001 Dec 1;

33(11):E132-134.
87. Richards, M.J., Angus, D. Possible sexual transmission of genitourinary tuberculosis [letter]. Int J Tuberc Lung Dis 1998; 2:439.
88. Das P, Ahuja A, Gupta SD. Incidence, etiopathogenesis and pathological aspects of genitourinary tuberculosis in India: A journey revisited. Indian J Urol. 2008 Jul; 24(3):356-361. doi: 10.4103/0970-1591.42618. PMID: 19468469; PMCID: PMC2684356.
89. Veenema, R.J., Lattimer, J.K. Genital tuberculosis in the male: clinical pathology and effect on fertility. J. Urol. 78, 65–77 (1957).
90. Sachan R, Patel ML, Gupta P, Verma AK. Genital tuberculosis with variable presentation: a series of three cases. BMJ Case Rep. 2012 Aug 27; bcr2012006665. doi: 10.1136/bcr-2012-006665. PMID: 22927283; PMCID: PMC4543748.
91. Samedi, V., et al. Congenital tuberculosis in an extremely preterm infant conceived after in vitro fertilization: case report. BMC Pregnancy Childbirth. 2017 Feb 20; 17(1):66.
92. Taweevisit, M., et al., Intrauterine Tuberculosis Manifesting as Acute Chorioamnionitis: A Case Report and Review of the Literature. Pediatr Dev Pathol. Jul-Aug 2015; 18(4):335-338.
93. Munoz, L., Santin, M. Prevention and Management of Tuberculosis in Transplant Recipients: From Guidelines to Clinical Practice. Transplantation 2016; 100:1840–1852.
94. Belay, M., et al., Detection of Mycobacterium tuberculosis complex DNA in CD34-positive peripheral blood mononuclear cells of asymptomatic tuberculosis contacts: an observational study Lancet Microbe. 2021 Jun; 2(6):e267-e275
95. Tornak, J., et al., Human and Mouse Hematopoietic Stem Cells Are a Depot for Dormant Mycobacterium tuberculosis. PLoS One. 2017 Jan 3; 12(1):e0169119.
96. Das, B., et al., CD271+ Bone Marrow Mesenchymal Stem Cells May Provide a Niche for Dormant Mycobacterium tuberculosis. Sci Transl Med. 2013 Jan 30; 5(170):170ra13.
97. Mayito, J., et al., Anatomic and Cellular Niches for Mycobacterium tuberculosis in Latent Tuberculosis Infection. J Infect Dis. 2019 Feb 15; 219(5):685-694.
98. Albert, D.L., Raven, R.L. Ocular Tuberculosis. Microbiol Spectr. 2016 Nov; 4(6):10.1128/microbiolspec.TNMI7-0001-2016.
99. Yeh, S., et al., Update on ocular tuberculosis. Curr Opin Ophthalmol. 2012 Nov; 23(6):551-556.
100. Dubord, P.J., et al., Eye Banking and Corneal Transplantation Communicable Adverse Incidents Current Status and Project NOTIFY. Cornea. 2013 Aug; 32(8):1155-1166.
101. Catedral, E.J., et al., Detection of Mycobacterium tuberculosis in corneas from donors with active tuberculosis disease through polymerase chain reaction and culture. Br J Ophthalmol. 2010 Jul; 94(7):894-897.
102. Canham, E.C., Iseman, M. Guillain-Barré syndrome related to pulmonary tuberculosis. Ann Am Thorac Soc. 2014 Jun; 11(5):855-857.
103. Choyke, P.L. Adult-onset pulmonary tuberculosis. Radiology. 1983;

148(2):357.
104. Krysl, J. Radiologic features of pulmonary tuberculosis: an assessment of 188 cases. Can Assoc Radiol J. 1994; 45(2):101.
105. Khan, M.A. Clinical and roentgenographic spectrum of pulmonary tuberculosis in the adult. Am J Med. 1977; 62(1):31.
106. Barnes, P.F., et al., Chest roentgenogram in pulmonary tuberculosis. New data on an old test. Chest. 1988; 94(2):316.
107. Arango, L., et al., The spectrum of tuberculosis as currently seen in a metropolitan hospital. Am Rev Respir Dis. 1973; 108(4):805.
108. MacGregor, R.R. A year's experience with tuberculosis in a private urban teaching hospital in the postsanatorium era. Am J Med. 1975; 58(2):221.
109. Pérez-Guzmán, C. Does aging modify pulmonary tuberculosis? A meta-analytical review. Chest. 1999; 116(4):961.
110. Seiden, H.S., Thomas, P. Endobronchial tuberculosis and its sequelae. Can Med Assoc J. 1981; 124(2):165.
111. Rieder, H.L., et al., Extrapulmonary tuberculosis in the United States. Am Rev Respir Dis. 1990; 141(2):347.
112. Peto, H.M., et al., Epidemiology of extrapulmonary tuberculosis in the United States, 1993-2006. Clin Infect Dis. 2009; 49(9):1350.
113. Golzarian, J., et al., Tuberculous pseudoaneurysm of the descending thoracic aorta: successful treatment by surgical excision and primary repair. Tex Heart Inst J. 1999; 26:232–235.
114. Mayosi, B.M., Burgess, L.J., Doubell, A.F. Tuberculous pericarditis. Circulation. 2005; 112:3608–3616.
115. Choi, E.H., et al., Gastrointestinal tuberculosis. Microbiol Spectr. 2016 Dec; 4(6).
116. Vinnard, C., Blumberg, E.A. Endocrine and metabolic aspects of tuberculosis. Microbiol Spectr. 2017 Jan; 5(1):10.
117. Shah, M., Reed, C. Complications of tuberculosis. Curr Opin Infect Dis. 2014 Oct; 27(5):403-410.
118. Leonard, M.K., Blumberg, H.M. Musculoskeletal tuberculosis. Microbiol Spectr. 2017 Apr; 5(2).
119. Hogan, J., et al., Mycobacterial Musculoskeletal Infections. Infect Dis Clin North Am. 2017 Jun; 31(2):369-382.
120. Al-Qattan, M.M., et al., Tuberculosis of the Hand. J Hand Surg Am. 2011 Aug; 36(8):1413-1421.
121. Franceschi, F., et al., Isolated tuberculosis of the patellar tendon. J Bone Joint Surg Br. 2007 Nov; 89(11):1525-1526.
122. Varshney, M.K., et al., Isolated tuberculosis of Achilles tendon. Joint Bone Spine. 2007 Jan; 74(1):103-106.
123. Abdel Razic, M.M., el Morsy, F.E. Genitourinary mycobacteria in infertile Egyptian men. Fertil Steril. 1990 Oct; 54(4):713-717.
124. Lenk, S., Schroeder, J. Genitourinary tuberculosis. Curr Opin Urol. 2001 Jan; 11(1):93-98.
125. Muneer, A., et al., Urogenital tuberculosis - epidemiology, pathogenesis and clinical features. Nat Rev Urol. 2019 Oct; 16(10):573-598.
126. El Sahly, H.M., et al., Mycobacterium tuberculosis bacteraemia: experience

from a non-endemic urban centre. Clin Microbiol Infect. 2014 Mar; 20(3):263-268.

127. Asghar, M., et al., Sputum Smear and Culture-negative Tuberculosis with Associated Pleural Effusion: A Diagnostic Challenge. Cureus. 2018 Oct; 10(10): e3513.
128. Clinical Laboratory Standards Institute (CLSI) standards in M48, Laboratory Detection and Isolation of Mycobacteria. (current edition).
129. Centers for Disease Control and Prevention. Diagnosing Latent TB Infection & TB Disease. https://www.cdc.gov/tb/testing/diagnosing-tuberculosis.html?CDC_AAref_Val=https://www.cdc.gov/tb/topic/testing/diagnosingltbi.htm
130. Lewinsohn, D.M., Leonard, M.K., LoBue, P.A., et al., Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention. Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. Clin Infect Dis. 2017; 64(2):e1–e33.
131. Ahmed, A., et al., Interferon-γ release assays in children <15 years of age. Pediatrics. 2020; 145(1):e20191930.
132. Pai, M., Denkinger, C.M., Kik, S.V., et al., Gamma interferon release assays for detection of Mycobacterium tuberculosis infection. Clin Microbiol Rev. 2014; 27(1):3–20.
133. Pai, M., Zwerling, A., Menzies, D. "Systematic review: T-cell-based assays for the diagnosis of latent tuberculosis infection: an update," Ann of Intern Med. 2008; 149(3)177–184.
134. Metcalfe, J.Z., et al., "Interferon-γ release assays for active pulmonary tuberculosis diagnosis in adults in low- and middle-income countries: systematic review and meta-analysis," J of Infect Dis, 2011; 204(S4):S1120–S1129.
135. Whitworth, H.S. Clinical utility of existing and second-generation interferon-γ release assays for diagnostic evaluation of tuberculosis: an observational cohort study. Lancet Infect Dis. 2019 Feb; 19(2):193-202.
136. Schmidt, T., et al., Comparative Analysis of Assays for Detection of Cell-Mediated Immunity Toward Cytomegalovirus and M. tuberculosis in Samples From Deceased Organ Donors. Am J Transplant. 2014 Sep; 14(9):2159-2167.