Interferon gamma release assays for tuberculosis screening

Clinical Policy ID: CCP.1067

Recent review date: 12/2023

Next review date: 4/2025

Policy contains: automated real-time nucleic acid amplification, interferon-gamma release assays, Mantoux test, tuberculosis screening.

Keystone First VIP Choice has developed clinical policies to assist with making coverage determinations. Keystone First VIP Choice's clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by Keystone First VIP Choice when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Keystone First VIP Choice's clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Keystone First VIP Choice's clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Keystone First VIP Choice will update its clinical policies as necessary. Keystone First VIP Choice's clinical policies are not guarantees of payment.

Coverage policy

Interferon-gamma release assays for diagnosis of tuberculosis is clinically proven and, therefore, may be medically necessary when any of the following criteria are met (Lewinsohn, 2017):

- Members over age five who meet the following criteria: (1) are likely to be infected with *Mycobacterium tuberculosis*, (2) have a low or intermediate risk of disease progression, (3) testing for latent tuberculosis infection is warranted, and (4) either have a history of bacille Calmette-Guerin vaccination or are unlikely to return to have their tuberculin skin test read.
- Members over age five who are likely to be infected with *Mycobacterium tuberculosis*, who have a low or intermediate risk of disease progression, and in whom testing for latent tuberculosis infection is warranted.
- Members over age five who are likely to be infected with *Mycobacterium tuberculosis* who have a high risk of progression to disease and in whom diagnostic testing for latent tuberculosis infection is warranted (a tuberculin skin test may be used as well).

- If testing is obliged by law or credentialing bodies, for members over age five who are unlikely to be infected with *Mycobacterium tuberculosis* despite guidelines to the contrary, including a second test if the initial test is positive.

Limitations

Interferon gamma release assays for diagnosis of tuberculosis is investigational/not clinically proven and, therefore, not medically necessary, for:

- Members at low risk for *Mycobacterium tuberculosis* infection and disease progression.
- Healthy members under age five for whom diagnostic testing for latent tuberculosis infection is warranted; a tuberculin skin test should be used.

Alternative covered services

- Skin testing with a Mantoux test.
- Acid Fast Bacillus sputum culture.

Background

Tuberculosis remains a significant health concern in both emerging and developed economies. Tuberculosis is caused by the bacterium *Mycobacterium tuberculosis,* an airborne pathogen that can settle in the lungs and move through the blood to other parts of the body. Two conditions exist — latent (asymptomatic and noninfectious) tuberculosis infection and active tuberculosis disease (Centers for Disease Control and Prevention, 2016a).

In the United States, 8,300 new tuberculosis cases were reported in 2022, and the majority of cases occurred among non–U.S.-born individuals. An estimated 13 million Americans live with latent tuberculosis infection, and without treatment, an estimated 10% of them will develop active tuberculosis disease at some point in their lifetime. For people with compromised immune systems, the risk is higher (Schildknecht, 2023).

Tuberculosis is treatable and curable in most cases. Early diagnosis and treatment of both conditions with rifamycin-based regimens is essential for controlling the spread of disease, as improperly treated tuberculosis disease can be fatal (Centers for Disease Control and Prevention, 2016a).

Key to control of tuberculosis is cost-effective screening of high-risk populations. Over the past century, such screening has been performed with the tuberculin skin test, or Mantoux skin test. This involves the intradermal injection of purified protein derivative and measurement of any subsequent area of induration (a delayed hypersensitivity reaction of tuberculin antigen within the individual) at the test site. Although widely used, the skin test has a low sensitivity and many limitations including a cross reactivity with environmental and non-tuberculosis inducing mycobacteria (Lombardi, 2019).

Interferon-gamma release assays are blood studies for active and latent tuberculosis infection based upon the release of interferon gamma from white blood cells after their in vitro exposure to *Mycobacterium tuberculosis* antigens. The U.S. Food and Drug Administration has approved three tests for commercial use. The QuantiFERON®-Tuberculosis Gold In-Tube and QuantiFERON Gold Plus (Cellestis Inc., Valencia, California) tests employ enzyme-linked immunosorbent assay to measure interferon gamma in the blood. The T-SPOT® tuberculosis test (Oxford Immunotec Inc., Marlborough, Massachusetts) is an enzyme-linked immunosorbent assay immunospot test measuring the number of cells releasing interferon gamma (U.S. Food and Drug Administration, 2023).

Interferon-gamma release assays can be taken in a single visit, and results are available within 24 hours. The assay does not alter responses to future tuberculosis tests, and is unaffected (i.e., not subject to false positive

tests) by earlier bacille Calmette-Guérin vaccinations. Drawbacks of the assays include reduced accuracy of results after any errors in sample collection, transportation, running, or misinterpretation. It is not known if positive results of interferon-gamma release assays predict later development of tuberculosis (Centers for Disease Control and Prevention, 2023).

All current blood testing methods for tuberculosis are indirect tests that measure the body's response to tuberculosis and do not assay the causative organism directly. As such, the accuracy of these tests suffers from the inability to have a direct control for comparison.

An additional concern in tuberculosis testing is the increasing prevalence of the multidrug resistant *Mycobacterium tuberculosis* organism. The Xpert® MTB/RIF assay (Cepheid, Sunnyvale, California) is a tuberculosis-specific, cartridge-based nucleic amplification assay that detects *Mycobacterium tuberculosis* complex with rifampicin- and isoniazid-resistant mutations in the sputum. Its advantages over standard cultures and drug resistance testing are rapid results and minimal training requirements to run the test. Mycobacterial culture is required to ensure the availability of isolates for drug susceptibility testing and genotyping (Centers for Disease Control and Prevention, 2016b).

Findings

A guideline from the American Thoracic Society, Infectious Diseases Society of America, and Centers for Disease Control and Prevention outlines criteria on medical necessity of screening for tuberculosis using interferon gamma release assays; see coverage section of this policy for more detail (Lewinsohn, 2017).

The U.S. Preventive Services Task Force updated its recommendations based on an evidence review by Jonas (2023). The Task Force recommends screening asymptomatic adults at increased risk of latent tuberculosis infection. Populations with an increased prevalence of active disease and increased risk of exposure include persons who were born in, or are former residents of, countries with high tuberculosis prevalence and persons who live in, or have lived in, high-risk congregate settings (U.S. Preventive Services Task Force, 2023).

In high-risk populations, testing for latent tuberculosis infection is often considered part of standard disease management. In patients with autoimmune inflammatory rheumatic diseases, the European Alliance of Associations for Rheumatology recommends screening for latent tuberculosis prior to starting disease-modifying antirheumatic drugs and recommends consideration of screening prior to initiating glucocorticoids and immunosuppressants. The interferon-gamma release assay should be preferred over tuberculin skin test, where available, based on evidence suggesting that interferon-gamma release assays perform better than tuberculin skin tests in the diagnosis of latent tuberculosis infection and are less affected by current treatment regimens (Fragoulis, 2023).

An evidence review of 112 studies (total n = 69,009) for the U.S. Preventive Services Task Force found no studies evaluating the direct benefits and harms of screening for latent tuberculosis infection in adult populations. Both tuberculin skin tests and interferon-gamma release assays are moderately sensitive and highly specific (range of 0.95 to 0.99) within countries with low tuberculosis rates (Jonas, 2023).

Among solid organ transplantation recipients, a systematic review and meta-analysis of 43 studies (n = 36,403) from multiple countries examined the likelihood of active tuberculosis post-transplant with either a positive or a negative latent tuberculosis infection test result. In all, 344 participants were diagnosed with active disease. The posttransplant positive predictive value and negative predictive value for interferon-gamma release assays were 1.2% and 99.6%, respectively, and 2.13% and 95.5% for tuberculin skin tests. As expected, the positive predictive value for both tests was higher in populations with a higher pretest probability for active disease. High negative predictive values imply that a transplant recipient with a negative test has very low risk for active tuberculosis (Yahav, 2023).

A systematic review and meta-analysis of 403 studies of varying quality (n = 486,886) examined the indeterminate rate of interferon gamma release assays in screening latent tuberculosis infection. In this setting, an estimated one in 26 tests yields an indeterminate result. Failed positive controls caused most of the indeterminate results. Compared to T-SPOT, the pooled indeterminate rate for QuantiFERON-TB was similar (odds ratio = 0.88, 95% confidence interval 0.59 to 1.32, 55 studies), but for newer versions of QuantiFERON testing, the indeterminate rate trended lower. The pooled indeterminate rate was significantly higher in the immunocompromised than in immunocompetent controls (5.7% versus 1.9%, odds ratio = 3.51, 16 studies) and higher in children than adults (odds ratio = 2.56, seven studies). In human immunodeficiency virus-positive patients, the indeterminate rate increased as the CD4+ cell count decreased. Among children, the indeterminate rate decreased with increasing age (Zhou, 2023).

The same investigator group conducted a systematic review and meta-analysis of 458 head-to-head studies to determine the positive rates of interferon-gamma release assay and tuberculin skin test in detecting latent tuberculosis infection. Meta-regression modeling revealed that immune status, tuberculosis burden of the area, bacille Calmette-Guérin vaccination, and age influenced the diagnostic properties of both tests. In immunocompromised populations, the positive rates of both tests were lower than those of controls, but more so with the tuberculin skin test. In immunocompetent populations in the setting of low tuberculosis burden, the positive rate of interferon-gamma release assay among bacille Calmette-Guérin-vaccinated individuals was significantly lower than that of the tuberculin skin test. However, in the setting of high tuberculosis burden areas, this difference between tests became significantly less. In children and young adults, the positive rate of the interferon-gamma release assay test was lower than that of the tuberculin skin test, but in the elderly, the positive rates between the two tests were similar (Zhou, 2022).

A systematic review of 32 studies examined the cost utility of screening methods of latent tuberculosis infection in the following high-risk populations — migrants, people with human immunodeficiency virus, the immunocompromised, health care workers, and children. Inclusion of interferon-gamma release assays in screening strategies was cost effective in high-income settings for high-risk populations, but the cost effectiveness was sensitive to the underlying prevalence of latent tuberculosis infection in study populations. Less robust evidence supports tuberculin skin tests or no testing in lower risk populations, including children without increased risk factors. More evidence is needed to support different testing strategies in low to middle income countries and countries with a high disease burden (Mahon, 2022).

A systematic review of 32 studies (n = 4,856) compared the ability of interferon-gamma release assays and tuberculosis skin tests to accurately diagnose tuberculosis in persons with human immunodeficiency virus. The QuantiFERON-Tuberculosis Gold In-Tube assay detected the same number of latent tuberculosis cases as did the skin test. All interferon-gamma release assays detected more positive tuberculosis cases than the skin test in subjects with active tuberculosis (Overton, 2018).

A systematic review and meta-analysis compared the sensitivity and specificity of interferon-gamma release assays and T-SPOT tuberculin testing for the prediction of progression to clinical tuberculosis. The evidence following individuals who had undergone testing and progressed to clinical tuberculosis is sparse. The study was unable to judge which method was superior (Auguste, 2019).

Another systematic review and meta-analysis of the ability of interferon-gamma release assays to detect tuberculosis in persons with human immunodeficiency virus included 11 studies. Sensitivity rates of QuantiFERON-Tuberculosis Gold In-Tube and the T-SPOT tests were 69% and 89%, while specificity rates were 76% and 87%, respectively. While the new assays are not optimal for detecting tuberculosis in this population, T-SPOT testing appears to be more effective (Huo, 2016).

A large analysis of 157 studies found that in testing immunocompetent adults, the sensitivity of tuberculin skin testing (84%) was far greater than that of QuantiFERON-Tuberculosis Gold In-Tube (52%). Specificity of

QuantiFERON in persons with and without bacille Calmette-Guérin vaccination (93% and 97%) compared favorably with specificity for skin testing (79% and 100%). In immunocompetent adults, T-SPOT sensitivity is superior to that of QuantiFERON-Tuberculosis Gold In-Tube (68% versus 52%) and comparable in specificity (97% each). In non-vaccinated children, results are the same (sensitivity 98% versus 82%; specificity 98% each). Authors state that the results challenge the belief that interferon-gamma release assays are more accurate than skin tests, but they should be preferred in bacille Calmette-Guérin vaccinated populations (Doan, 2017).

A systematic review/meta-analysis of 24 studies showed no difference in the accuracy of diagnosing latent tuberculosis infection between QuantiFERON-TB Gold Plus and QuantiFERON-TB Gold In-Tube (Oh, 2021).

A systematic review/regression meta-analysis of 34 studies (581,956 person-years) using interferon gamma assays showed increased risk of progression from latent to active tuberculosis increased with higher levels of assay, based on 788 cases. Compared to 0 international units per milliliter, the relative risk of progression to active tuberculosis steadily rose from 1.64 (at 0.35 units) to 22.31 (at 20 units) (Ledesma, 2021).

A systematic review/meta-analysis of 40 studies (n = 50,592 individuals in 41 cohorts) showed that pooled risk ratio for the rate of disease progression in untreated individuals who were positive by interferon gamma release assays and tuberculin skin tests were 9.35 and 4.24, respectively. Pooled positive predictive values for the two groups were 4.5% and 2.3%, while negative predictive values were 99.7% and 99.3%. Authors conclude that individuals positive from interferon gamma release assays, but not those positive from tuberculin skin tests, might benefit from preventive treatment (Zhou, 2020).

A systematic review of 53 studies (n = 6,687) found in immunocompromised populations, the most cost-effective strategy was the QuantiFERON-Tuberculosis Gold In-Tube followed by the tuberculin skin test; in children, the most cost-effective approach was the reverse strategy. In children recently arrived from countries with a high prevalence of tuberculosis, the skin test only was less costly and more effective than a combination (Auguste, 2016).

The same research team also performed a systematic review of 17 studies, including five in children, 10 in immunocompromised people, and two in persons recently arrived in the United States, and compared the effectiveness of interferon-gamma release assays with tuberculin skin tests. The studies of children and persons recently arrived documented mixed results, while the studies of immunocompromised persons showed no difference between interferon-gamma release assays and tuberculin skin tests. The quality of the data was substandard —highly uncertain, a high risk of bias, and highly heterogeneous (Auguste, 2017).

A systematic review and meta-analysis of 15 studies assessed the efficacy of diagnosing active *Mycobacterium tuberculosis* in immunocompetent children under age 18. No differences were detected in sensitivity of QuantiFERON-Tuberculosis Gold In-Tube (89.6%), T-SPOT (88.5%), and tuberculin skin tests (88.2%). Specificity was greater for the two interferon-gamma release assays (95.4% and 96.8%) compared to 86.3% for skin tests (Laurenti, 2016).

A systematic review included 31 studies (n = 6,183 children) for QuantiFERON-Tuberculosis Gold In-Tube, 14 studies (n = 2,518 children) for T-SPOT, and 34 studies (n = 6,439 children) for tuberculin skin tests. In high-income countries, sensitivity rates for the two interferon-gamma release assays were 0.79 and 0.67 for all studies. In low-income nations, comparable rates were 0.57 and 0.61. In microbiologically confirmed cases, no difference existed between high- and low-income countries. Higher specificity for interferon-gamma release assays compared to tuberculin skin testing was observed in high-income countries (97 – 98% versus 92%) but not in low-income countries (85 – 93% versus 90%) (Sollai, 2014).

A systematic review and meta-analysis of 34 studies (n = 1,812) assessed the ability of interferon-gamma release assays to diagnose tuberculous pleural effusion. The pooled sensitivity and specificity for the blood assays were

0.77 and 0.71, respectively, and 0.72 and 0.78 for pleural fluid assays, both considered to have poor diagnostic accuracy for patients suspected to have tuberculous pleural effusion (Aggarwal, 2015).

In 2023, we added new guidelines, systematic reviews, and meta-analyses and deleted several older references. The new evidence confirms previous findings, and no policy changes are warranted.

References

On September 25, 2023, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were "tuberculosis," "interferon-gamma," "tuberculosis screening," and "gamma interferon assay tuberculosis." We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

Aggarwal AN, Agarwal R, Gupta D, Dhooria S, Behera D. Interferon gamma release assays for diagnosis of pleural tuberculosis: A systematic review and meta-analysis. *J Clin Microbiol*. 2015;53(8):2451-2459. Doi: 10.1128/JCM.00823-15.

Auguste P, Tsertsvadze A, Pink J, et al. Accurate diagnosis of latent tuberculosis in children, people who are immunocompromised or at risk from immunosuppression and recent arrivals from countries with a high incidence of tuberculosis: Systematic review and economic evaluation. *Health Technol Assess*. 2016;20(38):1-678. Doi: 10.3310/hta20380.

Auguste P, Tsertsvadze A, Pink J, et al. Comparing interferon-gamma release assays with tuberculin skin test for identifying latent tuberculosis infection that progresses to active tuberculosis: Systematic review and meta-analysis. *BMC Infect Dis*. 2017;17(1):200. Doi: 10.1186/s12879-017-2301-4.

Auguste P, Madan J, Tsertsvadze A, et al. Identifying latent tuberculosis in high-risk population: Systematic review and meta-analysis of test accuracy. *Int J Tuberc Lung Dis*. 2019;23(11):1178-1190. Doi: 10.5588/ijtld.18.0743.

Centers for Disease Control and Prevention. Tuberculosis (TB). Basic TB facts. https://www.cdc.gov/tb/topic/basics/default.htm. Last reviewed March 20, 2016. (a)

Centers for Disease Control and Prevention. Tuberculosis (TB). Testing for TB infection. https://www.cdc.gov/tb/topic/testing/tbtesttypes.htm. Updated July 11, 2023.

Centers for Disease Control and Prevention. Tuberculosis (TB). TB Diagnostic Tool: Xpert MTB/RIF Assay fact sheet. https://www.cdc.gov/tb/publications/factsheets/testing/igra.htm# Last reviewed May 4, 2016. (b)

Doan TN, Eisen DP, Rose MT, Slack A, Stearnes G, McBryde ES. Interferon-gamma release assay for the diagnosis of latent tuberculosis infection: A latent-class analysis. *PLoS One*. 2017;12(11):e0188631. Doi: 10.1371/journal.pone.0188631.

Fragoulis GE, Nikiphorou E, Dey M, et al. 2022 EULAR recommendations for screening and prophylaxis of chronic and opportunistic infections in adults with autoimmune inflammatory rheumatic diseases. *Ann Rheum Dis*. 2023;82(6):742-753. Doi: 10.1136/ard-2022-223335.

Huo ZY, Peng L. Accuracy of the interferon-γ release assay for the diagnosis of active tuberculosis among HIV-seropositive individuals: A systematic review and meta-analysis. *BMC Infect Dis*. 2016;16:350. Doi: 10.1186/s12879-016-1687-8.

Jonas DE, Riley SR, Lee LC, et al. Screening for latent tuberculosis infection in adults: Updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2023;329(17):1495-1509. Doi: 10.1001/jama.2023.3954.

Laurenti P, Raponi M, de Waure C, Marino M, Ricciardi W, Damiani G. Performance of interferon-γ release assays in the diagnosis of confirmed active tuberculosis in immunocompetent children: A new systematic review and meta-analysis. *BMC Infect Dis*. 2016;16:131. Doi: 10.1186/s12879-016-1461-y.

Ledesma JR, Ma J, Zheng P, Ross JM, Vos T, Kyu HH. Interferon-gamma release assay levels and risk of progression to active tuberculosis: A systematic review and dose-response meta-regression analysis. *BMC Infect Dis*. 2021;21(1):467. Doi: 10.1186/s12879-021-06141-4.

Lewinsohn DM, Leonard MK, LoBue PA, 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):111-115. Doi: 10.1093/cid/ciw778.

Lombardi G, Pellegrino MT, Denicolò A, et al. QuantiFERON-TB performs better in children, including infants, than in adults with active tuberculosis: A multicenter study. *J Clin Microbiol*. 2019;57(10):e01048-19. Published online 2019 Sep 24. Doi: 10.1128/JCM.01048-19.

Mahon J, Beale S, Holmes H, et al. A systematic review of cost-utility analyses of screening methods in latent tuberculosis infection in high-risk populations. *BMC Pulm Med*. 2022;22(1):375. Doi: 10.1186/s12890-022-02149-x.

Oh CE, Ortiz-Brizuela E, Bastos ML, Mensies D. Comparing the diagnostic performance of QuantiFERON-TBV Gold Plus to other tests of latent tuberculosis infection: A systematic review and meta-analysis. *Clin Infect Dis*. 2021;73(5):e1116-e1125. Doi: 10.1093/cid/ciaa1822.

Overton K, Varma R, Post JJ. Comparison of interferon-γ release assays and the tuberculin skin test for diagnosis of tuberculosis in human immunodeficiency virus: A systematic review. *Tuberc Respir Dis (Seoul)*. 2018;81(1):59-72. Doi: 10.4046/trd.2017.0072.

Schildknecht KR, Pratt RH, Feng PI, Price SF, Self JL. Tuberculosis — United States, 2022. *MMWR Morb Mortal Wkly Rep* 2023;72:297–303. https://www.cdc.gov/mmwr/volumes/72/wr/mm7212a1.htm?s_cid=mm7212a1_w.

Sollai S, Galli L, de Martino M, Chiappini E. Systematic review and meta-analysis on the utility of Interferon-gamma release assays for the diagnosis of Mycobacterium tuberculosis infection in children: A 2013 update. *BMC Infect Dis*. 2014;14 Suppl 1:S6. Doi: 10.1186/1471-2334-14-S1-S6.

U.S. Food and Drug Administration. Premarket Approval (PMA) database searched using product codes NCD and OJN. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm. Page last updated September 25, 2023.

U.S. Preventive Services Task Force, Mangione CM, Barry MJ, et al. Screening for latent tuberculosis infection in adults: U.S. Preventive Services Task Force recommendation statement. *JAMA*. 2023;329(17):1487-1494. Doi: 10.1001/jama.2023.4899.

Yahav D, Gitman MR, Margalit I, Avni T, Leeflang MMG, Husain S. Screening for latent tuberculosis infection in solid organ transplant recipients to predict active disease: A systematic review and meta-analysis of diagnostic studies. *Open Forum Infect Dis*. 2023;10(8):ofad324. Doi: 10.1093/ofid/ofad324.

Zhou G, Luo Q, Luo S, et al. Indeterminate results of interferon gamma release assays in the screening of latent tuberculosis infection: A systematic review and meta-analysis. *Front Immunol*. 2023;14:1170579. Doi: 10.3389/fimmu.2023.1170579.

Zhou G, Luo Q, Luo S, et al. Interferon-gamma release assays or tuberculin skin-test for detection and management of latent tuberculosis infections: A systematic review and meta-analysis. *Lancet Infect Dis*. 2020;S1473-3099(20)30276-0. Doi: 10.1016/S1473-3099(20)30276-0.

Zhou G, Luo Q, Luo S, et al. Positive rates of interferon-γ release assay and tuberculin skin test in detection of latent tuberculosis infection: A systematic review and meta-analysis of 200,000 head-to-head comparative tests. *Clin Immunol*. 2022;245:109132. Doi: 10.1016/j.clim.2022.109132.

Policy updates

11/2013: initial review date and clinical policy effective date: 3/2014

11/2014: Policy references updated.

11/2015: Policy references updated.

11/2016: Policy references updated.

11/2017: Policy references updated.

11/2018: Policy references updated.

12/2019: Policy references updated. Policy ID changed to CCP.1067.

12/2020: Policy references updated.

12/2021: Policy references updated.

12/2022: Policy references updated.

12/2023: Policy references updated.