ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES

Interferon-Gamma Release Assay Testing for Latent Tuberculosis Infection

A Health Technology Assessment

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Ontario Health

Key Messages

What Is This Health Technology Assessment About?

Tuberculosis (TB) is a disease caused by bacteria that primarily affects the lungs and can be spread through an infected person's breath, especially through coughing or speaking. Symptoms include respiratory distress, organ failure and eventual death, but is curable when caught and treated early. Many people infected with TB bacteria experience a symptomless, inactive stage of infection. This stage is known as "latent tuberculosis infection" (LTBI). Screening for – and treating people with – LTBI can reduce the risk of symptoms appearing and spreading TB to others.

The interferon-gamma release assay (IGRA) can determine if an individual has been exposed to the bacteria that causes TB. This technology involves testing a blood sample for an immune system response in a laboratory. Currently in Ontario, only the tuberculin skin test (TST) is publicly funded as a test for LTBI. The IGRA test is considered an acceptable alternative to the TST for people who may have LTBI by the Canadian Tuberculosis Standards, published in 2022.

This health technology assessment looked at how accurate and cost-effective IGRA testing is for LTBI. It also evaluates the budget impact of publicly funding IGRA. We reached out to people with LTBI to learn about their experiences, preferences, and values, but were unable to complete interviews. Instead, we spoke to 53 health care providers who order and rely on the results of TB tests.

What Did This Health Technology Assessment Find?

We found good evidence for the diagnostic accuracy of IGRA when used to test for LTBI. Compared with TST, IGRA may yield fewer false-positive findings (results showing that a person has LTBI when they don't), particularly in people who had previously received the BCG vaccine against TB. IGRA may also be informative for people with immunocompromising conditions who are at risk of a false-negative finding (results showing a person does not have LTBI when they do) by a TST.

Using IGRA (either as a standalone test or in sequence with TST) for LTBI was found to be cost-effective or cost-saving compared with TST alone in populations identified by Canadian TB Standards for being recommended for IGRA testing. We estimated that publicly funding IGRA in Ontario (for populations in alignment with the current Canadian TB Standards) over the next 5 years would cost between $2.99 million and $18.80 million, depending on how the test is used. These figures represent the final costs after considering the costs of IGRA testing and treatment for people who might otherwise be misdiagnosed as not having LTBI, as well as the savings from avoiding unnecessary testing and treatment in people who might be incorrectly identified as having LTBI.

Health care providers we surveyed explained that most patients prefer IGRA as a standalone test. This is mainly due to the single visit to the clinic required by IGRA compared to the two visits required for TST.

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Abstract

Background

Many people infected with the *Mycobacterium tuberculosis* complex (the bacteria that cause tuberculosis [TB]) have an inactive stage of infection known as latent tuberculosis infection (LTBI). A person with LTBI is at risk of developing active TB. Screening for, and treating people with, LTBI is an important part of preventing adverse health outcomes, reducing the risk of reactivation and the further spread of tuberculosis in a community. We conducted a health technology assessment of interferon-gamma release assay (IGRA) for the detection of LTBI, compared to the standard tuberculin skin test (TST) to evaluate the diagnostic accuracy, cost-effectiveness, the budget impact of publicly funding, and health care provider preferences and values.

Methods

We performed a systematic literature search of the clinical evidence as an overview of systematic reviews. We reported the findings of the identified reviews, including their quality assessment of the body of evidence. We performed a systematic literature search of the economic evidence and included published Canadian cost-effectiveness studies. We assessed the quality of the body of evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. We developed a probabilistic decision-tree model to estimate the incremental costs of IGRA strategies versus TST alone over 1 year in eligible population subgroups. IGRA was examined as a single test and in a sequential pathway with tuberculin skin test (TST; the test order depended on the type of population). We considered subpopulations at high risk of LTBI for whom IGRA would be preferred, as indicated by the Canadian TB Standards published in 2022 (hereinafter, the Standards); e.g., people who received a Bacille Calmette-Guérin (BCG) vaccine, such as BCG-vaccinated immigrants and people identified in contact investigations. We also considered people with comorbid conditions or who were undergoing treatments that may cause low immune function and, hence, may test incorrectly negative. We estimated the total 5-year budget impact (in 2024 CAD) for publicly funding IGRA testing in Ontario. To contextualize the potential value of IGRA, we spoke with health care providers about people requiring TB testing for LTBI. We attempted to reach out to people who had experience with IGRA or TST but did not receive any feedback.

Results

We included 12 systematic reviews that included over 500 unique primary studies in the clinical evidence overview of reviews and found good evidence aligned with the uses of IGRA outlined in the Standards. This overview of reviews summarizes the existing evidence on diagnostic accuracy and the clinical utility of IGRA for LTBI. Interferon-gamma release assay was found to have good evidence as a rule-in test for LTBI due to consistently high specificity. The reviews reported slightly lower sensitivity among people who have underlying immunosuppression conditions (e.g., people who are HIV positive or have received an organ transplant, or are on cancer treatment or dialysis) compared to a more general population. However, compared to TST (the standard test for TB), IGRA appears to have fewer false-positive results, as signaled by a lower risk difference of developing active TB among those who tested positive on both LTBI tests in head-to-head comparisons. This was particularly notable in immunocompromised populations and was also observed in children and the elderly (e.g., people in nursing homes) and those who have received an anti-tuberculin vaccination known as the BCG vaccine.

Additionally, IGRA may be informative for people with immunocompromising conditions who are at risk of a false-negative result from a TST, as it yields indeterminate findings, signaling that further clinical investigation may be needed.

We included 5 economic studies from Canada (using a public payer perspective), which found that IGRA, either as a sequential test following TST or as a standalone test, was cost-effective or cost-saving compared with TST alone for LTBI in high-risk populations as identified in the Standards. All reviewed studies were of good quality and 3 studies were directly applicable to the Ontario context (GRADE: High). Therefore, we did not conduct a primary economic evaluation for Ontario.

Our reference case budget impact analysis showed that publicly funding IGRA in Ontario in all examined subpopulations over the next 5 years was associated with additional costs ranging from $2.99 million (IGRA alone) to $18.80 million (IGRA in sequential pathways with TST). These overall estimates include potential savings in some subpopulations and additional costs in others. In the population-specific analyses, we estimated cost savings of $1.63 million or higher over 5 years with publicly funded IGRA testing in BCG-vaccinated immigrants or BCG-vaccinated people identified via contact investigations (who are susceptible to a false positive result with the TST alone). These cost-savings resulted from reductions in costs of follow-up evaluation and treatment (due to prevention of reactivated LTBI). We found additional costs of about $6.26 million or higher over 5 years with publicly funded IGRA testing in immunocompromised people due to increased appropriate medical evaluations for those who were previously incorrectly identified as negative. In sensitivity analyses, if we assumed a high chance of reactivation of LTBI into active TB in immunocompromised populations, then IGRA testing resulted in cost savings.

Health care providers who we surveyed had positive comments about IGRA, and expressed it as patients' preferred test for LTBI, partly because this test requires only 1 office visit (compared to the multiple visits needed for TST), thus reducing the effect of barriers such as transportation, language, childcare and employment arrangements.

Conclusions

Interferon-gamma release assay testing was found to have good diagnostic accuracy and to be cost-effective or cost-saving for LTBI in populations aligned with the recommended uses of the Standards. We estimate that publicly funding IGRA in Ontario for all examined population subgroups would result in additional costs of between $2.99 million and $18.80 million over 5 years, depending on how the test is used. In the population-specific analyses, we estimate a cost savings of $1.63 million or higher with IGRA testing in eligible BCG-vaccinated immigrant populations or BCG-vaccinated people identified via contact investigations. There was a preference for IGRA among health care practitioners, particularly to support people who may have challenges with the available alternative tests (e.g., TST).

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Objective

This health technology assessment summarizes the clinical and economic evidence for interferon-gamma release assay (IGRA) testing for latent tuberculosis infection. It also evaluates the budget impact of publicly funding IGRA and the experiences, preferences, and values of health care providers who order and rely on the results of tuberculosis (TB) tests.

Background

Health Condition

Tuberculosis is an infectious disease caused by bacteria in the *Mycobacterium tuberculosis* complex.[1] Symptoms of TB disease include respiratory distress (i.e., bad cough with phlegm and sometimes blood), lack of appetite, weight loss, weakness, fatigue, and fever.[1] While it is well known that TB disease commonly impacts the lungs, it may also affect other organs and body systems, including the brain, kidneys, spine, bones, and lymphatic system.[1] If left untreated, it can lead to organ failure and eventual death.[1] Tuberculosis disease is highly infectious and is airborne—TB can spread through an infected person's cough or speech or through singing. Young children (under 5 years of age) are particularly vulnerable to TB infection progressing to a severe form of TB disease.[2]

Tuberculosis is curable when caught early. Treatment can prevent adverse health outcomes, but it can also reduce the risk of reactivation and the further spread of TB in a community.[1] Treatment for TB disease can be burdensome for patients, requiring a regimen of multiple antibiotics that typically lasts 6 to 12 months, but can continue for over 18 months (email communications, Robin Taylor, MD, Melissa Greenblatt, PhD, Kevin Schwartz, MD, and of Health, December 2023; Elizabeth Rea, January 2024).

Latent TB Infection

Many people infected with TB-causing bacteria have an inactive stage of infection, also known as latent tuberculosis infection (LTBI).[3] People with LTBI have the bacteria in their body, but they have no symptoms and cannot spread TB to others in their community.[3] However, a person with LTBI is still at risk of developing active TB. There is an effective preventive treatment targeting the *M. tuberculosis* bacteria at the LTBI stage to substantially reduce the risk of LTBI developing into TB disease.[4] Preventive treatment in people with LTBI is less arduous and with a shorter treatment period (typically 4 months or less) than the treatment for people with active TB disease (email communications, Robin Taylor, MD, December 2023; Elizabeth Rea, MD and Kevin Schwartz, MD, May 2024). However, not everyone will complete treatment. While estimates in Ontario are uncertain, 1 study from the United States found about 70% of patients complete their treatment for LTBI.[5]

Clinical Need and Target Population

In 2022, TB was the second greatest cause of mortality by infectious disease, behind only COVID-19.[6] The World Health Organization (WHO) estimated that 1.3 million people died from tuberculosis disease and 10.6 million were ill because of it.[6] The key risk factor for acquiring *M. tuberculosis* (Mtb) is direct exposure to others with infectious active TB, which occurs at higher rates in congregate living settings

such as crowded housing, prisons, long-term care homes, homeless shelters, and hospitals.[7] People with medical conditions that weaken the immune system are at higher risk of developing TB disease.[8]

Tuberculosis disease was reported in 1,829 people in Canada in 2021[9] and in 2022, there were 119 deaths due to tuberculosis.[10] The incidence rate has been relatively stable, between 4.6 and 5.1 cases per 100,000 people from 2012 to 2021.[9] The highest rates of TB in Canada are seen among Canadian-born Indigenous Peoples, at 12.7 cases per 100,000 people (almost triple the average rate), with the highest rates among Inuit Canadians, at 135 cases per 100,000 people.[9] However, the majority of cases (76.7% of active TB cases) are among those in Canada who are foreign born.[9] In Ontario, foreign-born individuals make up 89% of people with active TB disease, with the median time of diagnosis of TB being around 8 years after arrival in Canada.[11] There is a national goal for TB elimination in Canada.[6]

There is a vaccine available to protect against TB infection, known as the Bacille Calmette-Guérin (BCG) vaccine. The BCG vaccine is only 51% effective in preventing TB disease overall, though up to 78% effective in protecting newborns from disseminated or meningeal TB.[7] The BCG vaccine is not routinely given in Canada due to the overall low rates of TB; however, it may be given under certain local circumstances (e.g., high-risk community or a local outbreak).[7] As well, most foreign-born Canadians have arrived vaccinated due to differing policies around the world.[12] Ending the global tuberculosis epidemic by 2030 is one of the key health targets of the United Nations Sustainable Development Goals.[6] To support efforts to achieve this goal, many countries are using the BCG vaccine to control population spread of tuberculosis.[6]

Latent TB Infection

Because TB can persist for many years in an inactive form, it is difficult to get an accurate estimate of how many people in Ontario are currently infected with TB bacteria, but the global burden is estimated at 23% (in 2014), and 1 Canadian study estimated the prevalence in Ontario among foreign-born people is 22% (in 2016).[13,14] There are no standard monitoring or reporting practices for LTBI in Canada.[15] Most people with LTBI will remain unaffected; however, 5% to 15% of patients will experience a “reactivation” that will become active TB disease.[16] The highest risk of reactivation is within the first 2 years after an initial infection.[17] Some immunocompromising health conditions and lifestyle factors may put people at higher risk for developing active TB, namely living with HIV, silicosis, diabetes, being an organ transplant recipient, having advanced-stage chronic kidney disease, receiving immunosuppressing drugs (including chemotherapy), and heavy alcohol or cigarette use.[18] It is recommended that people be tested and treated for LTBI when there is potential for preventing active TB and reducing the risk of spread.[18,19]

One large public health unit in Ontario monitors their cases through various epidemiological methods, including TB genotyping, and has estimated that 5% to 8% of their active TB cases arise due to contact with a TB case, known as “secondary cases” (email communication, Elizabeth Rea, MD, January 2024). It is also well understood that this number is an underestimate of the true spread due to transmission between people, as pre-existing positive cases exist in Ontario, and some individuals identified as contacts will take preventative treatment while others will not. Some of those will go on to become active TB cases themselves in the future (email communication, Elizabeth Rea, MD, January 2024).

Current Testing Options

People are tested for LTBI for several reasons, including having had close contact with a person who has TB disease, has arrived from a high TB incidence country, or is about to undergo certain

immunosuppressant therapies.[20,21] As well, screening is a requirement for certain employment scenarios, such as in a health care setting.[20]

In Ontario, there is currently only 1 publicly funded test for LTBI, the tuberculin skin test (TST).[22] The TST has been in use for over a century and today's version (sometimes referred to as the Mantoux) is conducted by injecting a small amount of a purified protein derivative extract of the *M. tuberculosis* bacteria into the forearm under the skin.[18] This spot is marked and checked by a health care provider 48 to 72 hours later, thus requiring a second clinic visit.[18] If there is an induration (i.e., a reddish bump) of a specific size, then the injected person is having an immune system response, indicating they have been infected.[18] The TST is an imperfect test. If a person has received the BCG vaccine, they may display a false-positive immune response, and if they are immunocompromised, they may display a false-negative response. There is no gold-standard test to confirm LTBI, the only true confirmative test is clinically confirmed TB (or absence of developing active TB), which is diagnosed through a variety of methods, such as sputum microbiologic tests and x-rays.[2,12,23,24]

In addition to TB testing with TST, Ontario publicly funds any required additional diagnostic test and treatments for LTBI and active TB disease. There is also some public funding for those who may not qualify for coverage under the Ontario Health Insurance Plan (OHIP), Interim Federal Health (IFH), or any other provincial, territorial, or private health insurance plan through a program known as the TB Diagnostic and Treatment Services for Uninsured Persons (TB-UP).[25] Individuals who are uninsured and who may be eligible for TB-UP typically include those with vulnerable social determinants of health, either being a recently landed immigrant (<3 months), homeless, a foreign visitor or student, or a person without legitimate immigration (long-term visitor) or recently discharge from prison.[25]

A person may access testing through a variety of clinical pathways. Some people will go to their primary care provider to conduct the TST or be referred to a community lab, while others may access testing through a hospital or community specialist physician, or through public health units as part of contact tracing investigations (email communication, Ontario Ministry of Health and Robin Taylor, MD, December 2023; Elizabeth Rea MD, January 2024) The most recent version of the Canadian Tuberculosis Standards, 8th edition (hereafter, "the Standards"), was published in 2022. It considers testing for tuberculosis infections a key feature of identifying individuals who are at greater risk of developing TB disease and who would benefit from LTBI treatment.[2,19,23] Similarly, there are recommendations for people to be tested for TB infection regularly for employment environments with high potential exposure, such as in health care, or upon a known exposure to someone with active TB.[18] Public Health Ontario,[20] Ontario Ministry of Health,[19] and Health Canada[7] documents about tracking and managing tuberculosis all refer to the Standards as a key resource.

Health Technology Under Review

In the early 2000s, a new test known as the interferon-gamma release assay (IGRA) was developed to determine if an individual was previously exposed to the *M. tuberculosis* bacteria by measuring their immune response.[26] To conduct an IGRA test, a sample of blood is drawn from the patient and tested for a response to specific antigens in a laboratory.[27]

As with a positive TST, a positive finding with IGRA cannot distinguish between active TB disease and LTBI. Further diagnostic tests such as sputum microbiology or chest x-ray may be required.[20,27] Unlike with TST, this type of assessment of the antibody immune response at the cellular level does not cause a false-positive result among people who have previously received the BCG vaccine.[27] People who are

immunocompromised, who are at risk for a false negative with a TST, may receive an "indeterminate" result from IGRA. An indeterminate result may be an indication of LTBI, which might be otherwise missed.[28]

The IGRA test has been considered an acceptable alternative to the TST for people who may have LTBI by the Standards (summarized below),[2,23] as well as many other jurisdictions around the world.[12]

Canadian Tuberculosis Standards

For the use of IGRA for the diagnosis of tuberculosis, the Canadian Tuberculosis Standards, 8th edition, states:

> *We strongly recommend both the tuberculin skin test and interferon-gamma release assay as acceptable alternatives for TB infection diagnosis. Either test can be used for TB infection screening in any of the situations in which testing is indicated. However, there are preferences and exceptions detailed in subsequent recommendations (good evidence).*[18]

IGRA is recommended for adults and children, with the understanding there may be a higher false-negative rate for very young children related to immune system immaturity.[2] The preferences and exceptions are summarized in Table 1.

Table 1: Summary of Recommended Uses of IGRA as Per the Canadian Tuberculosis Standards, 8th Edition[18]

Timing in the clinical pathway	Recommended uses for IGRA
IGRA as the preferred first line test in certain populations (Figure 1, A)	For people who have been previously vaccinated with BCG or exposed to non-tuberculosis mycobacteria infection (as the TST can give false-positive results) • Specifically, for children who have been vaccinated and aged 2–10 years, and for those aged > 10 years if they received their BCG vaccine after infancy (aged > 1 year) When TST is unavailable, such as when there is a lack of trained personnel When a person is considered unlikely or unable to return to have their TST results read, as required When TST is otherwise contraindicated
IGRA as part of sequential testing in certain circumstances (Figure 1, B)	After a negative TST result if the risk for infection or a poor outcome from progression to TB is high • Includes circumstances where a person's conditions or habits may reduce the sensitivity of the TST (e.g., people living with HIV or other immunocompromising conditions) After a positive TST result if the likelihood of TB infection is low or there is a risk of a false positive, such as due to BCG vaccine
Serial testing	IGRA is not considered acceptable for infection monitoring, or for workplace monitoring

Abbreviations: BCG, Bacille Calmette-Guérin; IGRA, interferon-gamma release assay; TST, tuberculin skin test.

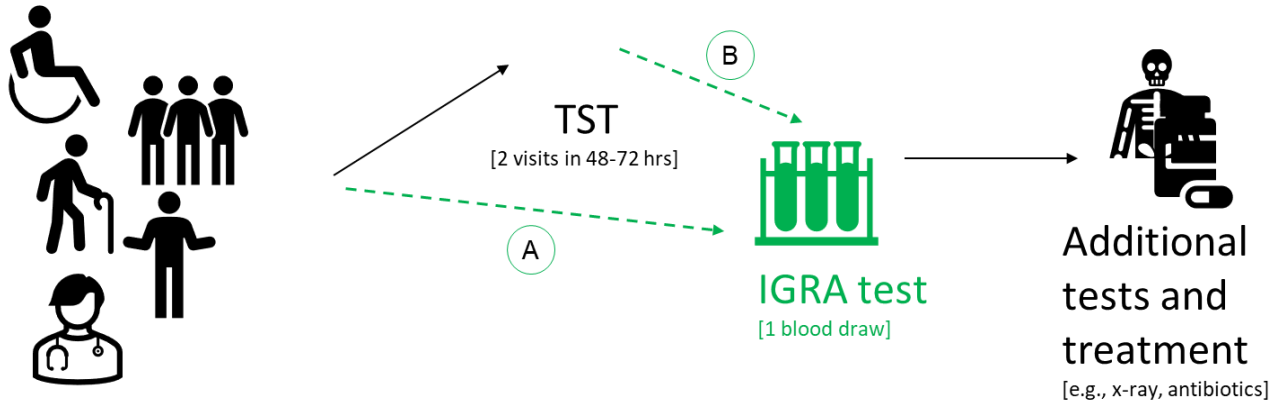

Figure 1: Simplified clinical pathway of people recommended for IGRA testing in Canada

In accordance with the Canadian Tuberculosis Standards, 8th edition,[2,23] IGRA is recommended as a first line test (A) for people who have previously been vaccinated with BCG (common in high-incidence countries around the world; Canadian Tuberculosis Standards includes additional details defining specific ages and vaccine status); capacity or training for TST is not available, but is available for IGRA; when a person is unable or unlikely to return to have their TST result read; or when TST is otherwise contraindicated. Sequential testing (B) is used when TST is positive and there are concerns of a false positive (e.g., the person may have been BCG vaccinated), when TST is negative and there is a high risk for infection (e.g., person has been exposed to active TB, progression to TB is elevated, a poor outcome from active TB is anticipated, or there are other conditions or habits that may reduce the sensitivity of the test).
Abbreviations: BCG, Bacille Calmette-Guérin; IGRA, interferon-gamma release assay; TB, tuberculosis; TST, tuberculin skin test.

Regulatory Information

Two companies make IGRA tests for LTBI, both with Health Canada approval as class 3 devices: the T-SPOT by Oxford Immunotec LTD (Health Canada Licence No. 69598)[29] and the QuantiFERON-TB Gold Plus by Qiagen Sciences (Health Canada licence No. 72209).[30] These tests have had several iterations over the years and remain the leading brands internationally. We've been able to confirm T-SPOT having the CE mark (Europe) and FDA approval (United States), as well as regulatory approval in China, Japan, Taiwan, Russia, Singapore, Thailand, Peru, Nigeria, and Mexico.[31] QuantiFERON-TB Gold Plus is recognized by the WHO, the Centers for Disease Control (CDC, United States), and the European Centre for Disease Prevention and Control (ECDC, Europe).[32] New IGRA tests are in development, but to our knowledge, none currently have Health Canada approval.[33]

Ontario, Canadian, and International Context

In Ontario, IGRA is available as an out-of-pocket expense (about $95 to $105) for patients through community labs such as Dynacare and Lifelabs.[34,35] Additionally, we have been informed by clinical experts that The Hospital for Sick Children (SickKids) covers the expense of IGRA testing within their hospital, and their volumes have grown nearly 6-fold since 2019 (personal communication, Melissa Richard-Greenblatt, PhD, November 2023). We have also heard reports of other Ontario hospitals paying SickKids to perform IGRA testing on inpatients and select outpatients (e.g., on dialysis or with HIV; email communication, Kevin Schwartz, MD, December 2023). Toronto Public Health's TB Program covers the cost of IGRA testing for some contacts of people with infectious TB as part of their contact follow-up (email communication, Elizabeth Rea, MD, January 2024).

Ten Canadian provinces and territories publicly fund IGRA (email communication, Ontario Ministry of Health, May 2024). We are unable to confirm the detailed criteria for the various funding models, with the exception of British Columbia, which publicly funds the use of IGRA[36] in general alignment with the recommendations of the Standards,[37] including the use of IGRA prior to commencing dialysis.[38]

Internationally, IGRA is widely available; however, public funding is uncertain. In the United Kingdom, certain visa applications require people to pay for their own testing, while other people may have access to testing for free.[39,40] The use of IGRA is recommended in documents about tuberculosis from the United Kingdom[41] and Australia,[42] and is funded by the BlueCross BlueShield[43] in parts of the United States. In a 2018 summary of 18 international guidelines, the ECDC a found that there was a trend towards including IGRA as part of screening strategies.[24]

Equity Context

We use the PROGRESS-Plus framework to help explicitly consider health equity in our health technology assessments.[44] PROGRESS-Plus is a health equity framework used to identify population and individual characteristics across which health inequities may exist. These characteristics include place of residence, race or ethnicity, culture or language, gender or sex, disability, occupation, religion, education, socioeconomic status, social capital, and other key characteristics (e.g., age) that stratify health opportunities and outcomes.[44] We also used the Benkhalti et al[45] checklist to guide equity considerations in HTAs to explore potential factors related to inequities, as available in the published evidence.

In Ontario, there is currently inequity in access to LTBI testing as health units across the province report that many primary care clinicians have stopped offering TST over the last decade for a variety of reasons, notably the logistics of the second visit, and particularly for children (email communication, Elizabeth Rea, MD, January 2024; Meb Rashid, MD, April 2024). Additionally, the TST requires a person to be seen by a clinical professional to inject and recheck the injection site 48 to 72 hours later, which is not always feasible for people who may have to take time off work, have caregiver responsibilities, or for whom traveling to a doctor's office is a burden. In Ontario, this includes many low-paid health care workers, such as personal support workers who are required to have TB screening for work, many of whom are immigrants and BCG-vaccinated (email communication, Elizabeth Rea, MD, January 2024). The IGRA test requires only a single visit for a blood draw.

The use of IGRA testing would streamline the process for the individual and from a public health perspective. When public health officials track all individuals to confirm the results, IGRA results would be known after a single visit, and only those considered for treatment would require the resourcing efforts for follow-up (email communication, Elizabeth Rea, MD, January 2024; Innocent Magocha, MPH, and Jo Ann Majerovich, MD, June 2024). The Standards take into consideration challenges patients may have by including a recommendation for the use of IGRA when a person is unable or unlikely to return to have their result read.[18]

Screening for latent tuberculosis has been recommended for people immigrating to Ontario from countries with a high incidence of TB[46] because they may have been previously vaccinated with BCG. Thus, there are equity concerns due to out-of-pocket costs for IGRA testing. Notably, the population that would most benefit from access to IGRA (i.e., people who, as immigrants to Canada, have had a prior BCG vaccine) are also more likely to be unable to afford the cost (i.e., recent immigrants are more likely to belong to lower-income groups).[47] People who have been vaccinated with BCG have a higher rate of a

false-positive findings from TST. Positive findings require additional testing, and false-positives may lead to unnecessary treatment while further investigations are conducted to confirm the result.

Conversely, the experience of the Toronto Public Health TB program, and others, is that some patients and clinicians who know about the concerns with BCG vaccination discount the results of a positive TST. Those people may in fact have LTBI, as the vaccine is only partially effective over the long term. Without treatment, they are at risk of developing TB disease (email communication, Robin Taylor, MD, December 2023; Elizabeth Rea, MD, May 2024). IGRA is suggested to be less likely to give a false-negative result in people who are immunocompromised. Compared with the TST, IGRA tests provide results that are more nuanced and may lead to appropriate further investigations in circumstances where a negative TST might be the end of the diagnostic journey. Overall, access to IGRA testing is proposed to streamline this process and the downstream impact on the health care system considerably.

Canadian Indigenous populations have the highest rates of TB in the country (along with immigrants from high-incidence countries), and as such many Indigenous communities opted to provide universal BCG vaccines for their population until around 2014 (email communication, Jo Ann Majerovich, MD, Innocent Magocha, MPH, June 2024). Appreciating there is diversity among the First Nations, Inuit, Métis, and urban Indigenous populations,[48] concerns around LTBI testing among the Canadian Indigenous populations are anticipated to be aligned with other BCG-vaccinated Canadians. IGRA may offer improved accuracy while reducing follow-up appointments (as these are needed to review results for TST). The IGRA test is currently being used with limited public funding in 1 Indigenous community in Ontario with an active TB outbreak. However, access is limited and hindered by the expense required to ship samples far distances to a laboratory that can process the test.

Implementation of publicly funded IGRA, and the need for education for health care providers and patients, may look different across the province. For example, clinicians in areas with more TB or with higher populations of immigrants (who may have false-positive results on a TST), are likely more familiar with IGRA tests; clinicians in remote areas where even non–publicly funded IGRA is not currently available are less likely to be familiar. Certain public health units, such as Toronto, are already doing limited IGRA testing for contacts and already have internal protocols in place that may allow them to adopt testing more readily than other regions (personal and email communication, Elizabeth Rea, MD, Patrick Galange, MD, and Rehannah Khan, April to May 2024).

At least 1 rural Ontario hospital that services remote and First Nations communities has purportedly expressed interest in offering IGRA testing in their region (email communication, Jo Ann Majerovich, MD, Innocent Magocha, MPH, June 2024). This would not only improve access but also reduce shipping costs, which dominate budgets in this space and thus limit the number of tests available to communities in need. Current funding for TB testing for First Nations communities is provided through a patchwork of provincial and federal funding. Current access to IGRA tests for select First Nations communities is limited and is being supported out of the Canadian Federal budget as a TB outbreak response (email communication, Jo Ann Majerovich, MD, Innocent Magocha, MPH, June 2024).

Implementation of programs to access IGRA should respect the diversity of individuals and groups across the province. This includes diversity in preferred language as English and French are not first languages for many potentially affected people living in Ontario, including Indigenous peoples.[48] Consulted experts surmise that if IGRA were to become broadly publicly funded in Ontario, local hospitals would build the capacity to conduct IGRA testing and thusly greatly reduce the expense of transportation while

increasing capacity and access to the people in need (personal and email communication, Jo Ann Majerovich, MD, Innocent Magocha, MPH, January and June 2024, respectively).

Finally, advancements in recent versions of IGRA tests have improved the pre-analytics steps, allowing for easier operationalization of transporting samples from collection to laboratory.[31,32] This improves the potential accessibility of IGRA in geographic regions where courier services may be extended or delayed and laboratories are not available to meet the short turnaround requirements for processing.[31,32]

Expert Consultation

We engaged with experts in the specialty areas of public health, microbiology, pediatric and adult infectious disease, primary care, and health justice to help inform our understanding of aspects of the health technology and our methodologies and to contextualize the evidence.

PROSPERO Registration

This health technology assessment has been registered in PROSPERO, the international prospective register of systematic reviews (CRD42024504025), available at crd.york.ac.uk/PROSPERO.

Clinical Evidence

Purpose

Because interferon-gamma release assay (IGRA) is already accepted and recommended for use by the current Canadian Tuberculosis Standards (8th edition; hereafter, "the Standards"), the purpose of this review is to summarize existing evidence on diagnostic accuracy and clinical utility.

Research Questions

- What is the diagnostic accuracy of IGRA for latent tuberculosis infection when used: (1) as first-line diagnostic test, and (2) in sequential testing (after a tuberculin skin test [TST])?
- What is the clinical utility of IGRA for assessing latent tuberculosis infection compared with TST?

The population of interest is adults and children, with a focus on the assessment of IGRA when used for the diagnosis of latent tuberculosis infection (LTBI) in circumstances aligned (at least in part) with the recommended population for IGRA testing as per the Standards.[18]

Methods

Clinical Literature Search

We performed a clinical literature search on January 9, 2024, to retrieve studies published from database inception until the search date. We used the Ovid interface in the following databases: MEDLINE, Embase, the Cochrane Database of Systematic Reviews, and the National Health Service Economic Evaluation Database (NHS EED). We used the EBSCOhost interface to search the Cumulative Index to Nursing & Allied Health Literature (CINAHL).

A medical librarian developed the search strategies using controlled vocabulary (e.g., Medical Subject Headings) and relevant keywords. We used a methodological filter to limit retrieval to systematic reviews, meta-analyses, and health technology assessments in keeping with the overview of reviews methodology, since several systematic reviews that potentially answered our research question were identified during the scoping period. The final search strategy was peer-reviewed using the PRESS Checklist.[49]

We created database auto-alerts in MEDLINE, Embase, and CINAHL and monitored them until April 2024. We also performed a targeted grey literature search of the International HTA Database, the websites of health technology assessment organizations and regulatory agencies, and systematic review registries, following a standard list of sites developed internally. See Appendix 1 for our literature search strategies, including all search terms.

Eligibility Criteria

Studies

Systematic reviews that met the inclusion criteria were prioritized based on multiple factors, in alignment to the Cochrane methods for overview of reviews,[50] including:

- Recency and comprehensiveness (i.e., are they sufficiently up to date?)
- Sufficiently homogenous so that they are aligned to the health technology assessment (HTA) research questions criteria and contextually relevant to Ontario
- Sufficiently homogenous in their reporting of the outcomes of interest and how the data are presented
- Present sufficient data (amount and type) to inform the HTA research questions
- Report risk of bias and quality assessment of primary studies (e.g., they use GRADE)
- Considered to be at sufficiently low risk of bias and of high methodological quality (as supported through the use of ROBIS)

Inclusion Criteria

- English-language full-text publications
- Systematic reviews reported as standalone publications or within HTAs, meta-analyses, or guidelines
    - Included systematic reviews must have transparent, defined inclusion criteria and a description of the search terms and databases searched

Exclusion Criteria

- Narrative reviews, primary studies (i.e., diagnostic accuracy studies, randomized controlled studies)
- Editorials, commentaries, case reports, conference abstracts, letters
- Animal and in vitro studies

Participants

Inclusion Criteria

- Adults > 18 years old and children 2–17 years old
- IGRA testing for the diagnosis of LTBI in circumstances aligned (at least in part) with the recommended population for IGRA testing as per the Standards[18]

Exclusion Criteria

- IGRA testing for conditions other than LTBI (e.g., active tuberculosis [TB])

- IGRA testing that is not aligned with the Standards, including for screening (e.g., general populations, employment [such as for health care workers], and serial testing) and for confirming active TB

Interventions

Inclusion Criteria

- IGRA testing

Exclusion Criteria

- Laboratory-developed IGRA, noncommercially available tests

Reference Test (for Diagnostic Accuracy)

Inclusion Criteria

- Clinically confirmed, such as through microbiological testing
  - Development of active TB may be used as the reference test when comparing accuracy of IGRA to TST

Comparators

Inclusion Criteria

- Tuberculin skin test

Exclusion Criteria

- No testing
- Comparisons between versions of IGRA

Outcome Measures

- Diagnostic accuracy: sensitivity, specificity, and predictive values (PPV/NPV)
- Clinical utility: impact on clinically important outcomes, including but not limited to progression to active TB and subsequent clinical effects for patients
- Indirect measures of clinical utility: impact on health services resources (e.g., diagnostic tests such as x-rays) or impact on medical decision-making (e.g., antibiotic use and adherence to taking prescribed medications)

Literature Screening

Two reviewers screened titles and abstracts to assess the eligibility of a sample of 100 citations to validate the inclusion and exclusion criteria. Greater than 80% agreement was achieved, and all

disagreements were discussed until consensus was reached. A single reviewer then screened all remaining citations using Covidence[51] and obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. The same reviewer then examined the full-text articles and selected studies eligible for inclusion. The reviewer also examined reference lists and consulted content experts for any additional relevant studies not identified through the search.

Data Extraction

One reviewer extracted relevant data on study characteristics of the systematic reviews and their included primary studies (as reported within the systematic reviews). The reviewer also extracted risk-of-bias, results, and PICOTS (population, interventions [reference-standard], comparator, outcomes, time, and setting) of the primary studies, as reported by the systematic reviews.

Equity Considerations

Equity issues related to the effect of IGRA for LTBI across various populations, including those with immune compromising conditions and/or are Bacille Calmette-Guérin (BCG) vaccinated, are reported to the extent that information was available in the included studies (see subgroup analyses, below, for a full list of groups considered).

Statistical Analysis

As an overview of reviews, we narratively summarize findings of the individual systematic reviews. Systematic reviews were considered for the presence and extent of clinical, methodological, and statistical heterogeneity as part of the inclusion selection and when interpreting and reporting the results. Meta-analyses conducted within the included systematic reviews were reported where considered appropriate and relevant.

Subgroup Analyses

We reported on the following subgroups where present in the included systematic reviews to explore the differences in accuracy based on known biological principles that may affect the accuracy:

- Specific IGRA test (with a preference for findings most relevant to Ontario, where currently only the QuantiFERON-TB Gold Plus is available)
- Confounding immunocompromising health conditions (e.g., HIV positive, being an organ transplant recipient, advanced-stage chronic kidney disease, diabetes due to its associated complications, receiving immunosuppressing drugs [including chemotherapy]) and lifestyle factors (heavy alcohol or cigarette use) that put people at higher risk for developing active TB [18]
- Specific age groups (e.g., children < 18 years of age or adults > 65 years of age)
- Settings (e.g., high-prevalence countries with an annual incidence of > 40 people affected per 100,000 population, congregate living settings, or as defined by individual reviews)
- BCG vaccination status (which is often associated with high-incidence countries), including where BCG status is unknown
- Pre-test probability (e.g., general screening vs. close-contact screening)

Critical Appraisal of Evidence

We assessed the risk of bias of any eligible systematic reviews using ROBIS.[52] We also limited the overview of reviews to individual systematic reviews that reported their own critical appraisal of evidence of the primary studies and reported their findings where possible.

Due to this being an overview of reviews, which relied on others' compilation and interpretation of the body of primary evidence, we were unable to evaluate the quality of the body of evidence for each outcome according to the *Grading of Recommendations Assessment, Development, and Evaluation* (GRADE) *Handbook*.[53]

Results

Clinical Literature Search

The search of the clinical literature yielded 467 citations published between database inception and January 9, 2024, including grey literature searches and after duplicates were removed. We identified no additional eligible studies from other sources, including database alerts (monitored until April 2024). In total, we identified 49 systematic reviews that met our inclusion criteria, of which 12 were considered to represent the most comprehensive body of evidence for the purposes of this overview of reviews as they were the most recently published (from 2020 onward). See Appendix 4 for a list of selected studies excluded after full-text review. Figure 2 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the clinical literature search.

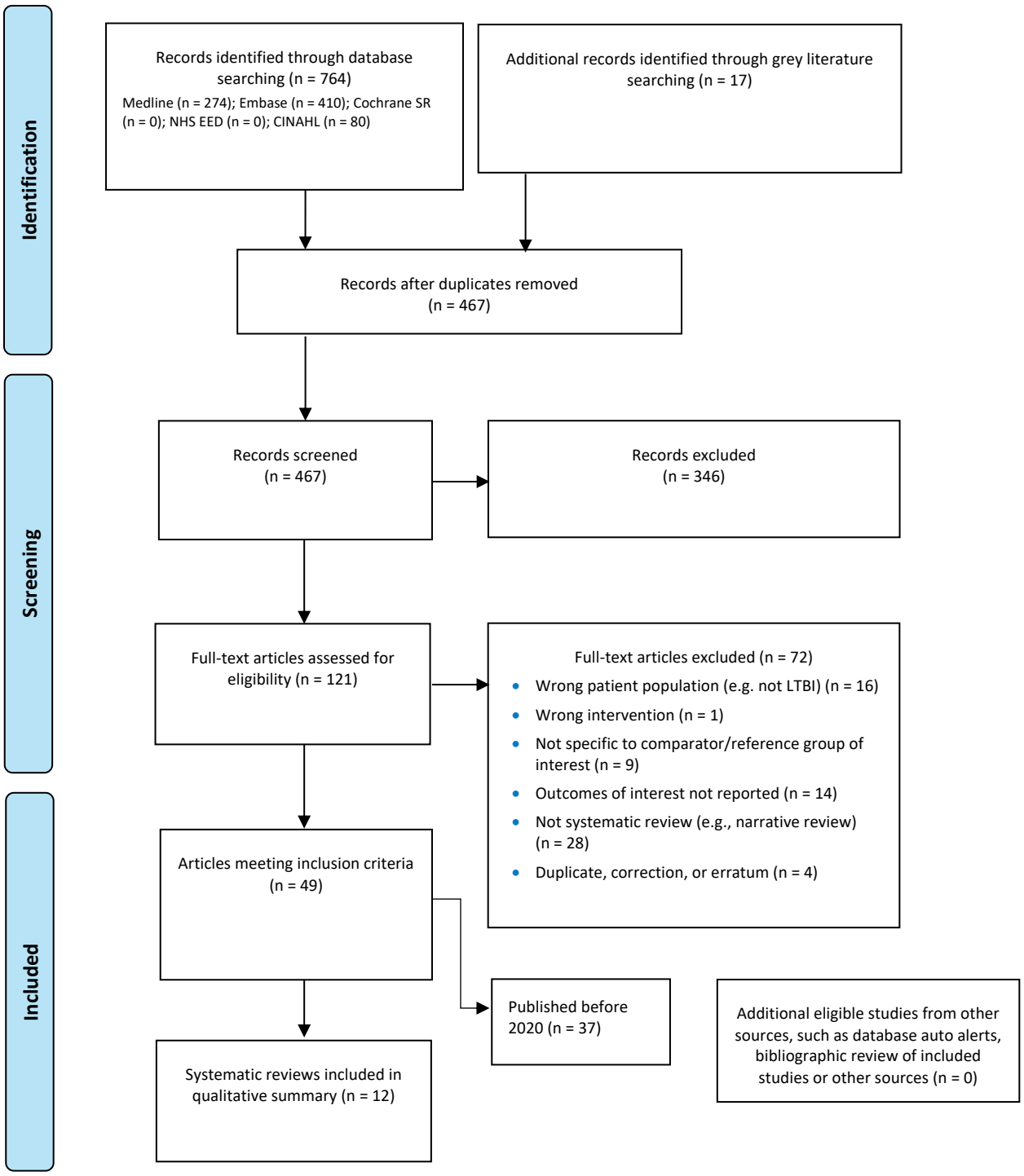

Figure 2: PRISMA Flow Diagram – Clinical Systematic Review

PRISMA flow diagram showing the clinical systematic review. The clinical literature search yielded 467 citations, including grey literature results and after removing duplicates, published up to January 9, 2024. We screened the abstracts of the 467 identified studies and excluded 346. We assessed the full text of 121 articles and excluded a further 72. In the end, we excluded all 37 studies published before 2020 because they were updated by later reviews or focused on older versions of IGRA and included 12 systematic reviews in the qualitative synthesis.

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

Source: Adapted from Page et al.[51]

Characteristics of Included Systematic Reviews

Our full-text screening identified 49 systematic reviews that met our inclusion criteria. After consideration of the identified individual reviews, we found that the body of evidence was well captured within the 12 reviews published from 2020 onward. All older systematic reviews (i.e., published before 2020; see Appendix 5) were reviewed in detail and considered to contain evidence that was directly or indirectly updated by more recently published reviews or focused on older versions of IGRA. Therefore, we report results from only the 12 systematic reviews published in 2020 or later.

One of the included systematic reviews was published twice, once as a grey literature report and again in a peer-reviewed journal.[54,55] Both publications were consulted, but we count them as 1 in our analysis.[55]

The 12 systematic reviews (Table 2) examined more than 500 unique primary studies. They applied various inclusion and exclusion criteria: some focused on specific populations (e.g., adults, children, people with select immunocompromising conditions such as HIV, or excluding primary studies with people who are immunocompromised), and some applied different limits to acceptable TST induration cutoffs, anti-tubercular treatment use, as well as TB incidence in country of origin. All systematic reviews acknowledged there is no gold standard for the diagnosis of LTBI. Reviews also differed in how they managed primary study reference standards. Some authors limited their reviews to longitudinal development of active TB, some accepted primary studies that confirmed with sputum culture–positive TB, and others did not specify limits to the inclusion criteria.

The included reviews reported primary studies from a balanced mix of sexes (male/female) and a variety of ages, from very young to elderly. Primary studies included in the systematic reviews represented countries from around the world, including the Americas, Europe, Asia, Africa, and Oceania. The systematic reviews considered BCG status differently, with some reviews simply mentioning BCG vaccination rates in supplemental tables describing the primary studies, while other reviews conducted subgroup analyses by BCG status. None of the reviews addressed the timing of IGRA versus TST testing. They all examined IGRA as an alternative replacement to TST.

Table 2: Characteristics of the Systematic Reviews Included in the Clinical Literature Review

Author, year	Review design			IGRA inclusion criteria (actual included IGRA tests)	Characteristics of included studies	
	Search dates, databases searched	Review methods	Population(s)		N studies (n participants)	Quality assessment
Volkman et al, 2024[56]	1998 to June 27, 2023 MedLINE, EMBASE, and Cochrane databases	English language Excluded case reports	Children < 5y old with no immune compromising conditions (e.g. HIV) Subgroup: BCG vaccination status	QFT-GIT	17 (4,335)	QUADAS Review considered them high quality (fulfilling ≥ 10 of 14 criteria)
Zhou et al, 2023[57]	Up to November 2022 Pubmed, Embase, Cochrane Library databases	Excluded abstracts, letters, case reports, reviews Results invalidated due to technical errors were counted as indeterminate	Adult and child populations considered high-risk for TB (recent contacts, immunocompromised, occupational risk, possible immunosuppression such as in children, nursing home residents, and homeless)[a]	Commercially available IGRAs Included: QFT-Plus; QFT-GIT (3rd gen); QFT-Gold (2nd gen); T-SPOT. TB	403 (486,886)	QUADAS-2 315 studies were of high quality and 53 were of moderate quality
Yahav et al, 2023[58]	Up to June 2022 Medline, Embase, and Cochrane CENTRAL	English language Excluded case reports and case series with < 10 participants	Adults who had ≥ 1 solid organ transplant (lung, heart, kidney, liver, pancreas, small bowel)	Commercially available IGRAs Included: QFT-GIT; QFT-G; T-SPOT.TB	17 (5,510)[b]	QUADAS-2 12 had risk of bias and 5 were found to have low risk of bias
Jonas et al, 2023[55]	Up to January 20, 2023 PubMed/MEDLINE, Cochrane Library, trial registries, references, experts, literature surveillance	English language Excluded screening close-contacts of active TB	Adults at increased risk for LTBI,[c] but also no underlying immunosuppression (e.g., HIV)	Commercially available IGRAs Included: QFT- Plus, QFT-GIT; T-SPOT.TB	79 (13,493)[b]	Fair or good quality Quality assessed with 8 point questions about study design, including patient selection and analyses methodologies
Zhou et al, 2022[59]	Up to March 12, 2022 EMBASE, PubMed, and Cochrane Library	No population or language restrictions Head-to-head comparative studies within 4 wk for receiving both tests; TST Excluded study if only IGRA or TST positive/negative patients were included, non-commercially available IGRAs	Adult and child populations considered high-risk for TB (recent contacts, immunocompromised, occupational risk, possible immunosuppression such as in children, nursing home residents, and homeless)[a]	Commercially available IGRAs Included QFT; T-SPOT.TB	458 (204,787)	QUADAS-2 ~75% were considered high or moderate quality

Author, year	Review design			IGRA inclusion criteria (actual included IGRA tests)	Characteristics of included studies	
	Search dates, databases searched	Review methods	Population(s)		N studies (n participants)	Quality assessment
Park et al, 2022[60]	Up to November 2021 Medline, EMBASE, Cochrane Library databases	English language Excluded abstracts and studies focused on pediatric patients	Inflammatory bowel disease Subgroups: people on immunosuppressants vs. not, other subgroups based on IGRA device, BCG status etc.	Commercially available IGRAs Included: QFT-GIT; T-SPOT.TB	20 (4,045)	Newcastle Ottawa Scale (all studies considered high quality with combined scores > 7)
Chen et al, 2022[61]	Up to September 30, 2021 PubMed, Web of Science, Cochrane, and Embase	No population restrictions Included articles, briefs, conference abstracts in any language	People living with HIV	IGRA, no limits specified Included: QFT-GIT; T-SPOT.TB	7 (1,267)[b]	QUADAS-2 Overall low risk of bias[d]
Oh et al, 2021[62]	January 2013 to May 2020 MEDLINE, Embase, Web of Science, Cochrane Database of Systematic Reviews	Original full text reports that were conducted with blind assessment Excluded editorials, narrative reviews, letters, and conference abstracts.	Adults at higher risk for TB[e] (excluded studies with very low risk of LTBI: age < 50 y, life-long residents of countries with < 25/100,000 TB incidence, no known exposure, and health care workers]	QFT-Plus Also included as comparators: QFT-GIT,T-SPOT.TB	24 (6,357)	QUADAS-2 Low to high risk of bias
Zhou et al, 2020[63]	Up to October 18, 2019 PubMed, Embase, Web of Science, Cochrane Library	No language restriction, cohort design Excluded abstracts, letters, case reports and reviews, or if LTBI progressed to active TB within 3 months	High risk population for TB, according to WHO recommendations (e.g., people living with HIV infection, transplantation, dialysis, health-care workers and immigrants)[a]	IGRA, no limits specified Included: QFT-G; QFT-GIT; T-SPOT.TB	40 (50,592)	Modified Newcastle-Ottawa Scale Moderate to low risk of bias
Yamasue et al, 2020[64]	August 1992 to October 22, 2018 PubMed, Cochrane Central Register of Controlled Trials, EMBASE database	English language, multivariate analysis assessing risk factors that influence false negatives of IGRA Excluded abstracts and studies focused on children only	Adults Subgroups explored: gender, advanced age, low peripheral lymphocyte counts, HIV positivity, extrapulmonary TB, and BMI Also classified by low incidence TB country vs. middle and high incidence country (as per WHO criteria)	Commercially available IGRAs Included: QFT-GIT; T-SPOT.TB; QFT-Gold; ELISPOT	17 (9,470)	Cochrane handbook, and MOOSE guidelines Modified Heyden's criteria: studies averaged meeting 3.5 of 6 criteria indicating moderate quality
Campbell et al, 2020[65]	January 1, 1990 to May 17, 2019 Medline, Embase, Cochrane Controlled Register of Trials	English or French > 12-mo follow up, at least 10 participants, untreated Excluded BCG vaccinated; studies of people with HIV in high TB incidence countries	People in higher risk groups for developing TB	QFT-Gold QFT-GIT T-SPOT.TB	102 (116,197)	MOOSE, QUADAS-2 60% moderate to high quality

Author, year	Review design			IGRA inclusion criteria (actual included IGRA tests)	Characteristics of included studies	
	Search dates, databases searched	Review methods	Population(s)		N studies (n participants)	Quality assessment
Alrajhi et al 2020[66]	June 2011 to April 2018 Medline, Embase, Cochrane databases	Adults, English, abstract, letters and full texts included Excluded if < 10 IBD patients	Inflammatory bowel disease Subgroups: people on immunosuppressants vs. not	QFT-QFT-G, QFT-GIT	16 (2,488)	QUADAS-2 Most studies had low risk of bias, 3 studies possible high risk of bias

Abbreviations: BCG, Bacille Calmette-Guérin; BMI, body mass index; HIV, human immunodeficiency virus; IBD, Inflammatory bowel disease; IGRA, Interferon-Gamma Release Assay; LTBI, latent tuberculosis infection; QFT, QuantiFERON-TB; QFT-G, QuantiFERON-TB Gold; QFT-GIFT, QuantiFERON-TB Gold-In-Tube; QFT-Plus, QuantiFERON-TB Gold-Plus; TB, tuberculosis; TST, tuberculin skin test.

[a]We opted to include this review in our overview of reviews as the majority of studies were in our population of interest.

[b]Review included additional studies, beyond the scope of this overview of reviews.

[c]According to WHO criteria.

[d]Risk of bias reported only on full cohort of studies.

[e]One included study had age limits of 15 years and older.

Risk of Bias in the Included Studies

Risk of bias in the reviews was assessed using ROBIS (see Appendix 2). This overview selected for systematic reviews that were considered well done, and this is reflected in the high-quality ROBIS scores of the included publications.

The 12 systematic reviews from which we extracted data all conducted quality assessment of the primary studies comprising their respective bodies of evidence and generally found moderate to low risk of bias across the included studies (Table 2). However, except for Jonas et al[55] and Oh et al,[62] they did not report quality for each individual outcome for the outcomes of sensitivity and specificity (Table 3).

Diagnostic Accuracy

Diagnostic accuracy was reported in 6 systematic reviews. Sensitivity and specificity, as well as positive and negative predictive values, were pooled in a number of reviews. High values were reported for specificity across all reviews and subpopulations explored; however, sensitivity was found to be lower among those experiencing immunosuppression, such as people with HIV, in alignment with clinical expectations due to the suppressed immune response of a person overall; results are summarized in Tables 3 and 4.

Additionally, Volkman et al[56] reported a pooled diagnostic odds ratio of 18.84 (95% CI, 7.33–48.41) and a summary receiver operating characteristic (SROC) curve of 0.7812, which they reported as good diagnostic accuracy. Yamasue et al[64] explored risk factors associated with false-negative findings of IGRA and reported that advanced age, as well as immunosuppressive conditions such as HIV positivity, lower peripheral lymphocyte counts, and being on immunosuppressive therapy (including cancer immunotherapies), were all significantly associated with false-negative findings.

Table 3: Sensitivity and Specificity of IGRA

Author, year	Population	Study group details N studies (n participants)	Pooled sensitivity	Pooled specificity	Quality assessment as reported
Volkman et al, 2024[56]	Children < 5 with no underlying immunosuppression	Overall 17 (4,335)	0.45 (95% CI, 0.42–0.48)	0.96 (95% CI, 0.96–0.97)	Not reported by outcome, overall high quality
Yahav et al, 2023[58]	Adults with ≥ 1 solid organ transplant	QFT-GIT 10 (NR)	37.5%	77.9%	
		T.SPOT 3 (NR)	82.3%[a]	73.5%	
Jonas et al, 2023[55]	Adults at increased risk for LTBI, with no underlying immunosuppression	QFT-Plus Total: 11 studies Sens: 11 (939) Spec: 1 (211)]	0.89 (95% CI, 0.84–0.94)	0.98 (95% CI 0.95–0.99)	Moderate for sensitivity; low for specificity
		QFT-GIT Total: 51 studies Sens: 48 (7,055) Spec: 3 (2,090)	0.81 (95% CI, 0.79–0.84)	0.99 (95% CI, 0.98–0.99)	High for sensitivity, moderate for specificity

Author, year	Population	Study group details N studies (n participants)	Pooled sensitivity	Pooled specificity	Quality assessment as reported
		Studies with BCG vaccination prevalence > 50%	0.78 (95% CI, 0.73–0.83)	Not estimable	
		T-SPOT.TB Total: 39 studies Sens: 37 (5,367) Spec. 2 (1,664)	0.90 (95% CI, 0.87–0.92)	Ranges: 0.95 (95% CI, 0.91–0.97) to 0.97 (95% CI, 0.96–0.98)	High for sensitivity, moderate for specificity
		Studies with BCG vaccination prevalence > 50%	0.89 (95% CI, 0.86–0.92)	Not estimable	
Chen et al, 2022[61]	People living with HIV	7 studies,[b] 1,267 participants	0.64 (95% CI, 0.61–0.66)	Not estimable	
		QFT 5 studies, 691 participants	0.66 (95% CI, 0.56–0.70)[c]	Not estimable	
		T-SPOT 3 studies, 576 participants	0.60 (95% CI, 0.56–0.64)	Not estimable	
Oh et al, 2021[62]	Adults at higher risk for TB	QFT-Plus 7 studies in sensitivity, 2 in specificity	91.4% (95% CI, 87.5–94.2%)	97.8% (95% CI, 95.5–98.9)	QUADAS-2 Sensitivity: high risk of bias Specificity: low risk of bias
		QFT-GIT 7 studies in sensitivity, 2 in specificity	91.4% (95% CI, 88.9–93.4)	98.7 (95% CI, 96.7–99.5)	QUADAS-2 Sensitivity: low risk of bias Specificity: low risk of bias
		T-SPOT.TB 2 studies in sensitivity, 1 in specificity	90.2% (95% CI, 61.9–98.1)	98.1% (95% CI, not applicable)	QUADAS-2 Sensitivity: low risk of bias Specificity: low risk of bias

Abbreviations: CI, confidence interval; LTBI, latent TB infection; NR, not reported; TB, tuberculosis.

[a]Systematic review authors suggested findings are skewed due to very limited studies.

[b]One publication's results for QFT and T-Spot were extractable separately.

[c]Data reported here comes from the supplemental information of the systematic review and differs slightly from the published abstract.

Table 4: Positive and Negative Predictive Value of IGRA

Author, year	Population	Study group details, if specified N studies (n participants)	Diagnostic accuracy of IGRA PPV (95% CI)	 NPV (95% CI)
Yahav et al, 2023[58]	Adults with solid organ transplant	All IGRA	1.2% (NR)	99.6% (NR)
		QFT	0.86% (NR)	99.6% (NR)
		T-Spot	1.59%(NR)	97.6% (NR)
Zhou et al, 2020[63]	High risk population for TB, according to WHO recommendations	All IGRA tests PPV: 38 studies (4,212) NPV: 40 studies (23,607)	4.5% (3.5–5.8)	99.7% (99.5–99.8)
		QFT	4.8% (3.3–6.7)	99.6% (99.4–99.8)
		T-SPOT.TB	3.9% (2.7–5.4)	99.8% (99.6–100)

Abbreviation: CI, confidence interval; IGRA, interferon-gamma release assay; NPV, negative predictive value; NR, not reported; PPV, positive predictive value; TB, tuberculosis; WHO, World Health Organization.

Concordance Between IGRA and TST

In the absence of a gold standard, concordance likely represents similarities between the tests, while discordance might be suggestive of improved accuracy of IGRA compared to TST (see below). Lower positivity rates with IGRA compared to TST are seen by the field to represent fewer false-positive rates and thus a consideration in favour of IGRA for certain populations.

Table 5 shows a representative sample summarizing reported risk differences in positivity rates between the IGRA test and TST, as conducted by 1 systematic review. It reports varying degrees of lower positive rates for IGRA compared to TST across different subpopulations. Particularly notable due to its applicability to the Ontario context is the observed lower positive rates among BCG-vaccinated people in areas with a low TB burden (risk difference, −0.19), which can be indicative of lower false-positive rates with IGRA, especially when taken together with the outcomes of clinical utility reported later in this report.

Table 5: Risk Difference of Positivity Rates Comparing IGRA and TST Findings

Author, year	Population	N studies (n people)	Risk difference (95% CI)
Zhou et al, 2022[59]	General population of adults at higher risk for TB	66 studies (53,799)	−0.11 (−0.15 to −0.07)
	Immunocompromised patients	130 studies (24,143)	0.05 (0.02 to 0.07)
	Children	7 studies (5,226)	−0.26 (−0.46 to −0.05)
	Nursing home residents	3 studies (427)	−0.26 (−0.36 to −0.17)
	Low TB-burden area (< 100 per 100,000)		
	Not BCG vaccinated	33 studies (23,213)	−0.02 (−0.07 to 0.02)
	BCG vaccinated	66 studies (27,851)	−0.19 (−0.25 to −0.14)
	High TB-burden area (> 100 per 100,000)		
	Not BCG vaccinated	11 studies (2,825)	0.02 (−0.08 to 0.11)
	BCG vaccinated	15 studies (5,574)	−0.05 (−0.09 to −0.01)

Abbreviations: BCG, Bacille Calmette-Guérin; CI, confidence interval; IGRA, interferon-gamma release assay; TB, tuberculosis; TST, tuberculin skin test.

Zhou et al[59] also reported discordance. When IGRA was used, there were significantly higher pooled PPV and NPV than when TST was used (p = .002); however, Yahav et al[58] reported no differences in PPV and NPV between IGRA and TST results (mean difference, 0.000 to 0.001). Additional measures of concordance and discordance are reported in Appendix 3, Table A2.

Indeterminate Rate

Zhou et al[57] conducted a systematic review focused on indeterminate findings rates of IGRA. In their review, they reported on 403 studies (486,886 individuals) and found that the pooled indeterminate rate for IGRA was 3.9% (95% CI, 3.5%–4.2%).

The authors analyzed various subgroups and reported slightly higher rates of indeterminate findings (5.7%; 95% CI, 4.8%–6.6%) among the 48,379 people in 134 studies who are immunocompromised (e.g., people with HIV or cancer, receiving hemodialysis, undergoing organ transplant, or are drug and alcohol abusers).[57] Children have higher rates (4.3%) of indeterminate findings than adults (odds ratio [OR] 2.56; 95% CI, 1.79–3.57). There were some differences between the IGRA brands, with the lowest rates of indeterminate findings observed in the newest generation.[57]

Other systematic reviews report similar findings, with indeterminate rates ranging from 0% to 4.5%.[55,56] People with inflammatory bowel disease or on immunosuppressive therapy have higher indeterminate rates (compared to people not on therapy), with an OR of 2.91 (95% CI, 1.36–6.24).[60]

Clinical Utility

One key measure of clinical utility is the progression to active TB. As there is no reference standard for LTBI, part of the concern about the TST is that there is a high rate of false-positives and therefore people who receive treatment unnecessarily. Thus, it is clinically important to determine if both tests can predict development into active disease and how IGRA compares to TST at doing so. Table 6 summarizes the findings from the 2 systematic reviews that report this outcome. While each review chose slightly different metrics to measure PPV, findings consistently demonstrate that a positive finding with IGRA is associated with a higher likelihood of a person going on to experience active TB, suggesting that IGRA may have a higher rate of true positives than TST.

Zhou et al[57] reported statistically significant differences in IGRA and TST (P = .008). Findings were similar in a sensitivity analysis limited to the body of evidence of the direct head-to-head studies.

Table 6: Disease progression among *positive* LTBI test results

Author, year	Population	N studies (n people)[a]	Results[a]	
			Risk ratio (95% CI)	
Zhou et al, 2020[63]	Adults at higher risk for TB	33 studies (26,212)	With IGRA	9.35 (6.48–13.49)
		16 studies (22,120)	With TST (> 10 mm)	4.28 (3.29–5.56)
	Subgroup of head-to-head studies of tests being used in the same population	10 studies (5,337)	With IGRA	7.12 (3.39–14.94)

Author, year	Population	N studies (n people)[a]	Results[a]	
		5 studies (3,828)	With TST (> 10 mm)	4.30 (2.03–9.10)
		5 studies (1,454)	With TST (> 5 mm)	2.81 (0.69–11.42)
			Incident rate ratio (95% CI)	
Campbell et al, 2020[b] [65]	Exposed contacts, at higher risk for TB	20 studies (4,078)	With IGRA	11.6 (6.6–20.5)
		29 studies (18,446)	With TST (> 10 mm)	4.1 (2.6–6.5)
	Recent immigrant or refugee	4 studies (1,597)	With IGRA	10.9 (6.3–18.9)
		4 studies (10,785)	With TST (> 10 mm)	4.0 (2.1–7.7)
	Immune suppressing medication	4 studies (141)	With IGRA	4.5 (0.1–262.8)
		7 studies (234)	With TST (> 5 mm)	6.0 (2.0–17.6)

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; IGRA, interferon-gamma release assay; LTBI, latent TB infection; TB, tuberculosis; TST, tuberculin skin test

[a]Subgroups with various TST induration cut-offs shown in grey-scale.

[b]Campbell et al[65] also conducted many subgroups and reported similar conclusions for people with various immune compromising conditions, including HIV-positive status, transplant recipients, and aged > 65 years.

Indirect Measures of Clinical Utility

No systematic reviews were identified that reported on the measures of impact on health services resources, such as reduction in the number of unnecessary tests (e.g., x-rays). Nor were any identified that reported on the impact on medical decision making, such as changes to antibiotics prescribed or adherence by patients to prescribed medications.

Ongoing Studies

While there are many ongoing studies in the field of tuberculosis, and many include the use of IGRA and other novel tests, we are not aware of any pivotal ongoing study that has the potential to substantially impact the relevance of this review.

Discussion

This overview of reviews identified a large body of evidence comprising many well-done systematic reviews reporting moderate- to high-quality primary studies. The evidence supports the diagnostic accuracy of IGRA. While there were some differences in reported accuracy outcomes, we observed consistently high specificity and NPV values, thus making IGRA especially useful as a rule-in test. This finding is in alignment with the current recommendations from the Standards.[2,23]

Concordance between IGRA and TST was inconsistent. However, there is no gold-standard test for LTBI, and it is known that TST has false-positives. Therefore, discordance is thought to be representative of

the improved accuracy of IGRA compared to TST, particularly considering the observed lower rates of positivity with IGRA. These lower rates are believed to be reflective of the reduced amount of potentially unnecessary treatment in people who might otherwise have received a false-positive finding from a TST. There is a false-positive reaction with TST among people who have BCG vaccination, and differences in rates of positivity between IGRA and TST, as demonstrated in this overview, are in alignment with other bodies of evidence.[67]

Clinical utility, measured as the progression to active TB after a positive IGRA or TST result, is a key clinically important outcome. In this overview of reviews, we observed that there was an approximately 2-fold higher predictive value from a positive IGRA leading to active TB compared with TST. Taken together with the findings from this overview of reviews of lower positivity rates among those who received IGRA compared to TST, we can reason that IGRA has a lower false-positive rate, particularly for certain populations, such as people who have been BCG vaccinated. These findings are particularly notable in the subgroup analyses by Zhou et al,[63] which was limited to head-to-head studies where all patients received both IGRA and TST and therefore isolates the likely impact of the differences in tests as it eliminates the potential impact of differences in after-test treatment access being the cause of observed differences.

Finally, IGRA tests are intended to yield binary results (yes/no), but there is also the potential for indeterminate results. With IGRA, an indeterminate result may indicate an underlying immunodeficiency, hyperactivity of interferon-gamma release, or a compromised state (e.g., the mitogen tube not having a reaction), among other possibilities (email communication, Angela Ma, PhD, May 21, 2024). It was observed that there are higher rates of indeterminate findings among people with immunocompromising disorders (e.g., transplant recipients and people living with HIV). According to clinical experts, an indeterminate finding within this group would be clinically meaningful as it is a flag for further investigation, whereas TST, which may simply yield a false-negative finding (email communication, Kevin Schwartz, MD, May 16, 2024; Elizabeth Rea, MD May 22, 2024).

Strengths and Limitations

The decision to conduct an overview of reviews was made after an exhaustive scoping effort, including consultation with clinical experts. In identifying systematic reviews for inclusion, we considered overall quality, ensuring the systematic reviews were well done with low risk of bias, with comprehensiveness, and in alignment with our research questions. We followed the principles of methods for conducting an overview of reviews in alignment with those published by Cochrane.[50]

There may be missing systematic reviews due to our inclusion criterion of English-language studies only, and we relied on other reviews having broader inclusion criteria to capture as broad a body of evidence as possible. Due to the use of an overview-of-reviews approach, we were also not able to capture the most recent primary studies. We are aware of 2 recent publications of studies of a large population that is very similar and relevant to the Ontario population and that followed up on the clinical utility of progression to disease. Findings from these 2 primary studies demonstrate alignment with the results reported in this overview of reviews.[68,69]

The technology surrounding IGRAs and TST is continually advancing, and we are limited to what has been published and included in other systematic reviews, potentially making our overview a few years behind the most current advancements in this space. With that said, this overview of reviews included many versions of IGRA tests, including the most recent versions that are currently in use in Ontario

(email communication, Angela Ma, PhD, May 21, 2024; Elizabeth Rea, MD, May 22, 2024), which have been demonstrated to have similar concordance.[33] This overview does not, however, account for the newest developments in laboratory methods for IGRA[70] or new types of skin testing based on antigen testing as an alternative to both IGRA and TST.[71]

Additionally, the TB population is broad and heterogeneous, and LTBI does not have a gold reference standard. This has led to an equally broad and heterogenous body of primary studies of evidence. Each review managed this diversity slightly differently; thus, there were differences in conclusions and interpretations. There were many more subgroup and sensitivity analyses within the included reviews than are presented in this overview of reviews. We selected and reported analyses that best aligned to our research questions and relevance to the Ontario context. However, none of the included reviews examined the optimal timing of multiple tests where conducting TST before or after IGRA may influence the overall diagnostic accuracy of test findings, as it is well known that there is a booster effect from both tests, which is an acknowledged consideration in the Standards.[18]

There are also limitations with the body of evidence itself. The absence of a proper reference standard has led to some studies using microbiologically confirmed LTBI as their reference, while others have used active TB as their reference. The included reviews acknowledge that not having a direct test is problematic as it requires extrapolation for both sensitivity with active TB and specificity with low-risk populations.[55] Additionally, active TB is clinically distinct from LTBI and therefore not seen as an adequate reference.[72]

Additionally, there is no universal standard for the TST, with accuracy depending on the induration cut-off used by the primary studies. Many reviews limited the primary study inclusion criteria to a specific cut off (e.g., > 5 mm) or conducted subgroup analyses based on 5, 10, or 15 mm cutoffs. The higher the cutoff used, when interpreting the TST, the more certainty there is that a positive result is a true positive. Thus, when comparing TST to IGRA, the manner in which TST was conducted may change the interpretation of how its results compare to the results from IGRA. The TST relies on the clinical skills of the person administering it for both placement and reading and is prone to interrater reliability errors.[73] Additionally, the incidence of TB in a region influences the pretest probability and therefore the calculations around accuracy of a diagnostic test. In regions with high TB incidence (e.g., > 100 per 100,000 people), there will be fewer false-positives from the TST, and thus results may appear more similar compared to the IGRA test even for populations with known accuracy concerns such as the BCG-vaccinated. This is reflected in many of the systematic reviews included in this overview of reviews.[55,56,58,59,66]

Finally, there are many other factors that were not consistently accounted for across the included systematic reviews. For example, Yamasue et al[64] identified advanced age as a risk factor for a false-positive finding with an IGRA test; however, this factor is rarely accounted for in our included reviews. As well, a review by Saag et al[74] (that did not meet our inclusion criteria) reflected that low body mass index was a risk factor for LTBI, but we did not see this explicitly accounted for in our included body of evidence.

Conclusions

This overview of reviews summarizes the existing evidence on diagnostic accuracy and the clinical utility of IGRA for LTBI. Interferon-gamma release assay was found to have good evidence as a rule-in test for LTBI due to consistently high specificity. The reviews reported slightly lower sensitivity among people

who have underlying immunosuppression conditions (e.g., people who are HIV positive or have received an organ transplant, or are on cancer treatment or dialysis) compared to a more general population. However, compared to TST (the standard test for TB), IGRA appears to have fewer false-positive results, as signaled by a lower risk difference of developing active TB among those who tested positive on both LTBI tests in head-to-head comparisons. This was particularly notable in immunocompromised populations and was also observed in children and the elderly (e.g., people in nursing homes) and those who have received an anti-tuberculin vaccination known as the BCG vaccine. Additionally, IGRA may be informative for people with immunocompromising conditions who are at risk of a false-negative result from a TST, as it yields indeterminate findings, signaling that further clinical investigation may be needed.

Therefore, the evidence supports the use of IGRA as an acceptable alternative to TST for testing LTBI, in accordance with situations outlined in the Standards.

Economic Evidence

Research Question

Based on the published evidence in a Canadian health care setting, what is the cost-effectiveness of the interferon-gamma release assay (IGRA) used alone (as a single test) or in sequential testing pathways with the tuberculin skin test (TST) compared with TST alone for supporting the diagnosis of latent tuberculosis infection (LTBI) in eligible populations, aligned with the recommendations of the eighth edition of the Canadian Tuberculosis Standards (hereafter, "the Standards")[75]?

The population of interest is adults aged ≥ 18 years and children aged 2 to 17 years, with a focus on the assessment of IGRA when used for supporting the diagnosis of LTBI, in circumstances aligned (at least in part) with the recommended population for IGRA testing as per the Standards.[75] The Standards proposed a strong recommendation for the use of IGRA as an alternative or additional test to TST for people who previously received a Bacille Calmette-Guérin (BCG) vaccine, immunocompromised people, people unable or unlikely to return to have their TST read, and people who are contraindicated for TST.

Methods

Economic Literature Search

We performed an economic literature search on January 10, 2024, to retrieve studies published from database inception until the search date. To retrieve relevant studies, we developed a search using the clinical search strategy with an economic and costing filter applied. In addition to the databases used for the clinical search, we also used the Ovid interface in the Cochrane Central Register of Controlled Trials.

We created database auto-alerts in MEDLINE, Embase, and CINAHL and monitored them until June 18, 2024. We also performed a targeted grey literature search following a standard list of websites developed internally, which includes the International HTA Database and the Tufts Cost-Effectiveness Analysis Registry. See Clinical Literature Search, above, for further details on methods used. See Appendix 1 for our literature search strategies, including all search terms.

Eligibility Criteria

Studies

Inclusion Criteria

- English-language full-text publications
- Cost–utility, cost-effectiveness, cost–benefit, or cost–consequence analyses

Exclusion Criteria

- Narrative or systematic reviews, non-comparative costing (feasibility) studies or cost-of-illness studies, letters/editorials, case reports, commentaries, abstracts, posters, unpublished studies

Study Setting

Inclusion Criteria

- Comparative primary economic analyses conducted from a public health care payer perspective; i.e., the government(s) of Canada or a Canadian province

Exclusion Criteria

- Comparative economic analyses conducted in a non-Canadian setting
- Comparative economic analyses conducted in Canadian settings from a wider (e.g., societal) or narrower (e.g., hospital) perspective, not reporting cost-effectiveness outcomes by the payer perspective (i.e., not able to extract outcomes from the perspective of the Ontario Ministry of Health)

Participants/Population

Inclusion Criteria

- Adults aged ≥ 18 years and children aged 2 to 17 years, undergoing testing with IGRA for the diagnosis of LTBI, with a preference for the circumstances recommended by the Standards[75]

Exclusion Criteria

- People undergoing testing with IGRA in circumstances that are not aligned with the Standards[75] including its use for screening (e.g., general populations, for employment such as health care workers or for confirming active cases of tuberculosis [TB] disease)

Interventions

Inclusion Criteria

- IGRA as a single test (IGRA alone) or in combination with TST (e.g., IGRA as a follow-up to TST as part of sequential testing)

Exclusion Criteria

- Laboratory-developed IGRA, noncommercially available or non–Health Canada approved tests

Comparators

Inclusion Criteria

- Tuberculin skin test

Exclusion Criteria

- No testing
- IGRA tests only (e.g., studies comparing various commercial types of IGRA tests)

Outcome Measures

- Costs
- Health outcomes (e.g., life-years, cases of active TB, quality-adjusted life years [QALYs])
- Incremental costs
- Incremental effectiveness
- Incremental cost-effectiveness ratios (ICERs; expressed as additional costs [in Canadian dollars] per active TB case averted or per 1 QALY gained)

Literature Screening

A single reviewer conducted an initial screening of titles and abstracts using Covidence[51] and then obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. The same reviewer then examined the full-text articles and selected studies eligible for inclusion. The reviewer also examined reference lists and consulted content experts for any additional relevant studies not identified through the search.

Data Extraction

We extracted relevant data on study characteristics and outcomes to collect information about the following:

- Source (e.g., citation information, study type)
- Methods (e.g., study design, analytic technique, perspective, time horizon, population, intervention[s], comparator[s])
- Outcomes (e.g., health outcomes, costs, incremental cost-effectiveness ratios)

Study Applicability and Limitations

We determined the usefulness of each identified study for decision-making by applying a modified quality appraisal checklist for economic evaluations originally developed by the National Institute for Health and Care Excellence (NICE) in the United Kingdom.[76] The NICE checklist has 2 sections: the first is for assessing study applicability, and the second is for assessing study limitations. We modified the wording of the questions of the first section to make it specific to Ontario. Using this checklist, we assessed the applicability of each study to the research question and Ontario context (directly, partially, or not applicable). Next, we assessed the limitations (minor, potentially serious, or very serious) of the studies that we found to be applicable.

Results

Economic Literature Search

The economic literature search yielded 487 citations published between database inception and January 10, 2024, including grey literature searches and after duplicates were removed. We did not identify any additional eligible studies from other sources, including database alerts (monitored until June 18, 2024). In total, we identified 5 studies that met our inclusion criteria. See Appendix 6 for some examples of studies excluded after full-text review. Figure 3 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the economic literature search.

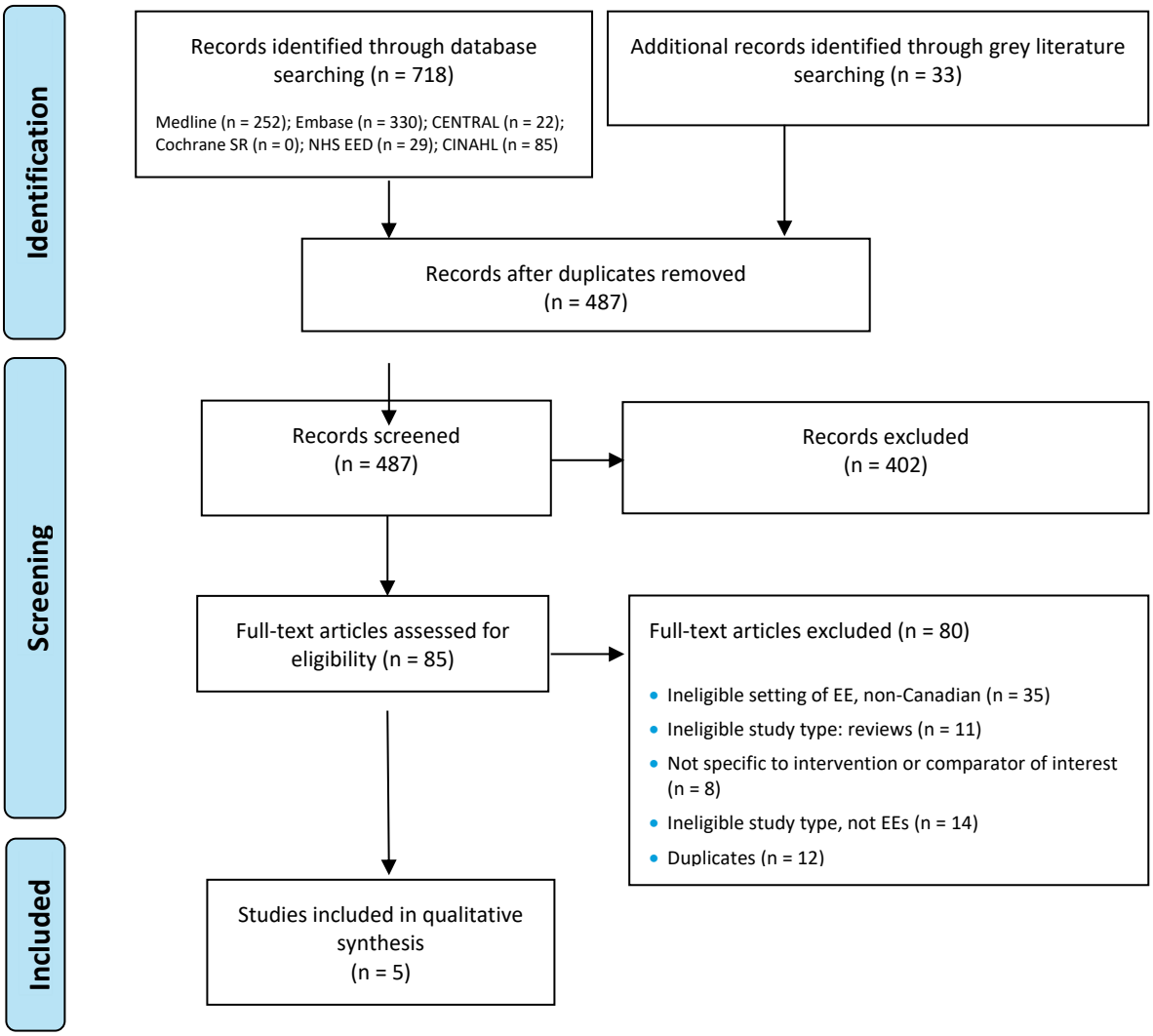

Figure 3: PRISMA Flow Diagram – Economic Systematic Review

PRISMA flow diagram showing the economic search strategy. The database search of the economic literature yielded 487 citations published from inception until January 10, 2024, including grey literature searches and after duplicates were removed. We identified no additional eligible studies from other sources. After removing duplicates, we screened the abstracts of 487 studies and excluded 402 citations. We assessed the full text of 85 articles and excluded a further 80. In the end, we included 5 articles in the qualitative synthesis.
Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; EE, economic evaluation.
Source: Adapted from Page et al.[51]

Overview of Included Economic Studies

Tables A3 and A4 (Appendix 7) present study designs, populations, outcomes, and results of the 5 included studies, which were published between 2007 and 2019.[77-81] Below, we summarize their findings.

Review of Methods of Included Economic Studies

Analysis Characteristics: Study Type, Perspective, Time Horizon, and Discounting

All included economic evaluations were model-based cost-effectiveness analyses. Four studies were conducted from the Canadian third-party payer perspective (i.e., the Ministry of Health, British Columbia).[81] One study did not specify the perspective used; instead, the authors reported that they considered government and health system costs (reflecting the Ontario Ministry of Health perspective) such as those related to LTBI screening and treatment, as well as patients' out-of-pocket costs. However, costs associated with TB-related death or disability were excluded.[81]

The included studies modeled the natural and clinical history of LTBI and TB across 2 populations. For the general population (immigrants and contacts),[77,79-81] studies projected outcomes over 10- to 25-year time horizons. For the immunocompromised population (i.e., patients with chronic kidney disease),[78] a shorter 5-year time horizon was used. All studies appropriately discounted both costs and health outcomes using the same discount rate, which was 3% in 3 studies[77,80,81] and 1.5% in 2 studies.[78,79]

Study Populations

All studies considered populations that conformed to the recommended eligibility criteria for LTBI screening by the Standards (7th and 8th editions).[75,82] Thus, study populations included a general population without comorbid conditions (all immigrants seeking permanent residence status[77,79,81]), a subgroup of immigrants who were flagged for post-medical TB surveillance,[79] and individuals who were close or casual contacts of confirmed or suspected active TB cases.[80,81] One study considered immunocompromised individuals, such as immigrants who had late-stage chronic kidney disease (CKD) and/or had initiated dialysis treatment.[78] Notably, no Canadian study specifically examined vulnerable populations, such as people who are experiencing homelessness, or children and young adults, as a separate population.

All studies addressed heterogeneity of the study populations regarding a potential risk of LTBI and used complex statistical procedures such as cohort stratification or variable adjustment to account for differences in age, BCG vaccination status, and incidence of TB in the country of origin. Data needed for these adjustments were sourced from the published literature or estimated from the provincial databases of British Columbia and Ontario and from federal immigration data. The populations were stratified as following:

- Oxlade et al[81] stratified the population by annual incidence of TB in the country of origin using the following categories: low (2/100,000), intermediate (60/100,000), and high (120/100,000)
- Campbell et al[77,79] accounted for differences in TB incidence in the country of origin using the following categories: low (<30 cases/100,000 persons/year), moderate (30–99 cases/100,000

persons/year), high (100–199 cases/100,000 persons/year), and very high (≥ 200 cases/100,000 persons/year)[78]

- Marra et al[80] examined contacts exposed to a TB case and stratified their cohort by ethnicity to foreign-born, non-aboriginal Canadian-born, and Aboriginal

For these cohorts subgrouped by risk of TB, the authors further estimated the LTBI prevalence:

- Indirectly, by using formulas to combine age of immigrants and incidence of TB in the country of origin [81] or age of contacts, TST-positivity rate in British Columbia, and country-specific incidence of TB [80]
- Directly, from linkages of the federal and provincial administrative database registry data[77-79]

Strategies: Interventions and Comparators

The intervention strategies across all studies included IGRA either as a standalone test or combined with TST (as part of sequential testing). In the sequential testing pathway, individuals who tested positive with TST were subsequently assessed with IGRA. If IGRA yielded an indeterminate finding, a second IGRA test was included. All models included therapy for LTBI or for active TB (if LTBI reactivated), following the positive test finding and additional work-up (where necessary).

In 2 studies in a general population of migrants[80,81] and 1 in people with CKD,[78] therapy with isoniazid (INH) was modeled (either as a preventative treatment for LTBI or therapy for active TB, depending on the modeled health state). The other 2 studies in migrants considered preventative treatment with either rifampin (RIF, 4 months) or INH (9 months) for LTBI. Therefore, these 2 studies included more interventions with IGRA to delineate the difference in LTBI treatment following a positive IGRA test result (e.g., IGRA/RIF, IGRA/INH, or sequential [SEQ] TST/IGRA testing: SEQ/RIF and SEQ/INH[77-79]).

In 2 studies, the main comparator of interest was TST,[79,80] while the remaining studies considered TST as the intervention and compared it to no testing. Given that TST was the main comparator for our review, we excluded results pertaining to the no-testing strategy and reported results only for the 2 studies comparing IGRA and TST.

Health Outcomes and Costs

Long-term decision models predicted 2 key health outcomes by the number of future active TB cases prevented (reported by 3 studies)[78,79,81] and QALYs (4 studies).[77-80] Utility weights used to estimate QALYs were sourced from published literature[77-79] and the British Columbia Centre for Disease Control (BC CDC) administrative databases.[80] Most studies indirectly estimated health utility weights using the Short-Form Six-Dimension (SF-6D) from the SF-36 questionnaire. These studies included individuals from British Columbia, Ontario, or Quebec (sample size range: 71–162) with active TB or LTBI. Utility weights were reported for various health states or events considered in the models: e.g., LTBI (0.81–0.83, where the weights for LTBI and full health were assumed to be equal), active TB (0.68–0.69), utility decrements due to hepatotoxicity of the treatment (adverse effect of the INH therapy: −0.2), or due to hospitalization (−0.5). The model that examined LTBI screening in CKD patients included additional utility weights related to late-stage CKD (e.g., living with CKD: 0.66, and initiation of dialysis: 0.62).

The second important outcome was the expected average total medical costs, often presented per person, in Canadian dollars. The total costs were predicted by simulating various cost categories, such as costs of screening with TST or IGRA, costs of diagnostic workup (e.g., x-ray, initial and follow-up physician visits, blood tests, sputum test where appropriate), and treatment costs for LTBI or active TB. The section below describes details on the model structures, sourcing, and estimation of key cost input parameters.

Analytic (Modeling) Technique and Model Inputs

The included economic analyses were supported by the complex decision-analytic models that simulated the natural and clinical course of LTBI and its progression to active TB over the long term (5–25 years), including the possibility of a secondary transmission. Thus, Oxlade et al[81] and Marra et al[80] developed Markov (state-transition) cohort models, and Campbell et al[77-79] created individual-level discrete event simulation (DES) models for a general migrant population[77,79] and for people with late-stage CKD.[78] All models started with screening or diagnostic testing with IGRA or TST, which was incorporated within the overall model structure[77-79,81] or distinguished as a separate decision tree followed by different state-transition submodels.[80] For example:

- Oxlade et al[81] developed a model with 4 distinct TB health states (i.e., noninfected, recent LTBI, active TB, and long-standing LTBI) and all diagnostic and treatment activities occurred in the first year of simulation. Depending on the test or treatment results, people who survived the first year remained in the same health state or moved to another state
- Marra et al[80] modeled the progression of LTBI in contacts by first simulating the diagnostic pathways stratified by ethnicity and BCG status. Each of these subcohorts had different probabilities of recent LTBI, remote LTBI, active TB, or no infection. LTBI was confirmed with IGRA or TST, and the cohort transitioned into the Markov submodel (named “reactivation of TB”) that included 4 health states: at risk of reactivation, active TB, previous TB, and death. The progressions of those with active TB or with no infection were simulated through another 2 submodels (“active TB” and “normal life” models, health states not reported in the article).

The DES models in migrants by Campbell et al[77-79] simulated individual-level event pathways for each person, accounting for various events and health states following immigration. Two cohorts were separated from the beginning of the simulation:

- A bigger cohort (i.e., healthy), not flagged for immigration TB medical surveillance (by a formal program at Immigration, Refugees, and Citizenship Canada [IRCC])
- A smaller cohort, flagged for immigration TB medical surveillance (i.e., about 6,100 individuals, or 2.4% of the whole cohort of 260,600 people). People flagged for the TB medical surveillance followed the screening steps (i.e., screening for LTBI with TST or IGRA). After testing, they transitioned into the healthy or LTBI state, depending on the test results. From these 2 health states, they could further transition to:
    - Active TB, which could occur from 1) LTBI reactivation, 2) full health after secondary transmission, and 3) relapse after TB treatment, or

- Death state, due to background (all-cause) mortality, TB, or an adverse reaction to TB therapy

The DES model for a CKD population simulated individual treatment pathways for LTBI or TB in people with CKD by including 4 health states after TST/IGRA screening: late-stage CKD, dialysis, active TB, and dead (all-cause or TB-related).[78]

Model Inputs

The model inputs in all studies represented the risk of LTBI or of active TB for the Canadian population. They accounted for medical evaluations associated with the screening (e.g., clinic visits, x-ray, additional workup for people who tested positive on x-ray) or treatment, based on Canadian data. They included the costs of LTBI or TB therapies and likelihood of adherence to and completion of the initiated treatments and they simulated a possibility of major TB treatment side effects such as hepatotoxicity and its consequences (e.g., hospitalization or death). As mentioned above, the models also accounted for the possibility of secondary transmission. Below, we discuss in detail inputs related to diagnostic testing of LTBI with IGRA or TST.

Uptake of LTBI Screening

Modeling of the uptake of IGRA or TST differed among the included studies. Both Oxlade et al[81] and Marra et al[80] assumed 100% uptake of the initial IGRA or TST test, but Marra et al accounted for some probability of not returning for the TST reading (i.e., second TST visit, 8% of the cohort) or not returning for the additional (second) screening test if recommended (30%). Campbell et al[77-79] assumed that all migrants would be offered LTBI screening, but accounted for their incomplete participation in surveillance (completed by 60% of the flagged cohort[79] and by 76.7% of migrants with CKD),[78] and nonadherence to a full medical evaluation following the screening (e.g., 78% of migrants and 88% of migrants with CKD). They also accounted for incomplete rates of reading of TST (completion rate: 72% of migrants to Canada and 91% of migrants with CKD).[78,79]

Sensitivity and Specificity of IGRA and TST for LTBI

In 2 studies by Oxlade et al[81] (in healthy migrants) and Marra et al[80] (in contacts), the sensitivity of TST and IGRA was assumed to be the same for both tests and close to perfect (0.95[81] and 0.99[80]). In the remaining 3 studies,[77-79] the sensitivity of IGRA was higher than that of TST. For example, in migrants, it was 0.89 versus 0.78; in people with CKD and dialysis (i.e., immunocompromised), the sensitivity of IGRA was 0.78 and 0.68, respectively, versus the sensitivity of TST, 0.65 and 0.52, respectively. Also, the sensitivity of these 2 tests did not depend on BCG vaccination status.

People's BCG vaccination status affected the specificity of TST, but it did not change the specificity of IGRA in all examined populations (e.g., healthy migrants and people with CKD). The specificity of TST in BCG-vaccinated people ranged between 0.60 and 0.69 in 4 studies.[77-80] One study additionally differentiated TST specificity by the age of vaccination. Thus, the specificity was 0.60 for those vaccinated in older childhood or adolescence, compared with 0.92 for those vaccinated in infancy.[81] In contrast, the specificity of TST in non-vaccinated people was almost perfect (0.97–0.99), and similar to the specificity of IGRA (0.96–0.98).[77-81]

The accuracy inputs for TST and IGRA for diagnosis of LTBI were informed by the published studies and the BC CDC registry. Oxlade et al[81] and Marra et al[80] ascertained the accuracy of 1 commercial brand of IGRA (i.e., QuantiFERON), while Campbell et al[77-79] conducted their own systematic reviews with meta-analyses that combined 2 commercial types of IGRA test (i.e., QuantiFERON and T.SPOT, which had similar diagnostic accuracies). In addition, 4 of the 5 modeling studies[77-80] considered a possibility of

indeterminate results with IGRA (probability range: 0.02–0.07, based on the published data) and a need for a second testing to resolve the indeterminate test result.

Costs of IGRA and TST

All studies costed either the QuantiFERON-TB or the QuantiFERON-Gold. The assumed cost was between $41 (2004 CAD)[81] and $54 (2016 CAD)[77-80] in the reference case, and it ranged between $31 and $62 (2016 CAD) in the sensitivity analysis. These costs include components related to the commercial kits, labour (staff time), equipment, and consumables. The IGRA cost was based on data from the BC CDC registry[77-80] or the manufacturer.[81] The cost of a complete TST was between $12 (2004 CAD) and $31 (2016 CAD) in the reference case, and between $24 and $38 (2016 CAD) in the sensitivity analysis. This included the test cost and labour time (2 visits with a nurse for skin injection and test reading) and was sourced from the literature[81] or BC CDC registry.[77-80] Campbell et al[77-80] included a separate cost for an incomplete TST at $21 (2016 CAD) in the reference case, ranging between $17 and $25 (2016 CAD) in the sensitivity analysis. None of the included studies reported if the IGRA or TST costs were adjusted for the mark-ups.

Statistical Analyses: Reference Case and Sensitivity Analysis

All studies used a deterministic approach for estimation of the expected mean costs and effects (i.e., the mean number of TB cases averted and mean QALYs) in the reference case analysis (also known as the base case). The sensitivity analyses examined changes in numerous input parameter values or assumptions related to the accuracy of IGRA, prevalence of LTBI or active TB, reactivation, secondary transmission or relapse rates, completeness of screening or adherence to therapy, effectiveness of LTBI and TB therapy, utilities, costs of tests and therapies, discount rate, duration of time horizon, and willingness-to-pay values. Two studies published in 2007[81] and 2008[80] also used numerous deterministic one- or two-way sensitivity analyses to address uncertainty in the model input values. Three more recent studies[77-79] assigned probability distributions to the input parameters and conducted probabilistic sensitivity analyses for individual-level state-transition models (including between 50,000 and 100,000 individuals [iterations] in the inner loop and between 1,000 and 2,000 replications in the outer loop). In addition, they used one-way deterministic analyses on the assigned range values for important input parameters to address robustness of the reference case model results. Lastly, the included studies reported estimates for all included strategies; thus, we were able to report these values as is or to estimate incremental costs and effects from the data reported for IGRA and TST strategies. Also, results of the sensitivity analyses that were compared with the results of the base case analyses that considered TST as a main comparator were deemed fully relevant to our review.

Summary of Findings: Incremental Cost-Effectiveness of IGRA Versus TST for LTBI

Reference Case Results

General Population: Migrants

Studies conducted in migrants suggested that IGRA as part of sequential diagnostic testing with TST or as a single test was cost-saving or cost-effective compared with TST alone, particularly for BCG-vaccinated people and for those coming from countries with intermediate (moderate) to very high TB incidence rates (Tables A3 and A4, Appendix 7).

A study by Oxlade et al[81] showed that:

- IGRA (QuantiFERON Gold [QFT]) alone and TST alone were equally effective in preventing active TB, regardless of differences in the country-specific TB incidence rates
- IGRA (QFT) alone was cost-saving for individuals receiving BCG vaccines in older childhood or adolescence because the specificity of TST for this group was 0.60, compared to 0.92 for BCG-vaccinated in infancy and 0.99 for non-vaccinated (savings of $6,220 to $64,740 per 1,000 persons). For the later 2 groups, IGRA (QFT) alone was associated with an increase in costs ($16,110 to $35,790, per 1,000)
- The sequential TST/QFT testing (i.e., TST as initial test followed by QFT in those who were TST-positive) compared with TST alone resulted in equal health benefit only for those migrating from low-TB incidence countries
- The sequential TST/QFT testing resulted in cost-savings for people coming from low-incidence countries regardless of BCG-vaccination status (savings per 1,000 people ranged between$2,951 for non-vaccinated people and $102,291 for BCG-vaccinated people who received the vaccine in older childhood or adolescence)
- The sequential TST/QFT testing in people who were non-vaccinated or were vaccinated in infancy migrating from countries with a medium or high incidence of TB resulted in additional costs ($3,632 to $27,412 per 1,000 persons) in general, with the exception of cost-savings for BCG-vaccinated migrants who received the vaccine in older childhood or adolescence (e.g., cost savings of $49,498 and $14,598 per 1,000 persons, for migrants from countries with intermediate and high TB incidences, respectively)

Two studies by Campbell et al[77,79] accounted for BCG-vaccination status but differently stratified the population of migrants, which caused slightly different and more nuanced findings:

- The first (2017) study[79] considered immigrants to Canada and reported results for the cohort flagged for TB medical surveillance (2.4% of the whole cohort, or about 6,100 people):
  - Compared with TST alone (followed by INH in people testing positive; i.e., TST/INH), IGRA alone (followed by INH or RIF in people testing positive; i.e., IGRA/INH or IGRA/RIF) was slightly more effective (small increments in QALYs) and more cost-saving than the sequential TST/IGRA options
  - For the whole cohort (N = 260,600 people), none of the IGRA interventions were less costly or cost-effective (ICERS > $100,000/QALY) compared with the reference case (IGRA/INH or IGRA/RIF vs. TST/INH for those flagged for surveillance)
- The second (2019) study[77] stratified migrants by incidence of TB in back-home countries:
  - Compared to TST/INH (i.e., TST alone combined with INH in people who test positive), all IGRA options were associated with lower costs and small QALY gains regardless of TB incidence
  - These findings differed slightly when IGRA options were compared to TST alone combined with RIF (TST/RIF), which was a cheaper and more effective comparator than TST/INH

- When the cost-effectiveness of all IGRA strategies was compared to TST/RIF and among themselves, the cost-effectiveness of IGRA depended on the country-specific TB incidence. The best option for migrants coming from:
  - Low, moderate, or high TB–incidence countries was sequential testing with TST/IGRA, followed by RIF therapy (i.e., SEQ/RIF)
  - Very high TB–incidence countries was IGRA alone, followed by RIF

We also estimated that for migrants coming from moderate and high TB–incidence countries, IGRA alone was cost-effective because the ICERs of IGRA/RIF vs. sequential TST/IGRA [SEQ/RIF] were less than $25,000/QALY gained (calculated ICERs for people coming from moderate, high, and very high TB–incidence countries were $23,620, $10,162, and $4,170 per QALY gained, respectively).

General Population: Contacts

Two studies in populations of contacts with undiagnosed LTBI who were exposed to people with active TB suggested that IGRA for BCG-vaccinated contacts only (not all contacts) was the most economically viable option.[80,81]

Oxlade et al[81] examined the use of TST and IGRA compared with no screening in close and casual contacts. Because of the lack of detailed reporting (i.e., mean costs/effects per strategy), we were not able to estimate cost-savings with QFT as compared to TST. However, this study showed that both QFT and TST were cost-saving options, but for close contacts who were BCG-vaccinated when in older childhood or adolescence, QFT was the preferred option (more cost-saving than TST).

Marra et al[80] found very small changes in QALYs (0.00–0.0004) with IGRA as a single diagnostic option or in sequential testing (for people with TST-positive results) compared with TST alone in foreign-born, Canadian-born, and Aboriginal contacts. Compared with TST alone, savings ranged from $0.61 per contact for using IGRA alone in BCG-positive contacts and TST in the rest, to $2.54 per contact for using sequential TST/IGRA approach in BCG-positive contacts and TST for the rest. Compared with TST, IGRA alone for all contacts was associated with additional costs of $30.08 per person and a small increase in QALYs of 0.0004. It was ranked as the least cost-effective option. The option with the highest net monetary benefit was selective use of IGRA for BCG-vaccinated people and reserving TST for all others.

Immunocompromised Populations

We found favorable economic evidence for the use of IGRA versus TST in Canada for the diagnosis and prevention of LTBI in 1 group of immunocompromised people (people with late-stage CKD). One Canadian study compared no LTBI testing to testing with IGRA or TST (both tests combined with INH for treatment of confirmed LTBI) in migrants with late-stage CKD and/or dialysis.[78] Based on the data reported in this study, we estimated that IGRA/INH dominated TST/INH because it was associated with small increments in QALYs and cost savings in both patient groups, regardless of the age or incidence of TB in the country of origin. The QALY gains ranged between 0.00004 and 0.0009 in people with late-stage CKD and between 0.0001 and 0.0014 in people with CKD who are initiating dialysis. The cost savings ranged from $46.05 to $79.32 per person for people with late-stage CKD and from $53.04 to $112.22 for those undergoing dialysis.

Sensitivity Analysis Results

In 2 studies that included the probabilistic sensitivity analysis, testing with IGRA (combined with LTBI therapy) remained highly likely to be cost-effective in a subgroup of migrants flagged for medical TB surveillance. The probability of cost-effectiveness ranged from about 99% at a willingness-to-pay (WTP) of $10,000/QALY gained and 95% at a WTP of $50,000/QALY gained to about 65% at a WTP of $100,000/QALY gained.[78] In migrants with late-stage CKD, it was > 75% at a WTP of $50,000/QALY gained.[77] As in the base case, IGRA screening of the whole population of migrants emigrating to Canada was not likely to be cost-effective.

The deterministic sensitivity analyses of the 2 studies[79,80] that used TST as the main comparator rather than no screening found the following:

- In migrants, Campbell et al[79] found that IGRA would not be cost-effective at a WTP of $100,000/QALY gained with the following input parameter changes: high sensitivity and specificity of TST (0.95 and 1.00, vs. 0.78 and 0.60 in the base case), perfect completion of TST testing (100% vs. 72%), high cost of treatment of LTBI/TB ($686 vs. $575), high probability of dying from TB (8% vs. 4%), low proportion of people adhering to TB treatment, high proportion of indeterminate IGRA results (18% vs. 6%), smaller probability of BCG vaccination in countries with high prevalence of LTBI and TB (50% vs. 94%), and higher cost of IGRA ($62 vs. $54 [2016 CAD])
- In contacts, Marra et al[80] found that IGRA for all contacts (not just BCG-vaccinated) would be cost-effective at a WTP of $50,000/QALY gained if they assumed a higher prevalence of LTBI (30% vs. 10% in the base case), higher completion rate of LTBI therapy (75% vs. 61%), higher rate of TB reactivation (0.24% to 0.60% vs. 0.18% to 0.55% in the base case), or a higher WTP value (> $100,000/QALY vs. $50,000/QALY gained). They also found a threshold price for IGRA at $57 (vs. $45 in the base case [2005 CAD]), above which IGRA testing would not be cost-effective at a WTP of $50,000/QALY gained.

In summary, favourable cost-effectiveness of IGRA versus TST testing in specific migrant populations or groups of contacts remained robust but could vanish if some important parameters take less likely, more extreme values.

Applicability and Limitations of the Included Studies

Appendix 8 provides the results of the quality appraisal checklist for economic evaluations applied to the included studies (Tables A5 and A6). Three studies[78-80] were directly applicable to the Canadian/Ontario setting and our research question because:

- They examined populations that are recommended for IGRA testing under the Standards[75,82]
- The incremental cost-effectiveness of IGRA versus TST could be estimated from the published data
- They were done from a third-party payer perspective and used population, resource, and cost parameters transferable to the Ontario health care system

- They used the discount rate for cost and utility outcomes, as recommended at the time of publication

The 2 more recent studies[78,79] discounted the future costs and QALYs at the rate of 1.5% currently recommended by CADTH guidelines, while the older (2008) study[80] used the previously recommended rate of 3%. The discount rate was not suggested to be the major driver of the cost-effectiveness results in these studies.

Two other studies judged as partially applicable were downgraded because they used "no screening/no testing" as the comparator.[77,81] Thus, we were not able to estimate the incremental cost-effectiveness versus TST alone for some populations considered in the analysis; nor were we able to extrapolate the applicability of the sensitivity analyses results as these studies applied the higher (3%) discount rate for their outcomes.

We found that all studies used very complex, comprehensive, and valid methods for modeling the natural and clinical courses of LTBI and active TB including the testing with IGRA or TST, and for assessing parameter and decision uncertainty. Therefore, we found that all studies were associated with minor limitations. Some limitations, such as the use of a probabilistic versus deterministic approach to the analysis, are related to older modeling practice guidelines that were in use at the time of publication.

All studies were done by academic groups recognised in the Canadian TB research field that reported no conflicts of interest. We did not detect any risk of publication bias.

In general, all studies were consistent in the overall conclusion pertinent to the use of IGRA testing to support the diagnosis of LTBI and prevention of future active TB in populations at high-risk of LTBI reactivation in Canada.

Discussion

We reviewed 5 model-based economic studies that examined the cost-effectiveness of IGRA testing for supporting the diagnosis of LTBI in high-risk populations (i.e., migrants without or with comorbid conditions and contacts), from the perspective of a third-party payer in Canada.[77-81] All included studies were of good quality (i.e., only minor methodological limitations), and 3 studies[78-80] were directly applicable to the Ontario context and the research question.

We found that, compared to TST alone, the cost-effectiveness of IGRA as a single test or in combination with TST (sequential testing) is the most favourable for BCG-vaccinated adults and for those at high risk of LTBI who are migrating from countries with moderate to very high incidences of TB. Other research studies (i.e., BCG-vaccination Atlas[83,84]) indicated that countries with moderate to very high incidences of TB generally implement nationwide BCG vaccination policies. This suggests that categorizing the cost-effectiveness findings by the number of active TB cases per country (or country-specific TB incidence) could serve as a proxy measure for an immigrant's BCG vaccination status.

Restricting access to IGRA testing to specific populations at high risk is in agreement with the current Standards,[75] which recommend consideration of IGRA as an alternative to TST for the following people or situations:

- Previously vaccinated with BCG in infancy (IGRA recommended for ages 2–10 years) or after infancy (IGRA recommended at any age)
- Limited TST capacity
- High chance of no return for second follow-up with TST (the TST reading appointment)
- High concern of a false-negative result with TST (e.g., people with immunocompromised conditions or associated therapies)

These recommendations are also aligned with the findings of 1 economic study included in our review that showed that screening all immigrants to Canada with IGRA would be cost prohibitive.[79]

All studies included adult populations. One of the included studies stratified the results by the age of BCG vaccination, which was closely related to differences in the specificity of TST: 0.92 if the BCG vaccine was given in infancy versus 0.60 if it was received when older (childhood or adolescence).[81] IGRA has been recommended for individuals > 2 years of age who received the BCG vaccine because TST alone was found to result in a higher rate of false-positive results.[85] In addition, Marra et al[80] included Canadian-born Indigenous people in their study population of contacts exposed to active TB, and they estimated input parameters from the British Columbia data: IGRA combined with TST for all BCG-vaccinated people was the most cost-effective strategy regardless of subgrouping for ethnicity.

We identified only 1 economic study in people with late-stage CKD and/or receiving dialysis who could be considered immunocompromised because of their underlying comorbid condition.[78] Compared to TST, IGRA testing was cost-effective in this population. In this study, the model inputs related to the test performance of IGRA were assumed to be higher for BCG-vaccinated people. Although the rationale behind this assumption remains unclear, it may be due to the ability of IGRA to provide indeterminate results in instances of an insufficient immune response, leading to fewer false negatives in the detection of LTBIs. In addition, research studies have also suggested higher sensitivity of IGRA in patients with CKD compared to TST.[86,87] Assuming similarities in relevant inputs related to the diagnostic cost-effectiveness modeling of IGRA and TST, we can expect similar cost-effectiveness findings for other patient populations with underlying immunocompromised conditions, such as people with human immunodeficiency virus (HIV), people with CKD, and people undergoing organ transplant.

Although the cost-effectiveness of IGRA across the included studies had a favourable direction for populations of interest, in sensitivity analyses, assessments of the parameter uncertainty suggested some influential drivers of cost-effectiveness results, especially when extreme values were applied. For example, Marra et al[80] found that IGRA would be the optimal strategy if its sensitivity was at least 0.80 (even if the specificity was at 0.90). Given that IGRA test accuracy is expected to increase with each new generation of the test, these threshold cost-effectiveness findings related to the lower sensitivity and specificity of IGRA might not be applicable. Furthermore, in a sensitivity analysis with a relatively large IGRA acquisition test cost, there would be cost increases with the IGRA testing strategy. Nevertheless, if high volumes of IGRA tests were offered to test LTBI in the populations of interest, the cost of the IGRA test could be contained. Also, substantial decreases in screening participation and completion of LTBI treatment could affect the cost-effectiveness of IGRA. While these results are hypothetical in nature, they show that barriers to IGRA testing (such as participation) ought to be considered seriously by policy- and decision-makers, and additional supports need to be ensured for successful implementation.

Findings of Other Systematic Reviews and Non-Canadian Economic Studies

Several systematic reviews were identified in the literature.[72,88-93] The most recent reviews found that the addition of IGRA for screening and supporting the management of LTBI in people at high risk represented good value for money. For example, Mahon et al[90] continued with the methods used in the Nienhaus et al review (2011)[91] and examined methods and results of 32 other economic studies published between 2011 and 2021 (including 3 studies from Canada[77-79]). These studies assessed the cost-effectiveness of LTBI testing (with IGRA and TST) in high-risk groups; populations such as migrants, contacts of people with active TB, children, health care workers, immunocompromised, and people with HIV. They found the quality of the primary studies to be high, while recognizing concerns in the variability of input parameters across the studies (as did Nienhaus et al[91]). Mahon et al[90] concluded that the inclusion of IGRA in LTBI screening in people at high risk was cost-effective for high-income countries, and that the cost-effectiveness of IGRA depended on the prevalence of LTBI. Yoopetch et al[93] reviewed 11 economic evaluations on LTBI screening of contacts of TB patients published until 2022 (including 2 studies from Canada[80,81]) and found that the use of either IGRA alone or IGRA as a confirmatory test after a positive TST was cost-effective in high-income countries (e.g., Germany, Switzerland, Canada, Japan, France, United States, and the United Kingdom). Greenaway et al[89] reviewed the effectiveness and cost-effectiveness of screening for LTBI among migrants to the European Union to inform migrant screening guidelines. They included 16 economic studies, of which 8 were model-based analyses (with 1 study from Canada[81]). Greenaway et al[89] concluded that the economic evidence was limited and that the most cost-effective approach could be targeting young migrants from high TB–incidence countries. They found that the cost-effectiveness of screening strategies was dependent on the test characteristics, comparative options, cost of tests, and BCG-vaccination status. The sequential approach to LTBI screening (TST followed by IGRA) was preferred over TST and IGRA as a single test, especially in people who had a high likelihood of a true positive TST result (i.e., LTBI prevalence > 5%) and were BCG-vaccinated after infancy.

In addition to these reviews, in 2016, Auguste et al[72] published a health technology assessment from the UK health care system perspective. They investigated the clinical and cost effectiveness of screening test (IGRAs [QFT-GIT {Gold-In-Tube} and T-SPOT.TB] and TST) for LTBI diagnoses in 3 populations at higher risk of progression from LTBI to active TB: children, immunocompromised people, and individuals who have recently arrived in the United Kingdom from high-incidence countries. The economic analysis showed that the most-cost-effective option for children and people with low immunity was sequential testing that includes IGRA (i.e., children: TST [≥ 5 mm] followed by IGRA if TST is negative, ICER [vs. TST] was £18,900 GBP per QALY gained; immunocompromised people: IGRA followed by TST if IGRA was negative: ICER is £18,700 GBP per QALY gained). The analysis in all recently arrived migrant cohorts to the United Kingdom did not categorize IGRA's diagnostic accuracy by BCG-vaccination status; thus, they found that TST alone (≥ 5 mm) was the most cost-effective strategy with an ICER of approximately £1,500 GBP per QALY gained compared with IGRA (QFT-GIT). More recently, Sousa et al[94] compared 2-step TST/IGRA (QuantiFERON Gold Plus) with the current IGRA-only screening strategy in 1,125 close contacts residing in Porto, Portugal (IGRA-only contacts included 578 immune-competent individuals exposed to individuals with respiratory TB). Using medical records registry data, they estimated the clinical effectiveness and costs (direct and non-direct medical costs related to LTBI screening, excluding treatment costs) of the two strategies. The cost of IGRA (QuantiFERON-TB Gold Plus) was estimated at €38.23 EUR (€37.66 for the test and €0.57 for disposables) and the cost of TST at €1.31 EUR (€1.00 for tuberculin and €0.31 for disposables). The IGRA-only strategy was costlier than the sequential option (e.g., total mean costs: €55.21 vs. €42.71 EUR per screened person), but was associated with increased odds of establishing the LTBI diagnosis, hence preventing more TB cases (adjusted OR, 2.12; 95% CI, 1.53–2.94). The authors reported an ICER of €106 EUR per LTBI diagnosis.

Several original non-Canadian economic analyses found favourable results for the cost-effectiveness of IGRA in immunocompromised people due to their underlying condition (e.g., people with HIV or organ transplant patients). For instance, Auguste et al[95] in their 2022 cost-effectiveness analysis in people with HIV (UK health care system perspective) found that sequential testing with IGRA (QFT-GIT) followed by TST was the most cost-effective option at a willingness-to-pay threshold of £20,000 GBP per QALY gained, but they noted the paucity of test accuracy studies in this population. Kowada et al[96] examined the cost-effectiveness of IGRA versus TST and no screening in adult kidney, liver, or lung transplant recipients (societal Japanese perspective) and found IGRA (QFT) to be the most cost-effective option, regardless of BCG-vaccination status.

Equity Considerations

Latent TB infections and active TB represent serious public health conditions frequently associated with stigma.[46] As mentioned in the clinical review (background), there is inequity in access to IGRA testing in Ontario because it is only available to those who can pay for it out of pocket or can access laboratories offering testing. Compared to TST, which requires 2 clinic visits, IGRA testing requires only a single visit and is more likely to be completed by some people—in particular, those with low-paying jobs who may not be able to miss 2 days of work. Also, unlike TST, the accuracy of IGRA is not affected by a person's BCG-vaccination status and it delivers fewer false negative results in immunocompromised patients. Therefore, IGRAs may represent the better clinical choice in certain populations as defined by the Standards.[75] The economic studies in this review accounted for many important factors indirectly related to inequities, such as variability in LTBI prevalence, BCG vaccination status, ethnicity, completion of TST reading (and costs associated with incomplete readings), and participation in screening.

Strengths and Limitations

We thoroughly assessed the published economic studies in Canada and found consistency in their methods and their results with respect to cost-effectiveness of IGRA compared to TST for some high-risk populations. This review fills in some gaps in the literature suggested by the most recent CADTH assessment of the evidence, including the TB guidelines.[97-99] The majority of the included studies considered the public-payer perspective; if they were to use the societal perspective and account for indirect (productivity loss) and nonmedical direct costs, then the incremental cost-effectiveness of IGRA (as a sequential or single test) versus TST alone would likely have been larger.

Limitations of our study are related to the limitations of the current evidence: the lack of Canada-based economic studies in immunocompromised people, in people unlikely to return for TST reading, and in children. Our review suggests that IGRA (as a sequential test to TST or as a single test) in certain populations likely represents good value for money, but our inferences are conditioned on the parameter assumptions of the published studies. Thus, in a new analysis, changes in QALYs would likely be similar to those reported, but the current list price of IGRA in Ontario could be higher than the one used in the published studies, even after adjustment for inflation, in which case, the reported savings could be smaller. Therefore, a budget impact analysis is needed to estimate the costs to support publicly funding IGRA testing as an alternative option to TST in certain eligible populations in Ontario. Last, this review did not consider newly developed TSTs,[100] which may have similar accuracy as IGRA, because these novel TSTs are currently unavailable in Canada.

Conclusions

Based on our review of the 5 economic studies from Canada, IGRA (either as a standalone test or in sequence with TST) is cost-effective compared with TST alone for supporting the diagnosis of LTBI in high-risk populations that are aligned with the current Standards.[75]

Primary Economic Evaluation

Based on our review of 5 economic studies from Canada,[77-81] the interferon-gamma release assay (IGRA), used either as a sequential test following the tuberculin skin test (TST) or as a standalone test, is considered cost-effective compared with TST alone for supporting the diagnosis and management of latent tuberculosis infection (LTBI) in high-risk populations, as recommended by the current Canadian Tuberculosis Standards, 8th edition (hereafter, "the Standards").[75] All reviewed studies were of good quality (i.e., minor methodological limitations), and 3 studies[78-80] were directly applicable to the Ontario context and our research question.

We evaluated the certainty of this body of evidence (i.e., directly applicable studies) using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. We did not identify any serious limitations in the following GRADE[101,102] domains (Appendix 9, Table A7; GRADE: High):

- Methodological quality of published models, including modeling (structural), method, and parameter assumptions (i.e., credibility of the models and their limitations)[102]
- Inconsistency and imprecision of the reported cost-effectiveness estimates[102] (e.g., variability of estimates in probabilistic and other sensitivity analyses, switch in the cost-effectiveness of the compared strategies)
- Applicability of the published study findings to the Ontario context and our research question (i.e., indirectness)[101,102]
- Publication bias[102]

If we were to conduct a primary economic evaluation, it would be highly likely that our cost-effectiveness analysis would use similar model structures and input parameter values as the existing studies.[77-81] Therefore, limitations in the currently published evidence would likely recur in our evaluations. Furthermore, we anticipate a very small difference in QALYs between IGRA and TST across all populations of interest; consequently, the cost-effectiveness of IGRA would primarily hinge on the differences in expected mean costs between the strategies. Therefore, we leveraged the existing directly applicable economic evidence[78-80] instead of conducting a primary economic evaluation for Ontario. We conducted a budget impact analysis to estimate the total costs, resources, and net budget impact of publicly funding IGRA testing for supporting the diagnosis and management of LTBI in certain eligible populations in Ontario, as defined by the Standards.[75]

Budget Impact Analysis

Research Question

What is the potential 5-year budget impact for the Ontario Ministry of Health of publicly funding an interferon-gamma release assay (IGRA) test as single test or in combination with the tuberculin skin test (TST), for latent tuberculosis (TB) infection in eligible people (see below) according to the Canadian Tuberculosis Standards, 8th edition (hereafter, "the Standards")?[75]

We estimated the budget impact of publicly funding IGRA testing in the following subgroups of people at high risk of latent TB infection (LTBI)[75] in whom IGRA is the preferred test as per the Standards[75]:

- People who have previously received a Bacille Calmette-Guérin (BCG) vaccine (e.g., immigrants to Ontario, certain First Nation communities), including:
  - Children aged 2 to 10 years who had previously received a BCG vaccine against TB
  - Persons aged ≥ 10 years who received a BCG vaccine after infancy (> 1 year of age) or who received a BCG vaccine more than once and/or are uncertain about when they received it
- Contacts (people recently exposed to active TB cases) who have been BCG vaccinated or who are unable or unlikely to return for the TST reading (their second TST visit)
- People with comorbid conditions, and/or who are undergoing treatments that may cause low immune function, and who may test incorrectly as negative (false negative) with TST, such as people with HIV, late-stage kidney disease, or cancer, organ-transplant recipients, and those taking immunosuppressant drugs

Methods

Analytic Framework

We estimated the budget impact of publicly funding IGRA testing using the cost difference between 2 scenarios: (1) current clinical and public health practice without public funding for IGRA testing (the current scenario), and (2) anticipated clinical and public health practice with public funding for IGRA testing (the new scenario). Figure 4 presents a schematic of estimation of the budget impact. More details about the budget impact model structure can be found in a later section.

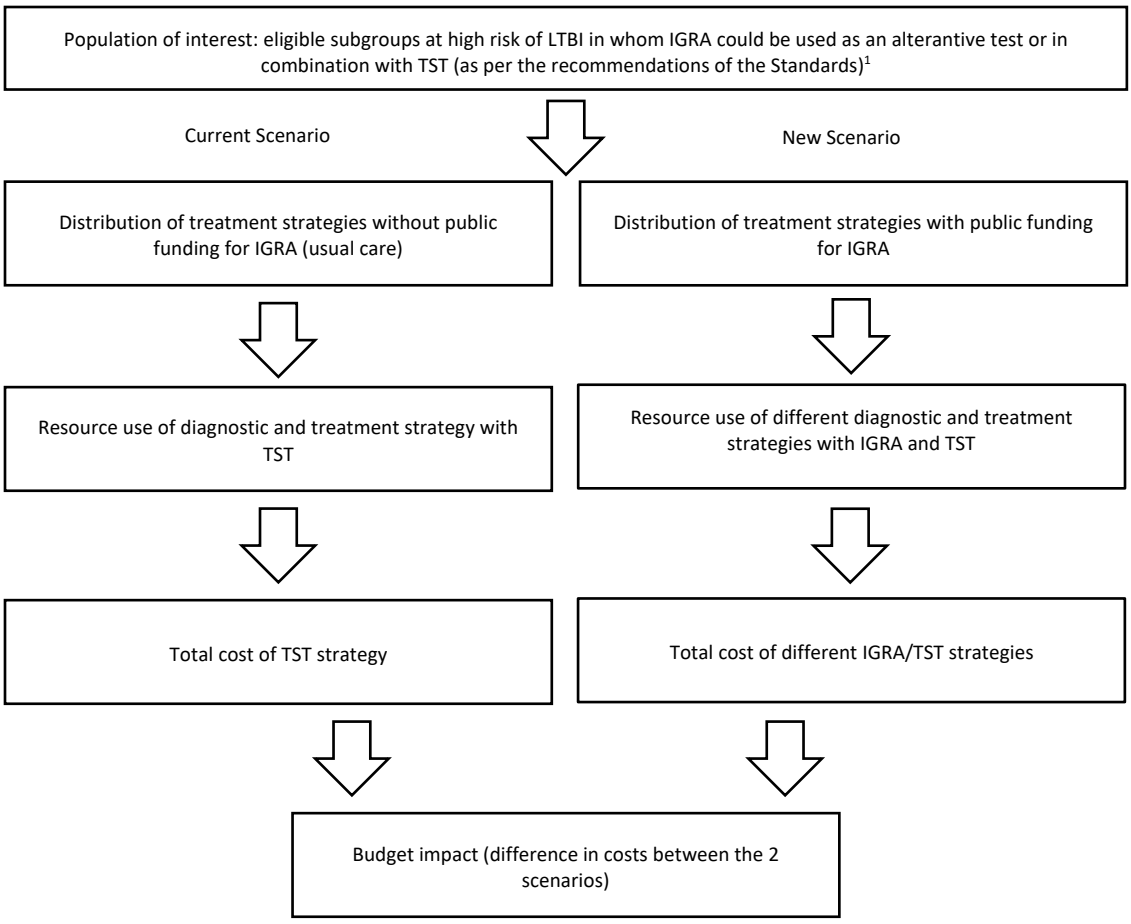

Figure 4: Schematic Model of Budget Impact

Flow chart describing a simplified model for the budget impact analysis. For a specific population of interest, we created 2 scenarios: the current scenario, which would explore the distribution of diagnostic and treatment strategies, resource use and total costs without public funding for IGRA (usual care); and the new scenario, which would explore the distribution of diagnostic and treatment strategies, resource use and total costs with public funding for IGRA. The budget impact would represent the difference in costs between the 2 scenarios.

Key Assumptions

The assumptions that apply to the budget impact analysis are listed under 2 main categories:

Modeling Assumptions Related to Clinical Parameters

- Situations where IGRA is the preferred method of testing as defined by the Standards[75] reflect the currently accepted best-practice and are determined at the discretion of treating physicians, primary responsible physicians, and public health units/programs. Of note, occupational health screening programs for health care providers is out of scope for this HTA; however, some health care providers who belong to the pre-defined population subgroups in this HTA[75] would be considered eligible for IGRA testing.

- Results of diagnostic testing for TB infection (i.e., LTBI) combined with additional clinical and/or laboratory medical evaluations are used to predict (justify) the initiation of the drug treatment for LTBI
- One year is generally sufficient for LTBI testing, diagnosis, and treatment
- Test accuracies (IGRA or TST) are based on published evidence that is generalizable to our populations of interest, and they will remain constant over the next 5 years
- Population-wide screening is not within the scope of this topic; thus, some people who are unaware of their risk for LTBI would not be diagnosed (LTBI is an asymptomatic condition)
- People identified would accept the diagnostic testing—this assumption of 100% participation in the testing was tested in our sensitivity analysis
- Uptake of IGRA strategies over 5 years was assumed to be different between the populations of interest, with a small annual uptake in immigrant populations (increase of 3% per year) and a large uptake in contact or immunocompromised populations (starting with 75% in year 1 and growing to 100% in year 5; oral communication, E. Rea, MD, April 25, 2024); this assumption was examined in sensitivity analysis

Assumptions Related to Determination of the Test Cost and Organization of Testing

- IGRA test cost is based on the cost of QuantiFERON–TB Gold Plus (QFT-Plus), which is the only currently available IGRA test used in the province; this cost (list price of $100 per person, available at LifeLabs[103]) includes all important cost components related to equipment, test kit, consumables, transportation/shipping, turnaround time, and labour
- Testing costs (TST or IGRA) would stay constant over 5 years
- No expansion of currently existing laboratory infrastructure in the next 5 years (start-up and implementation costs, including training, lab infrastructure or renovation, and accreditation or organizations of LTBI screening were not considered)
- IGRA testing is assumed to be de-centralized and done as needed, on the request of treating physicians or public health units (indications recommended by the Standards[75])
- IGRA is examined as an additional or optional test to TST, and is indicated in the same circumstances as TST, without any assumption on investments for IGRA/TST implementation in a large-scale (mass) screening programme
- The billing codes for IGRA are already in place for funding (in reality, additional policy work would be required), for example:
    - OHIP fee billing code: no changes to the specific OHIP fee codes would be required (oral and email communications, Infectious Diseases Policy and Programs Unit, Ontario Ministry of Health, November 16, 2023; April 9 and 30, 2024); however, an expansion and more detailed explanation of the eligibility criteria in the Physicians' Services Schedule of Benefits would be needed[104]

- Lab fee billing code if the test is provided and billed through Ontario labs: a new lab fee code for an IGRA test would be required in the Schedule of Benefits for Laboratory Services[104]

Population of Interest

The population of interest includes several subgroups of people who are eligible for testing with either IGRA or TST, based on the recommendations of the Standards.[75] These population subgroups are:

1. Individuals at high risk of exposure to TB (for primary care screening):
    a. Children > 2 and < 10 years of age who previously received the BCG vaccine in infancy (< 1 year of age)
    b. Persons ≥ 10 years of age who received a BCG vaccine after infancy (> 1 year of age), or received a BCG vaccine more than once and/or are uncertain about when they received a BCG vaccine (but are likely to have had the BCG vaccine based on routine immunization schedules)

- Individuals with known high risk of TB exposure; e.g., people identified as contacts through public health contact investigations, have been BCG-vaccinated as described above, or who meet criteria described above for LTBI screening or for occupational health LTBI screening, but are unable or unlikely to return for TST reading, or are contraindicated for TST
- Individuals at high risk of adverse outcomes if TB disease develops (as part of care for high-risk medical conditions):
    a. People (adults or children) with confounding immunocompromising health conditions and who are receiving immunosuppressive treatments are likely to be misdiagnosed as not having LTBI (false negative results) with a TST and are therefore not receiving proper treatment. As a result, they are at higher risk for developing active TB. This includes individuals living with human immunodeficiency virus (HIV), cancer, diabetes, or advanced stage chronic kidney disease, or who are an organ transplant recipient or are receiving immunosuppressing drugs, including chemotherapy

IGRA is currently being used in some circumstances, and on a case-by-case basis, for investigation of TB infection:

- In children with immunocompromising conditions or low immunity where a TST is highly likely to give a false-negative result because of underlying conditions (email and oral communications, M. Richard-Greenblatt, PhD, April 10, 2024)
- In children born in a TB endemic country or who are Indigenous Canadian and have received a previous BCG vaccination (email and oral communications, M. Richard-Greenblatt, PhD, April 10, 2024)
- In contacts who are part of epidemiologic public health field investigations (email and oral communications, E. Rea, MD, March 25, 2024)
- After informed consent discussion with the assessing physician where the patient is able to pay out of pocket and IGRA is recommended over TST by the Standards (email and oral communications, R. Taylor, MD, April 11 and June 3, 2024)

In addition, estimation of patient volumes from the IntelliHealth's OHIP claims data for identification of eligible patients with TB infection may not be reliable because the OHIP fee codes that may be used to render TST testing could be used for other purposes (e.g., combination of OHIP fee codes: A001, G372, and G373 for the diagnosis of LTBI/TB, and the diagnostic code for pulmonary TB: 011).

Therefore, we used the currently available data and published literature to make assumptions and estimate the size of each potentially eligible patient subgroup. In general, we assumed the following:

- No overlap or double counting of eligible persons between the subgroups
- BCG vaccination rate was based on the published studies and World Health Organization data,[78,79] with the assumption that the most recent immigration is mostly driven by migrants coming from the countries with high incidence of TB and population-wide BCG vaccination policies
- Immunocompromised people are eligible for IGRA irrespective of their BCG vaccination status;[75] the size of this population included people who previously received IGRA at the Hospital for Sick Kids, and we also made assumptions from data published for people with HIV, cancer, chronic kidney disease (CKD), and dialysis and organ kidney transplants

Overall Estimates

Table 7 presents the overall size of the eligible population, divided into 3 subgroups. We present the estimate for each subgroup in Tables 8A to 8C). Our assumptions were validated in expert consultation (oral and email communications, E. Rea, MD, R. Taylor, MD, L. Macdonald, MD, N. Persaud, MD, M. Richard-Greenblatt, PhD, A. Ma, PhD, S. Patel, PhD, M. Muhammad, MD, Victoria J. Cook, MD, I. Kitai, MB, Infectious Diseases Policy and Programs Unit, Ontario Ministry of Health, April to June 2024). In summary, over the next 5 years, we estimated that a total of 294,234 people would be eligible for testing with TST or IGRA to support the diagnosis of LTBI.

Table 7: Populations of Interest Eligible for IGRA/TST: Overall Estimates

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Total population	**55,339**	**57,059**	**58,812**	**60,595**	**62,429**	**294,234**
Immigrants	38,588	39,901	41,257	42,660	44,110	206,516
Contacts	1,817	1,872	1,928	1,986	2,045	9,648
Immunocompromised	14,934	15,286	15,627	15,949	16,273	78,069

Abbreviations: IGRA, interferon-gamma release assay; TST, tuberculin skin test.

Immigrant Populations

We estimated the number of new immigrants who may be eligible for LTBI (IGRA) testing as follows (Table 8A):

- First, we used published Ministry of Finance statistics for immigration to Ontario in 2023 (N = 194,982) and assumed a general annual growth rate of 3.4% for 2023.[105] We then projected the number of new immigrants coming to Ontario in the next 5 years (201,611 in Year 1, increasing to 230,461 in Year 5).

- Next, we assumed that IGRA testing would be offered only to those who are at risk or suspected of having LTBI.[75] It is highly uncertain how many people could potentially receive IGRA testing as this depends on many factors, including the specific eligibility criteria (e.g., whether the individual comes from a country with a moderate to high incidence of TB, is BCG-vaccinated, or is flagged for further immigration medical TB surveillance based on risk factors[79])
- To estimate the proportion of new immigrants who could be offered testing, we used data reported in a 2023 Canadian study by Jordan et al,[14] which estimated an overall prevalence of TB infection of 22% among foreign-born Canadians who immigrated to Ontario between 2001 and 2021
- Lastly, to estimate the number of people who are BCG-vaccinated, we applied a published BCG vaccination rate of about 87% to these population estimates,[106] assuming that the majority of immigrants to Canada are coming from countries where the incidence of TB is moderate to very high and a nation-wide BCG vaccination policy is in place[83,84]

Given these assumptions, we arrived at an estimate of about 39,000 to 44,000 people eligible for testing per year (Table 8A). Based on expert consultation, we assume that not all immigrants would receive IGRA testing since this is a large population and we are not suggesting screening. The specific size of the population would depend on the policy and could be just a proportion of the eligible population.

Table 8A: Immigrant Population: Assumptions and Calculations

Immigrants to Ontario	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Forecasted new immigrant population (2024–2028; growth per year of 3.4%)	201,611	208,466	215,554	222,883	230,461	1,078,975
Immigrants at risk of LTBI, assuming a prevalence of 22% for LTBI[14]	44,354	45,863	47,422	49,034	50,701	237,374
Total BCG-vaccinated immigrants at risk of LTBI who are eligible for testing with IGRA (assuming a BCG vaccination rate of 87%[106])[a]	**38,588**	**39,901**	**41,257**	**42,660**	**44,110**	**206,516**

Abbreviations: BCG, Bacille Calmette-Guérin; IGRA, interferon-gamma release assay; LTBI, latent tuberculosis infection.
[a] Calculated as the following example: 201,611 × 0.22 × 0.87 = 35,588.

Contact Investigations

All contacts who could have been exposed to an index case (i.e., people who could have been exposed to someone with active TB) need to be screened for TB infection and further evaluated for TB.[107] Contact investigations are particularly important when the index case is a child or young person.[107] We estimated the size of this subgroup as follows (Table 8B):

- The number of contacts screened with TST by Toronto Public Health Units ranged from 1,689 in 2017 to 2,054 in 2019 (email communication, E. Rea, MD, January 12, 2024). Based on these data, we assumed that there would be about 2,000 contacts tested for LTBI per year in Toronto

- According to clinical experts, Toronto has about 40% to 45% provincial caseload (email communication, E. Rea, MD, January 12, 2024). Therefore, we estimated that about 4,444 contacts per year (2,000/45%) could be screened in Ontario for LTBI
- We assumed that about 47% of screened contacts are foreign-born, based on estimates from the BC CDC reports that presented contact investigations in British Columbia[108]
- Finally, we assumed that 87%[106] of these individuals are BCG-vaccinated and estimated that between 1,817 and 2,045 contacts would be screened with IGRA per year, for a total of 9,648 over the next 5 years

Table 8B: Contacts: Assumptions and Calculations

Contacts[a]	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Contacts tested for LTBI per year in Toronto, estimated, (email communication, E. Rea, MD, January 12, 2024)	2,000	2,000	2,000	2,000	2,000	10,000
Contacts to be tested for LTBI per year in Ontario, estimated (assumes Toronto caseload is 45% of the provincial caseload)	4,444	4,444	4,444	4,444	4,444	22,220
Contacts to be tested for LTBI, foreign-born, estimated (assumes 47% of contacts are foreign-born[108])	2,089	2,089	2,089	2,089	2,089	10,444
Total BCG-vaccinated contacts at risk (87%)[106] eligible for testing with IGRA (4,444 × 0.47 × 0.87), assuming 3% increase per year	**1,817**	**1,872**	**1,928**	**1,986**	**2,045**	**9,648**

Abbreviations: BCG, Bacille Calmette-Guérin; IGRA, interferon-gamma release assay; LTBI, latent tuberculosis infection; TST, tuberculin skin test.
[a]People who have been exposed to active TB cases and are therefore eligible for LTBI testing.

Immunocompromised Populations

We used published data from Ontario to estimate the size of the potential immunocompromised populations represented by people with HIV, cancer (all non-solid tumors in the reference case; e.g., leukemias, Hodgkin and non-Hodgkin lymphoma, and myeloma), late-stage kidney disease and people who have received a kidney transplant (Table 8C). For instance, we predicted the number of people with HIV from a study that reported incident cases and prevalent cases of HIV between 2011 and 2020 (Appendix 10).[109] We used CIHI data to estimate the population from the reported incident cases with late stage CKD and kidney transplants between 2013 and 2022 (Appendix 10).[110] To estimate the number of people with cancer, we used Ontario Health (Cancer Care Ontario) projections for all nonsolid tumors in Ontario (adults and children) in the reference case and for all cancers combined in a scenario analysis (Appendix 10).[111]

In addition, the Hospital for Sick Children (Toronto) has been using IGRA tests for nearly a decade. In recent years, IGRA testing volumes have increased from 147 in 2019 to 699 in 2021 and 865 in 2023 (email communications, M. Richard-Greenblatt, PhD, November 24, 2023, and April 10, 2024). We

estimated that these volumes would increase by 30 tests per year and included these data into our calculations.

In summary, we estimated that about 78,100 people with immunocompromised conditions could be eligible for IGRA testing over the next 5 years (Table 8C).

Table 8C: Immunocompromised People, Assumptions and Calculations

Immunocompromised populations	Year 1	Year 2	Year 3	Year 4	Year 5	Total
HIV positive	797	793	789	785	780	3,944
Organ transplant recipient (kidney, adults and children)	3,507	3,563	3,618	3,674	3,729	18,091
End-stage CKD and dialysis	733	745	757	769	782	3,786
Cancer (non-solid tumors),all ages	9,032	9,291	9,538	9,766	9,997	47,624
Volume based on the current use[a]	865	895	925	955	985	4,625
Total, immunocompromised	**14,934**	**15,286**	**15,627**	**15,949**	**16,273**	**78,069**

Abbreviations: CKD, chronic kidney disease; HIV, human immunodeficiency virus.
[a]Hospital for Sick Children.

Budget Impact Model

We developed a standalone budget impact model to estimate the total costs for the current scenario with TST and for the new scenarios with IGRA used as an alternative or an addition to TST (see Table 9). The budget impact model considered the population-specific diagnostic test accuracy of IGRA and TST and probability of test completion, as well as costs of the tests, additional medical evaluations, and treatment for LTBI or active TB disease after a positive test result. As in prior economic analyses,[77-81] we assumed that testing to support the diagnosis of LTBI and its treatment would occur within 1 year. The structure of this diagnostic decision-analytic model and model parameters are described in Figure 5 and sections below. All analyses were done from a third-party payer perspective (i.e., the Ontario Ministry of Health). The budget impact was estimated per year and over a 5-year time horizon for the reference case and scenario analyses. We did not use the discount rate for costs in the calculations.

Interventions and Comparator

We considered two testing strategies with IGRA that are in line with the Standards[75] and currently available in British Columbia:

- IGRA as a single test: this would lead to substitution or replacement of some volume of TSTs with IGRA testing in the eligible populations (and no follow-up TST)
- IGRA in sequential pathways (in combination) with TST:
  - IGRA as a follow-up test in those who received a positive result from TST (i.e., BCG-vaccinated populations, immigrants, and contacts)
  - Combination of TST and IGRA (i.e., immunocompromised people):
    - TST used first, followed by IGRA in those who test negative with TST
    - IGRA used first, followed by TST in those who test negative with IGRA

- If the first IGRA test result is indeterminate, a second IGRA test should be conducted and is expected to produce a definitive result

Table 9: Interventions and Comparator for Specific Population Subgroups Used in the Economic Models

Interventions	Comparator	Population subgroups	Outcomes
1. IGRA alone 2. TST first, followed by IGRA in those who test positive with TST	TST alone	Immigrants and contacts, BCG vaccinated (healthy people at risk of LTBI)	Total costs in 2024 CAD
1. IGRA alone 2. TST first, followed by IGRA in those who test negative with TST 3. IGRA first, followed by TST in those who test negative with IGRA	TST alone	Immunocompromised people due to their underlying comorbid conditions at risk of LTBI	Total costs in 2024 CAD

Abbreviations: IGRA, interferon-gamma release assay; TST, tuberculin skin test.

Model Structure

In brief, we developed a probabilistic decision-tree model to estimate testing and treatment costs for LTBI, both in the new scenario (using IGRA as a single test or in combination with TST) and the current scenario (using TST alone). Figure 5 presents a simplified diagnostic testing model that accounted for the prevalence of LTBI and the test accuracies of TST and IGRA. As described in Table 9, in the new scenario, we considered various hypothetical IGRA testing pathways to explore changes in the total costs with a single test approach versus the sequential approaches. We also accounted for the costs of treatment for those who tested true or false positive and additional testing costs for indeterminate IGRA results. Sections below describe the input parameters that are used in the model.

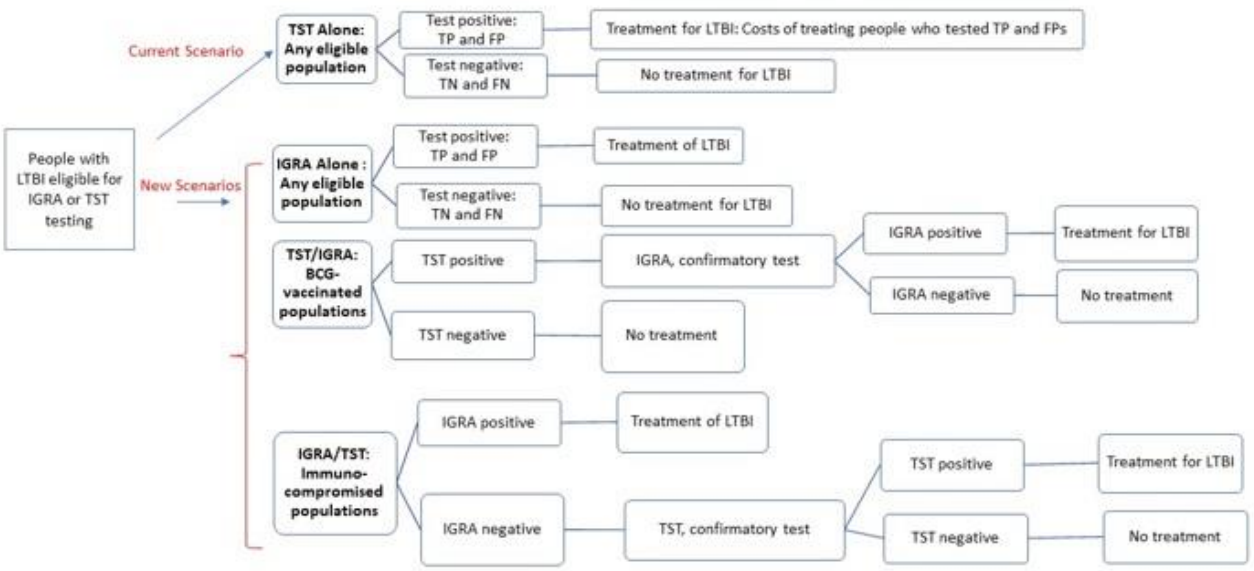

Figure 5: Structures of Simplified Model Pathways

We developed probabilistic decision-tree models for each subpopulation. This schematic summarizes the approach in general; it represents a simplified representation of the strategies and pathways that were included in the models for people eligible for IGRA testing or TST. Under the current scenario, people receive TST alone. People with a positive result, whether a true or false positive, receive treatment for LTBI. In a simplified schematic encompassing various models for different populations, 3 new scenarios are presented: IGRA alone for any eligible population, TST and IGRA for the BCG-vaccinated population, and IGRA and TST for immunocompromised populations. Under the IGRA alone scenario, all positive test results lead to treatment for LTBI and all negative test results lead to no treatment for LTBI. Under the TST and IGRA for BCG-vaccinated people, the TST is given first and people with positive results are given a confirming IGRA test before treatment is given for LTBI. Among immunocompromised populations, the IGRA test is given first and all people with positive results receive treatment for LTBI. People with negative results are given a TST for confirmation, with all people receiving a positive result from the confirming test given treatment for LTBI. Additional testing costs for indeterminate IGRA results were accounted in the models; for simplicity this pathway was not presented in the schematic.

Abbreviations: BCG, Bacille Calmette-Guérin; FN, false negative; FP, false positive; IGRA, interferon-gamma release assay; LTBI, latent tuberculosis infection; TN, true negative; TP, true positive; TST, tuberculin skin test.

Clinical Parameters

We obtained model parameter values from published studies identified in our clinical evidence and economic evidence reviews. We simplified the natural and clinical history of LTBI and accounted only for major clinical inputs that could affect the total costs:

- Variables related to the natural and clinical course of LTBI, such as prevalence of LTBI in Ontario and Canada, probability of reactivation of LTBI into active TB, probabilities of initiating and completing the preventative LTBI therapy and therapy for acute TB (Table 10A)
- Variables related to diagnostic testing with IGRA and TST, such as test accuracy and probability of indeterminate results (Table 10B)

Table 10A: Natural and Clinical History Inputs Used in the Economic Model

Model parameter	Reference case mean (95% CI)[a,b]	Sensitivity analysis	Sources
Prevalence of LTBI (pre-test probability), based on Canadian/Ontario data	0.22 (0.18–0.26)	0.36	Reference case: Jordan et al, 2023[14] Sensitivity analysis: Campbell et al, 2017[79]
Participation in LTBI testing with TST	1.00 (NA)	0.60–0.70	Assumption
- Immigrants		0.60–0.70	Campbell et al, 2017[79]
- Contacts		1.00	
- Immunocompromised			
Probability of developing active TB for people with LTBI (reactivation) [c]	0.0011[c] (NR)	NA	Campbell et al, 2017[79]
Probability of initiating and completing LTBI preventative therapy	0.55 (NR)	0.81	Reference case: PHO data request[112] Sensitivity analysis: Campbell et al, 2017,[79] ;[79] Alsdurf et al, 2016[113]
Probability of initiation of TB drug therapy in those diagnosed with TB:		NA	Campbell et al, 2017[79]
- Immigrants	0.94 (NR)		
- Contacts	1.00 (NA)		
- Immunocompromised	1.00 (NA)		

Abbreviations: CI, confidence interval; NA, not applicable; NR, not reported; TB, tuberculosis; TST, tuberculin skin test; LTBI, latent tuberculosis infection.

[a]Standard errors were estimated where data was available. Where data was not available, we assumed 10% to 25% around the mean.

[b]Beta distributions were assigned to the probability estimates in probabilistic analysis.

[c]This assumption is relevant for people who are false negative on the test, and in whom TB has been reactivated. In such cases, the full cost of TB treatment was applied.

Diagnostic Accuracy of IGRA and TST

As shown in Table 10B, we obtained reference case inputs from the clinical evidence review and additional published literature. The systematic reviews included in the clinical evidence review were of very high methodological quality. We sourced the inputs related to the sensitivity and specificity of TST and IGRA by subpopulation:

- The diagnostic accuracy of TST and IGRA was assumed to be the same for immigrant and contact subpopulations:
  - The sensitivity and specificity values of TST for these 2 populations were obtained from Pai et al[114] because this review accounted for BCG-vaccination status
  - The sensitivity and specificity values of IGRA (QFT-Plus) were sourced from Jonas et al[54,55]
- The diagnostic accuracies of TST and IGRA for immunocompromised populations were taken from a systematic review by Yahav et al[58] showing that the diagnostic accuracy of IGRA (QFT-GIT) was

slightly higher than the accuracy of TST. The sensitivity of IGRA and TST was markedly lower in immunocompromised populations compared with that in healthy immigrant/contacts populations

- The percentage of indeterminate results with IGRA was based on a review by Zhou et al,[57] which also categorized these results by subpopulation

In the sensitivity analysis, we examined the robustness of the reference case cost and budget impact estimates to various values for the diagnostic accuracies of TST and IGRA.

Table 10B: Inputs Related to Accuracy of TST and IGRA, Reference Case

Model parameters	Mean (95% CI)[a,b]	Source
TST		
Sensitivity		
Immigrants, BCG-vaccinated	0.77 (0.71–0.82)	Pai et al, 2008[114]
Contacts, BCG-vaccinated	0.77 (0.71–0.82)	Pai et al, 2008[114]
Immunocompromised	0.309 (0.218–0.417)	Yahav et al, 2023[58]
Specificity		
Immigrants, BCG-vaccinated	0.59 (0.46–0.73)	Pai et al, 2008[114]
Contacts, BCG-vaccinated	0.59 (0.46–0.73)	Pai et al, 2008[114]
Immunocompromised	0.779 (0.727–0.825)	Yahav et al, 2023[58]
Completion of the TST test (both visits)		
Immigrants, BCG-vaccinated	0.75 (NR)	Sester al, 2010[115]
Contacts, BCG-vaccinated	0.91 (NR)	Marra et al, 2008,[80]
Immunocompromised	0.91 (NR)	Campbell 2017,[79] 2019[78,80] Marra 2008,[80] Campbell 2017,[79], 2019[78]
IGRA		
Sensitivity		
Immigrants, BCG-vaccinated	0.89 (0.84–0.94)	Jonas et al, 2023[54,55]
Contacts, BCG-vaccinated	0.89 (0.84–0.94)	Jonas et al, 2023[54,55]
Immunocompromised	0.375 (0.117–0.631)	Yahav et al, 2023[58]
Specificity		
Immigrants, BCG-vaccinated	0.98 (0.95–0.99)	Jonas et al, 2023[54,55]
Contacts, BCG-vaccinated	0.98 (0.95–0.99)	Jonas et al, 2023[54,55]
Immunocompromised	0.799 (0.715–0.863)	Yahav et al, 2023[58]
Indeterminate results		
Immigrants, BCG-vaccinated	0.019 (0.016-- 0.022)	Zhou et al, 2023[57]
Contacts, BCG-vaccinated	0.019 (0.016–0.022)	Zhou et al, 2023[57]
Immunocompromised	0.057 (0.048-0.066)	Zhou et al, 2023[57]
Completion of the IGRA test, all populations	100%	Assumption

Abbreviation: BCG-vaccine, Bacille Calmette-Guérin vaccine; CI, confidence interval; IGRA, interferon-gamma release assay; NR, not reported; TST, tuberculin skin test.

[a]Standard errors were estimated where data was available. Where data was not available, we assumed 10% to 25% around the mean.

[b]Beta distributions were assigned to the probability estimates in probabilistic analysis.

Resources and Costs: Model Inputs

We estimated costs related to resource use and services for LTBI testing and management of LTBI and active TB (Tables 11A–11C and 12). The data were estimated through consultations with experts and from published literature sources. All costs are expressed in 2024 Canadian dollars. We used the Consumer Price Index to adjust values from previous years.[116]

Our analyses assumed that the billing codes for IGRA are already in place for public funding and are considered under the OHIP billing codes for TST (E.g., A001 [visit] and G372 [injection], oral and email communications, Infectious Diseases Policy and Programs Unit, Ontario Ministry of Health, April 9 to 30, 2024). In reality, additional policy work will be required with respect to the following:

- Expansion and more detailed explanation of the eligibility criteria in the Physicians' Services Schedule of Benefits[117] under the current OHIP billing codes for TST (changes to the Schedule of Benefits are negotiated jointly between the Ontario Ministry of Health and the Ontario Medical Association)
- For public funding of a new test, a new lab fee code for the IGRA test would have to be assigned and listed in the Schedule of Benefits for Laboratory Services[104]

Cost Parameters

Cost of Testing: TST and IGRA

Tables 11A and 11B (and Appendix 11) present our estimate of the cost inputs relevant to testing with either TST or IGRA. In our costing approach, we assumed that TST or IGRA would likely be performed differently between the examined subpopulations:

- For contact investigations and healthy immigrants, testing could be shared between public health units and medical doctors (MDs). For simplicity, we assumed this share in Ontario to be 50/50 for the reference case. We tested this assumption in sensitivity analyses (see Table A14, Appendix 12, Scenarios 8 and 9)
    - When we assumed the testing was done at a public health unit, the nurse labour time was included in the cost; if it was done at an MD's office, the labour was fully billed via OHIP (may include MD's and nurse's labour time, depending on the organization of the MD's office)
    - For contact investigations, we included travel time as part of the nurse labour because of the specific approach used for contact investigation testing. In this estimate, we used a conservative approach and we estimated the travel time cost component per person, and not per total number of people included in the field investigation visit
- For immunocompromised populations, the testing would likely be done by physicians (MDs; email and oral communications, E. Rea, MD; P. Galange, MD; M. Richard-Greenblatt, PhD, R. Taylor, MD, April 3 to June 10, 2024)

Costing: TST

Appendix 11 and Table 11A describe the approach and inputs used to estimate a total cost of TST for subpopulations. The cost of TST included the cost of the test and relevant consumables, labour time and, where appropriate, the cost of the initial TST visit (counted as a referral, depending on the type of population). The reference case accounted for the cost of TST vial wastage when TST was done at an MD's office (email communication, I. Kitai, MD, April 30, 2024).

As shown in Table 11A, the total cost of a fully completed TST is:

- For immigrant populations: about $71 per test (i.e., weighted cost by the share of public health unit (PHU); MD test setting: 50:50, reference case)
- For contact investigations: about $141 per test (i.e., weighted cost by the share of PHU; MD test setting: 50:50, reference case)
- For immunocompromised populations: about $74 (at MD's office, 100%, reference case)
- The total cost of an incomplete TST that includes only the components related to the first visit (e.g., cost of initial visit and TST planting) was estimated at about $65, $100, and $67 per test for immigrant, contact, and immunocompromised populations, respectively

Table 11A: Testing for LTBI With TST – Per-Person Costs in the Reference Case

Cost inputs	Unit cost[a]	Quantity/ duration	Total cost[a]	Source
TST: immigrant populations and contacts performed by MDs and PHUs				
TST at MD office				
Referral for TST: physician visit	$23.75	1	$23.75	GP visit, minor assessment, Physician SoB[117]: A001
Nurse's time, first visit: if nurse plants TST, time is covered by the OHIP billing code	$0	NA	NA	Oral communication, E Rea, MD, R, Khan, RN, P Galange, MD, April 25, 2024
TST, injection	$3.89	1	$3.89	Injection, with visit, Physician SoB[117]: G372
TST, PPD consumable, 1 vial	$206	NA	$206	Each vial can provide 10 doses, with 1 dose per person, if there is no wastage (email communications, E Rea, MD, R. Khan, RN, January 12 and April 10, 2024)
TST, PPD consumable, per dose	NA	1	$37.08	Estimate of cost of PPD per dose, including wastage, at MD office (assuming ~44% wastage of the vial due to low uptake of patients in MD office)

Cost inputs	Unit cost[a]	Quantity/ duration	Total cost[a]	Source
TST, other consumables (e.g., swabs, bib, syringe, containers)	$2.47	1	$2.47	Estimate (email communications, E Rea, MD, R. Khan, RN, January 12 and April 10, 2024)
TST, second visit: reading	$6.75	1	$6.75	Reading visit, Physician SoB[117]: G 373
Additional nurse's time for travel	$0	NA	NA	No additional travel time (both contacts and immigrants, TST at MD's office)
TST: total cost, test done at MD's office	—	—	**$73.94**	Calculated
TST at PHU				
Referral for TST physician visit	$0	1	$0	No visit claimed by PHU unit, according to the Medical Act (oral communications, E Rea, MD, R, Khan, RN, P Galange, MD, April 25, 2024)
Nurse's time, first visit: set-up, consent, review, TST plant, post-TST monitoring	$1.01	40 min	$40.40	Estimate (email communications, E Rea, MD, R. Khan, RN, January 12 and April 10, 2024)
Nurse's time, second visit: TST reading	$1.01	5 min	$5.05	Estimate (email communications, E Rea, MD, R. Khan, RN, January 12 and April 10, 2024)
TST, PPD consumable, vials	$206	1/10	$20.60	Estimate, PPD cost of 10-dose vial (email communications, E Rea, MD, R. Khan, RN, January 12 and April 10, 2024)
TST, other consumables (e.g., swabs, bib, syringe, containers)	$2.47	1	$2.47	Estimate (email communications, E Rea, MD, R. Khan, RN, January 12 and April 10, 2024)
Contact investigation only: additional nurse's time for travel Contact investigation only: mileage for 2 visits per contact)	—	1	$139.02	Assumed for contact investigation only: estimated total, 80 minutes, 30 km, $0.68/km (email communication, E Rea, MD, R. Khan, RN, January 12, 2024 and April 10, 2024)
TST: total cost, test done at PHU:				Calculated
Immigrants			**$68.52**	Immigrants
Contacts			**$207.54**	Contacts
Adjustment of the total test cost, based on test-market share				

Cost inputs	Unit cost[a]	Quantity/ duration	Total cost[a]	Source
Test cost at MD's office (share 50%)	$73.94	50%	$36.97	Calculations to include the share; simplifying assumption made for % share that was tested in sensitivity analysis (oral and email communications, E Rea, MD, R, Khan, RN, P Galange, MD, April 25 and June 13, 2024)
Test cost at PHU (share 50%) Immigrants Contacts	— $68.52 $207.54	50%	— $34.26 $103.77	Calculations to include the share; simplifying assumption made for 50% share that was tested in sensitivity analysis (oral and email communications, E Rea, MD, R, Khan, RN, P Galange, MD, April 25, and June 13, 2024)
Completed TST: overall total test cost: **Immigrants** **Contacts**	—	1	**—** **$71.23** **$140.74**	Calculated, adjusted for the share (i.e., adjusted to reflect that 50% of the testing is done by an MD and 50% at a PHU)
Incomplete TST: MDs and PHU, immigrants and contacts				
Incomplete TST: MD's office	—	1	$67.19	Estimated cost of 1 TST visit (initial visit; excludes second, TST reading, visit)
Incomplete TST: PHU Immigrants Contacts	—	1	— $63.47 $132.98	Estimated cost of 1 TST visit, including travel time (excludes TST reading and travel cost for second visit)
Incomplete TST: overall total test cost: **Immigrants** **Contacts**	**—** **$130.66** **$200.17**	**50%**	**—** **$65.33** **$100.09**	Calculated, adjusted for the share
TST, 100% tests performed by MDs: immunocompromised populations				
Initial visit	$23.75	1	$23.75	GP visit, minor assessment, Physician SoB[117]: A001
Injection	$3.89	1	$3.89	Injection, with visit, Physician SoB[117]: G 372
PPD consumable, 1 vial	$206	NA	$206	Each vial can provide 10 doses (1 dose per person) if there is no wastage (email communications, E Rea, MD, R. Khan, RN, January 12 and April 10, 2024)

Cost inputs	Unit cost[a]	Quantity/ duration	Total cost[a]	Source
PPD consumable, per dose	NA	1	$37.08	Estimated cost of PPD per dose, including wastage, at MD's office (assuming ~44% wastage of the vial due to low uptake in MD's office)
Other consumables (e.g., swabs, bib, syringe, containers)	$2.47	1	$2.47	Estimate (email communications, E Rea, MD, R. Khan, RN, January 12 and April 10, 2024)
Second visit: reading	$6.75	1	$6.75	Reading visit, Physician SoB[117]: G 373
Completed TST: total cost, immunocompromised	—	1	**$73.94**	Calculated
Incomplete TST: total cost, immunocompromised	—	1	**$67.19**	Calculated

Abbreviations: GP, general practitioner; LTBI, latent tuberculosis infection; NA, not applicable; OHIP, Ontario Health Insurance Plan; PPD, purified protein derivative; PHU, public health unit; SoB, Schedule of Benefits; TST, tuberculin skin test.

[a]All costs are in 2024 CAD. The input parameters related to the physician fees, lab fees and the list price of IGRA are treated as fixed and were not assigned the distribution in probabilistic analysis. For the rest of the cost inputs, we assigned a gamma distribution.

Costing: IGRA

Appendix 11 and Table 11B describe the approach and inputs used to estimate a total cost of IGRA for subpopulations. The cost of IGRA testing in the reference case considered the list price of IGRA (i.e., QFT-Plus at LifeLabs[103]). The list price of IGRA includes all important cost components, such as the cost of equipment, test kit/reagents, consumables, labor, and shipping cost (oral communication, M. Richard-Greenblatt, PhD, April 11, 2024). As shown in Table 11B, we estimated the total cost of IGRA for:

- Immigrant populations: about $125 per test (i.e., weighted cost by the share of PHU; MD test setting: 50:50, reference case)
- Contact investigations: about $160 per test (i.e., weighted cost by the share of PHU; MD test setting: 50:50, reference case)
- Immunocompromised populations: about $135 (at MD's office, 100%, reference case)

The total cost of a second (repeat) test for indeterminate IGRA results was estimated at about $113, $148, and $111 for immigrant, contact, and immunocompromised populations, respectively.

Table 11B: Testing for LTBI With IGRA—Per-Person Costs in the Reference Case

Cost inputs	Unit cost[a]	Quantity/ duration	Total cost[a]	Source
IGRA, reference case: immigrant populations and contacts performed by MDs and PHUs				
IGRA at MD's office				

Cost inputs	Unit cost[a]	Quantity/ duration	Total cost[a]	Source
Referral for LTBI	$23.75	1	$23.75	GP visit, minor assessment, Physician SoB[117]: A001
Blood sampling	$10.76	1	$10.76	L700, Ontario SoB: Laboratory Services
List price for IGRA, includes all cost components, such as kits, consumables, and shipping and handling	$100.00	1	$100.00	List price, LifeLabs[103]
Shipping and handling	$0	1	—	Included in the list price (expert oral consultation, E Rea, MD, R, Khan, RN, April 25, 2024; Mellisa Richard-Greenblatt, PhD, April 15, 2024)
Additional nurse's time for travel	$0	NA	NA	No additional travel time (both contacts and immigrants, TST at MD's office)
IGRA: total cost, MD's office			**$134.51**	Calculated
IGRA at PHU				
Referral for TST physician visit	$0	1	$0	No visit claimed by PHU unit, in accordance with the Medical Act (oral and email communications, E Rea, MD, R, Khan, RN, P Galange, MD, April 25, 2024)
Blood sampling, nurse time	$1.01	15 min	$15.15	Estimate (email communications, E Rea, MD, R. Khan, RN, January 12 and April 10, 2024)
List price for IGRA, includes all cost components, such as kits, consumables, and shipping and handling	$100.00	1	$100.00	List price, LifeLabs[103]
Shipping and handling	$0	1	–	Assumed to be included in the list price (oral and email communications, E Rea, MD; R, Khan, RN; April 25, 2024; M. Richard-Greenblatt, PhD, April 15, 2024)
Contact investigation only: additional nurse's time for travel Contact investigation only: mileage for 1 visit per single contact	$139.02	1/2	$69.51	Estimated half the cost for TST visit (email communication, E. Rea, MD, R, Khan, RN, January 12 and April 25, 2024)
IGRA: total cost, PHU	-	-		Calculated
Immigrants			**$115.15**	
Contacts			**$184.66**	
Adjustment of the total test cost, based on test-market share				

Cost inputs	Unit cost[a]	Quantity/ duration	Total cost[a]	Source
Test cost at MD's office (share 50%)	**$134.51**	50%	$67.255	Calculated to include the share; simplifying assumption made for % share was tested in sensitivity analysis (oral and email communications, E Rea, MD, R, Khan, RN, P Galange, MD, April 25 and June 13, 2024)
Test cost at PHU (share 50%)	—	50%	—	Calculated to include the share; simplifying assumption made for % share was tested in sensitivity analysis (oral and email communications, E Rea, MD, R, Khan, RN, P Galange, MD, April 25 and June 13, 2024)
Immigrants	**$115.15**		$57.55	
Contacts	**$184.66**		$92.33	
Completed IGRA: overall, total test cost, adjusted for the share:	—	1	**—**	Calculated, adjusted for the share
Immigrants			**$124.83**	
Contacts			**$159.585**	
Test repeat, indeterminate IGRA result:	—	1	—	Estimated, assumed the cost of 1 IGRA test without the initial MD visit
At MD's office			$110.76	
Test repeat, indeterminate IGRA result, at PHU :	—	1	—	Estimated, assumed the cost of 1 IGRA test without the initial MD visit
Immigrants			$115.15	
Contacts			$184.66	
Test repeat, indeterminate IGRA result, adjusted for the share of 50%	—	50%	—	Calculated, adjusted for the share
Immigrants	$225.91		**$112.96**	
Contacts	$295.42		**$147.71**	
IGRA, reference case: immunocompromised populations, 100% by MDs				
Referral for LTBI	$23.75	1	$23.75	GP visit, minor assessment, Physician SoB[117]: A001
Blood sampling	$10.76	1	$10.76	L700, Ontario SoB: Laboratory Services
List price for IGRA, includes all cost components, such as kits, consumables, and shipping and handling	$100.00	1	$100.00	List price, LifeLabs[103]
Shipping and handling	0	1	0	Included in the list price (oral and email communications, E Rea, MD; R, Khan, RN; April 25, 2024; M. Richard-Greenblatt, PhD, April 15, 2024)
Completed IGRA: total cost, MD's office	**—**	**—**	**$134.51**	Calculated

Cost inputs	Unit cost[a]	Quantity/ duration	Total cost[a]	Source
Test repeat, indeterminate IGRA result, immunocompromised	—	1	**$110.76**	Estimated, assumed the cost of 1 IGRA test without the initial visit

Abbreviations: GP, general practitioner; LTBI, latent tuberculosis infection; IGRA, interferon-gamma release assay; PHU, public health unit; SoB, Schedule of Benefits.

[a]All costs are in 2024 CAD. The input parameters related to the physician fees, lab fees, and the list price of IGRA are treated as fixed and were not assigned the distribution in probabilistic analysis.

Costs of Further Medical Evaluation

People who received a positive test result (with either TST or IGRA) underwent additional medical evaluation. We costed this clinical care pathway for Ontario based on previously suggested algorithms that included specialist visits and diagnostic assessments (x-ray and microbiology).[80] The total cost of follow-up was estimated at $267 per person (Table 11C).

Table 11C: Medical Evaluation—Per-Person Costs for Positive Test Results

Costs inputs	Unit cost[a]	Quantity/ duration	Total cost[a]	Source
Follow-up, medical evaluation				
Post-test visit with specialist	$108.95	1	$108.95	Limited consultation: respirologist (e.g., Physician SoB: A575)[117]
Chest x-ray (PA and lateral)	H: $21.90 P: $10.70	1	$32.60	SoB: X091, two or more views (H and P components) [117]
Lab testing: Sputum—culture and smear for tuberculosis, including ZN or fluorescent smear	$19.95	3	$59.85	Lab Schedule Fee: L631[104]
Follow-up visit, specialist	$65.90	1	$65.90	Medical specific re-assessment, respirologist (e.g., Physician SoB: A474)[117]
Total cost, follow-up	-	1	**$267.30**	Calculated

Abbreviations: PA, post-anterior; SoB, Schedule of Benefits; ZN, Ziehl-Neelsen stain.

[a]All costs are in 2024 CAD. The input parameters related to the physician fees, lab fees, and the list price of IGRA are treated as fixed and were not assigned the distribution in probabilistic analysis. For the rest of the cost inputs, we assigned gamma distribution.

Treatment Costs: LTBI and Active TB

Table 12 presents the cost inputs relevant to the management of LTBI and active TB. We estimated the cost of treatment of LTBI (often referred as TB infection) and drug-susceptible TB from a 2022 costing study by Campbell et al.[118] This study provided estimates for the total cost and cost components (in 2020 CAD) relevant to LTBI and various types of active TB incurred at 3 treatment centres in Canada (BC CDC, West Park Healthcare Centre [Ontario], and Montreal Chest Institute [Quebec]). For our analysis, we used the cost estimates reported for those who completed treatment in Ontario:

- The total cost of treatment for LTBI, estimated at $978 per person, included the cost of drugs (INH [isoniazid] or RIF [rifampin]) and the cost of post-treatment monitoring (the cost of hospitalization for LTBI is $0)

- The total cost of management of an active TB case, estimated at $18,063 per person, included the costs of diagnosis, therapy (i.e., for drug-susceptible TB and medications [INH and RIF]), post-treatment monitoring, hospitalization, and public health interventions
- We also accounted for the costs incurred for people who did not complete treatment (see Table 10A, 0.55–0.81). This cost was based on the median cost estimates reported across all 3 centers

Table 12: Per-Person Treatment Costs for LTBI and Active Tuberculosis

Costs inputs	Total mean cost[a]	Total mean cost (median; IQR range)[b]	Source
LTBI			
Completed treatment			
Preventative treatment, test positive	$916.41	$791 ($778; $558–$1,085)	Appendix Table 8, Table 12 in Campbell et al, 2022[118]
Post-treatment monitoring	$61.40	$53 ($18; $0–$93)	Appendix Table 8, Table 12 in Campbell et al, 2022[118]
Total costs, completed treatment	**$977.81**	NA	Estimated
Total cost, not completed treatment[c]	$244.45	NR ($211; $150–$481)	Appendix Table 4 in Campbell et al, 2022[118]
Active drug-susceptible TB			
Total cost for completed treatment, management of TB	$18,062.88	$15,591 ($13,328; $7,921–$19,080)	Appendix Table 8, Table 14 in Campbell et al, 2022[118]
Total cost for not completed treatment, management of TB	$14,413.46	NR ($12,441; $10,104–$18,574)	Appendix Table 4 in Campbell et al, 2022[118]

Abbreviations: IQR, interquartile range; LTBI, latent tuberculosis infection; NA, not applicable; NR, not reported; SEM, standard error of the mean; TB, tuberculosis.

[a]All costs are in 2024 CAD. We assigned gamma distributions (with 25% SEM) in probabilistic analysis.

[b]Reported costs from the original publication, based on data reported for Ontario (for those who completed the treatment). We adjusted the cost inputs for inflation using the CPI for January 2024 ($159.3), ratio: $159.3/$137.5 = 1.158.

[c]The mean costs were not reported for those who did not complete the treatment and were calculated as the median cost across all 3 Canadian sites (Table 4, Appendix in Campbell et al.[118]); the mean estimate for our analysis was based on the reported median.

Resources and Costs: Model Outputs, Reference Case

We simulated probabilistically the inputs described in the budget impact model and estimated the total costs and relevant cost components (i.e., model outputs) by population. The cost data (further used for the budget impact estimations) are shown below in Table 13A–13C.

In our probabilistic analyses, we estimated incremental mean changes in the costs per person between IGRA and TST strategies, by type of tested population, as follows:

- Immigrant population: IGRA alone vs. TST alone, mean savings of $85.93 (95% credible interval (CrI): −$193.63 to $14.37); sequential TST/IGRA vs. TST alone, mean savings of $181.75 (95% CrI: −$262.86 to −$111.80)

- Contact population: IGRA alone vs. TST alone, mean savings of $189.04 (95% CrI: −$313.20 to −$50.59); sequential TST/IGRA vs. TST alone, mean savings of $203.97 (95% CrI: −$296.26 to −$120.36)
- Immunocompromised population: IGRA alone vs. TST alone, mean cost increase of $89.77 (95% CrI: −$15.52 to $206.43); sequential TST/IGRA vs. TST alone, mean cost increase of $276.77 (95% CrI: $188.87 to $361.03); sequential IGRA/TST vs. TST alone, mean cost increase of $344.62 (95% CrI: $273.39 to $435.54)

Table 13A: Reference Case—Per-Person Cost Estimates: Immigrant Subpopulation

	Cost per person[a]		
	Current scenario: TST[b] Mean (95% CrI)[d]	**New scenario: IGRA alone[c]** Mean (95% CrI)[d]	**New scenario: sequential TST/IGRA (TST+, then IGRA)[c]** Mean (95% CrI)[d]
Total	**$408.53 ($308.06–$518.59)**	**$322.60 ($282.67–$366.78)**	**$226.78 ($185.52–$269.92)**
Testing	$69.75	$126.98	$115.83
Follow-up	$98.08	$56.49	$31.50
Treatment, LTBI	$237.75	$136.94	$76.36
Treatment, active TB	$2.94	$2.20	$3.09
Treatment, total cost	$240.69	$139.16	$79.45

Abbreviations: CrI, credible interval; IGRA, interferon-gamma release assay; LTBI, latent tuberculosis infection; TST, tuberculin skin test.
[a]All costs are in 2024 CAD.
[b]Current scenario, existing testing with TST.
[c]New scenario, new testing strategies with IGRA.
[d] 95% CrI provided for the total cost only.

Table 13B: Reference Case—Per-Person Costs Estimates: Contact Subpopulation

	Cost per person[a]		
	Current scenario: TST[b] Mean (95% CrI)[d]	**New scenario: IGRA alone[c]** Mean (95% CrI)[d]	**New scenario: sequential TST/IGRA (TST+, then IGRA)[c]** Mean (95% CrI)[d]
Total	**$547.03 ($407.17–$674.75)**	**$357.98 ($318.48–$401.69)**	**$343.06 ($273.92–$395.03)**
Testing	$137.09	$162.39	$209.35
Follow-up	$118.94	$56.47	$38.21
Treatment, LTBI	$288.32	$136.89	$92.63
Treatment, active TB	$2.68	$2.23	$2.87
Treatment, total cost	$291.00	$139.12	$95.50

Abbreviations: CrI, credible interval; IGRA, interferon-gamma release assay; LTBI, latent tuberculosis infection; TST, tuberculin skin test.
[a]All costs are in 2024 CAD.
[b]Current scenario, existing testing with TST.
[c]New scenario, new testing strategies with IGRA.

[d] 95% CrI provided for the total cost only.

Table 13C: Reference Case—Per-Person Costs Estimates: Immunocompromised Subpopulation

	Cost per person[a]			
	Current scenario: TST[b] Mean (95% CrI)[e]	**New scenario: IGRA alone[c]** Mean (95% CrI)[e]	**New scenario: sequential TST/IGRA (TST–, then IGRA)[c,d]** Mean (95% CrI)[e]	**New scenario: sequential IGRA/TST (IGRA–, then TST)[c,d]** Mean (95% CrI)[e]
Total	**$318.56 ($242.12–$385.15)**	**$408.33 ($320.93–$507.65)**	**$595.33 ($444.12–$708.93)**	**$663.17 ($578.70–$750.25)**
Testing	$73.33	$140.82	$170.71	$197.08
Follow-up	$58.45	$63.91	$102.00	$112.07
Treatment – LTBI	$183.40	$200.55	$320.08	$351.67
Treatment – active TB	$3.37	$3.04	$2.54	$2.36
Treatment – total cost	$186.78	$203.59	$322.61	$354.02

Abbreviations. CrI, credible interval; IGRA, interferon-gamma release assay; LTBI, latent tuberculosis infection; TST, tuberculin skin test.
[a] 2024 CAD.
[b] Current scenario, existing testing with TST.
[c] New scenario, new testing strategies with IGRA.
[d] In a sequential scenario, where the result of the first test (TST or IGRA) is negative, the other test will be performed.
[e] 95% CrI provided for the total cost only.

Current Intervention Mix

Testing with IGRA is not publicly funded in Ontario. It is offered at a few sites to selected patients such as Toronto PHU (contacts only, free of charge) or the Hospital for Sick Children and lab testing is done at the Hospital for Sick Children (where it is publicly funded from the hospital's global budget). Testing with IGRA is also offered at private labs (e.g., LifeLabs), where individuals pay for IGRA out-of-pocket. For simplicity, we assumed that, at present, only TST is used for LTBI screening in all subgroups described in Population of Interest, above.

Uptake of the New Intervention and New Intervention Mix

We estimated how quickly IGRA testing may be adopted with public funding. The uptake of IGRA in Ontario is uncertain and likely different between populations (e.g., uptake of the test for people identified in contact investigations or with immunocompromised conditions could be larger and faster than for immigrants because these populations could be easily identified in the system). Hence, we assumed that the uptake of IGRA testing strategies (as a replacement or in combination with TST) was different between the populations of interest, with a smaller annual uptake in immigrant populations (increase of 3% per year) and a larger uptake in the contact or immunocompromised populations (starting with 75% in year 1 and growing to 100% in year 5; email communications, clinical expert consultation, April 2024). We tested this assumption in our sensitivity analyses.

A small annual uptake in the reference case for the immigrant population was justified by the small and steady increase in uptake of IGRA in British Columbia. In British Columbia, IGRA testing officially began in a select group of people in October 2009. In 2010, IGRA volumes were less than 1,000, growing to about

7,000 in 2023 (email and oral communications, V. Cook, MD, M. Morshed, MD, January 30 and May 22, 2024). In addition, the participation of people in the TST or IGRA testing strategies was assumed to be 100% in the reference case, but this assumption was tested in our sensitivity analyses. As shown in Tables 14A–14C, we estimated the uptake of IGRA strategies by population as follows:

- Immigrant population (uptake rate of 3% per year, Table 14A): the total number of people to be tested by the new strategy (which includes IGRA) would be about 19,000 over the next 5 years (increasing from about 1,160 in Year 1 to 6,620 in Year 5)
- Contacts (uptake rate of 75% in Year 1, increasing to 100% in Year 5, Table 14B): the total number of people to be tested by the new strategy (which includes IGRA) would be about 8,620 over the next 5 years (increasing from about 1,363 in Year 1 to 2,045 in Year 5)
- Immunocompromised populations (uptake rate of 75% in Year 1, increasing to 100% in Year 5, Table 14C): the total number of people to be tested by the new strategy (which includes IGRA) would about 69,700 over the next 5 years (increasing from about 11,200 in Year 1 to 16,300 in Year 5)

Table 14A: Uptake of IGRA and TST in Ontario: Immigrant Populations

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Current scenario						
IGRA, n[a]	—	—	—	—	—	—
TST, n	38,588	39,901	41,257	42,660	44,110	206,516
New scenario[b]						
Uptake rate for the new strategy with IGRA	3%	6%	9%	12%	15%	—
IGRA, n[a]	1,158	2,394	3,713	5,119	6,617	19,001
TST, n	37,430	37,507	37,544	37,541	37,493	187,515
Total, both, n	38,588	39,901	41,257	42,660	44,110	206,516

Abbreviations: IGRA, interferon-gamma release assay; TST, tuberculin skin test.

[a]The new testing strategy includes testing with IGRA (depending on the type of intervention, this could be IGRA as a single test or IGRA in combination with TST). We assumed no or zero IGRA tests done in the current scenario.

[b]We calculated the volume of interventions from the total number multiplied by the uptake rate of the new intervention. For example, in the new scenario, the total volume in Year 1 is 38,588 and the uptake rate of IGRA is 3%, so the volume of IGRA in Year 1 is 38,588 × 3% = 1,158.

Table 14B: Uptake of IGRA and TST in Ontario: Contacts

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Current scenario						
IGRA, n[a]	—	—	—	—	—	—
TST, n	1,817	1,872	1,928	1,986	2,045	9,648
New scenario[b]						
Uptake rate for the new strategy with IGRA	75%	85%	90%	95%	100%	—
IGRA, n[a]	1,363	1,591	1,735	1,887	2,045	8,621

TST, n	454	281	193	99	0	1,027
Total, both, n	1,817	1,872	1,928	1,986	2,045	9,648

Abbreviations: IGRA, interferon-gamma release assay; TST, tuberculin skin test.
[a]The new testing strategy includes testing with IGRA (depending on the type of intervention, this could be IGRA as a single test or IGRA in combination with TST). We assumed no or zero IGRA tests done in the current scenario.
[b]We calculated the volume of interventions from the total number multiplied by the uptake rate of the new intervention.

Table 14C: Uptake of IGRA and TST in Ontario: Immunocompromised Populations

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Current scenario						
IGRA, n[a]	-	-	-	-	-	-
TST, n	14,934	15,286	15,627	15,949	16,273	78,069
New scenario[b]						
Uptake rate for the new strategy with IGRA	75%	85%	90%	95%	100%	
IGRA, n[a]	**11,200**	**12,993**	**14,064**	**15,151**	**16,273**	**69,681**
TST, n	3,734	2,293	1,563	798	0	8,388
Total, both, n	14,934	15,286	15,627	15,949	16,273	78,069

Abbreviations: interferon-gamma release assay; TST, tuberculin skin test.
[a]The new testing strategy includes testing with IGRA (depending on the type of intervention, this could be IGRA as a single test or IGRA in combination with TST). We assumed no or zero IGRA tests done in the current scenario.
[b]We calculated the volume of interventions from the total number multiplied by the uptake rate of the new intervention.

Internal Validation

The secondary health economist conducted formal internal validation. This process included checking for errors and ensuring the accuracy of parameter inputs and equations in the budget impact analysis.

Analysis

We conducted a model-based reference case analysis and sensitivity analyses. Our reference case analysis represents the analysis with the most likely set of input parameters and model assumptions. Our sensitivity analyses explored how the results are affected by varying input parameters and model assumptions. As shown in Model Outputs, the undiscounted mean cost estimates were made probabilistically by running 100,000 simulations that captured the uncertainty in the majority of the model parameters that we expected would vary. The probabilistic analyses were conducted using TreeAge Pro 2023.[119] The budget impact calculations were done using Microsoft Excel for Office 365.[120]

Sensitivity Analysis

We conducted the following scenario analyses to address uncertainty in the budget impact estimates (see Appendix 12 for details):

- Scenarios related to changes in the estimate of the populations of interest:

- ***Scenario 1***: immigrant and contact subpopulations estimated from LTBI episode data recorded in the integrated Public Health Information System (iPHIS) extracted by and obtained from Public Health Ontario (email communication, A. Saunders, MSc, April 1, 2024, PHO Data Request #2024-011,[112] and oral and email communications, L Macdonald, MD, A Saunders, MSc, M Whelan, MSc, and E. Rea, MD, June 10–14, 2024). The estimate and assumptions are shown in Table 15 and Appendix 13

Table 15: Scenario 1—Overall Population Estimates for Budget Impact: Immigrant and Contact Subpopulations Based on iPHIS Data

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Total population, n[a]	**42,503**	**43,793**	**45,103**	**46,427**	**47,787**	**225,614**
Immigrants, n[b]	17,203	17,788	18,393	19,018	19,665	92,068
Contacts, n[b]	10,366	10,718	11,083	11,460	11,849	55,477
Immunocompromised, n	14,934	15,286	15,627	15,949	16,273	78,069

Abbreviations: iPHIS, integrated Public Health Information System; LTBI, latent tuberculosis infection.

[a]Totals may appear inexact due to rounding.

[b]Calculated using LTBI data for extracted from iPHIS by Public Health Ontario.[112] See Appendix 13 for explanations of assumptions and calculations.

- ***Scenario 2***: Inclusion of all types of cancers into our estimate of the size of immunocompromised population (Table 16, see also Appendix 10 for details)

Table 16: Scenario 2—Overall Population Estimates for Budget Impact: Inclusion of All Types of Cancers

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Total population, n[a]	**146,139**	**149,848**	**153,546**	**157,383**	**161,255**	**768,171**
Immigrants, n	38,588	39,901	41,257	42,660	44,110	206,516
Contacts, n	1,817	1,872	1,928	1,986	2,045	9,648
Immunocompromised, n[b]	105,734	108,075	110,361	112,737	115,099	552,006

[a]Totals may appear inexact due to rounding.

[b]All cancers considered in the estimate of the immunocompromised populations.

- Scenarios related to changes in the uptake of IGRA strategies:
  - **Scenario 3**: large uptake for all subpopulations, starting at 75% in Year 1 (a substantial change in the uptake for the immigrant populations, which was 3% per year in the reference case)
  - **Scenario 4**: Low uptake of 5% per year for all subpopulations of interest (a large change in the uptake for contacts and the immunocompromised population, which was 75% in Year 1, increasing to 100% in Year 5 in the reference case)

  - **Scenario 5**: evenly spread uptake of 20% per year for the immunocompromised population (reaching 100% in Year 5) and the same uptake for the rest, as in the reference case
  - **Scenario 6**: smaller uptake of 10% per year for the immunocompromised population (reaching 50% in Year 5) and the same uptake for the rest, as in the reference case
- Scenarios related to uncertainty in the testing pathway with respect to:
  - **Scenario 7**: no cost of referral when the testing is done by MDs, thus assuming no cost of referral visit for all subpopulations (vs. no cost of referral for testing done by PHU in the reference case)
  - **Scenarios 8** and **9:** vary the share of TST and IGRA testing by MDs and PHUs for immigrant and contact subpopulations:
    - **Scenario 8**: all tests for immigrants and contacts are done by PHUs (vs. 50%/50% split in the reference case)
    - **Scenario 9**: all tests for immigrants done by MDs (vs. 50%/50% split in the reference case). We assumed that it would not be plausible to exclude PHUs from the testing for the contact investigations
  - **Scenario 10** (2 scenarios: 10a and 10b):
    - **Scenario 10a**: cost of purified protein derivative (PPD, which is derived from tuberculin and injected under the skin) per dose was $20.60 with no waste of the PPD vial at MD's office (vs. reference case cost of $37.08 with a 44% vial wastage)
    - **Scenario 10b**: cost of PPD per dose was: $103 with an 80% vial wastage (vs. reference case cost of $37.08 with a 44% vial wastage)
- Scenarios related to the cost of IGRA:
  - **Scenario 11**: the cost of IGRA decreased by 25% to $75 per test (vs. $100/test in the reference case)
  - **Scenario 12**: IGRA performed at an established hospital laboratory
    - **Scenario 12a**: shipping and handling **not costed separately** for PHU and assumed to be included in the overall IGRA cost at a hospital lab (i.e., shipping and handling covered by the current transportation routes)
    - **Scenario 12b**: shipping and handling **costed separately** for PHU and added to the overall cost of IGRA at a hospital lab

We estimated the cost of IGRA performed at an established hospital lab (e.g., Hospital for Sick Children), based on inputs obtained through expert consultation (email and oral communications, M. Richard-Greenblatt, PhD, November 2023 to April 2024). As shown in Table 17, we estimated the total cost of IGRA testing for 3 populations:

- Immigrants: about $130 per test (i.e., weighted cost by the share of PHU:MD test setting: 50%/50%)
- Contacts: about $165 per test (i.e., weighted cost by the share of PHU:MD test setting: 50%/50%)
- Immunocompromised: about $138 per test (MD's office: 100%)

The total cost of an indeterminate IGRA result, requiring a second IGRA test, was estimated at about:

- $119, $153, and $114 per test repeat for immigrant, contact, and immunocompromised populations, respectively

We conducted additional analyses under this scenario that accounted for the cost of shipping and handling of IGRA samples for immigrant and contact populations (Tables 17 and 24, Scenarios 12a and 12b). We assumed that immunocompromised populations would be tested at hospitals. In these cases, there would be no shipping costs (because the testing would have been performed at the laboratory site email and oral communications, M. Richard-Greenblatt, PhD, April 3 to May 31, 2024).

Table 17: Testing for LTBI with IGRA—Per-Person Costs Used in Scenarios 12a and 12b, IGRA done at an Established Hospital Laboratory

Cost inputs	Unit cost[a]	Quantity/ duration	Total cost[a]	Source
IGRA, immigrant population and contact testing performed by MDs and PHUs				
IGRA at MD's office				
Referral for LTBI	$23.75	1	$23.75	GP visit, minor assessment, Physician SoB[117]: A001
Blood sampling	$10.76	1	$10.76	L700, Ontario SoB: Laboratory Services
Test cost includes all cost components, such as kits, consumables and shipping and handling, done by personnel at the hospital laboratory	$103.00	1	$103.00	Cost, SickKids (email communication, M. Richard-Greenblatt, PhD, April 11, 2024)
Shipping and handling	$0	1	$0	Included in the list price (oral and email communications, E Rea, MD, R, Khan, RN, April 25, 2024, M. Richard-Greenblatt, PhD, April 15, 2024)
Additional nurse's time for travel	$0	NA	NA	No additional travel time (both contacts and immigrants, TST at MD's office)
IGRA: total cost, MD's office			**$137.51**	Calculated
IGRA at PHU				
Referral for TST, physician visit	$0	1	$0	No visit claimed by PHU unit (oral communications, E Rea, MD, R, Khan, RN, P Galange, MD, April 25, 2024)
Blood sampling, nurse's time	$1.01	15 min	$15.15	Estimate (email communications, E Rea, MD, R. Khan, RN, January 12 and April 10, 2024
Other consumables, such as needles, syringes, heparin, swabs, gauze, band aid, containers (test performed at PHU or hospital site)	$4.63	1	$4.63	Estimate (email communications, E. Rea, R, Khan, January 12 and April 25, 2024)

Cost inputs	Unit cost[a]	Quantity/ duration	Total cost[a]	Source
Test cost (includes all cost components, such as equipment, overheads, labour, kits, consumables, and shipping and handling, done by personnel at the hospital laboratory)	$103.00	1	$103.00	Hospital for Sick Children, (oral and email communications, M. Richard-Greenblatt, PhD, 11 April, 2024)
Scenario 12a: shipping and handling	$0	1	$0	Assumed to be covered by the current transportation routes (expert oral and email communications: E Rea, MD; R, Khan, RN; April 25, 2024; M. Richard-Greenblatt, PhD, April 15, 2024)
Scenario 12b: shipping and handling added to the cost of test, if it is shipped from the site to the lab, included in an additional scenario	$6.025	1	$6.025	Tsiplova, 2016
Contact investigations only: additional nurse's time for travel Contact investigation only: mileage for 1 visit per contact	$139.02	1/2	$69.51	Estimated to be half the cost of a TST visit (email communication, E. Rea, MD, R, Khan, RN, January 12 and April 25, 2024)
Scenario 12a: IGRA, total cost, PHU Immigrants Contacts	—	—	 $122.78 $192.29	Calculated (shipping/handling not costed separately for PHU)
Scenario 12b: IGRA, total cost, PHU Immigrants Contacts	—	—	 $128.81 $198.32	Calculated (shipping/handling cost costed separately)
Adjustment of the total test cost, based on test-market share				
Test cost at MD's office	$137.51	50%	$68.755	Calculated; we made simplifying assumptions for % share, which was tested in sensitivity analyses (oral and email communications, E Rea, MD, R, Khan, RN, P Galange, MD, April 25 and June 13, 2024)
Test cost at PHU Immigrants Contacts	— $122.78 $192.29	50%	— $61.39 $96.15	Calculated; We made simplifying assumptions for 50% share, which was tested in sensitivity analyses (oral and email communications, E Rea, MD, R, Khan, RN, P Galange, MD, April 25 and June 13, 2024)
Completed IGRA: total cost, shipping/handling not costed separately (**Scenario 12a**) Immigrants Contacts	—	1	— $130.455 $165.21	Calculated, adjusted for the 50% share

Cost inputs	Unit cost[a]	Quantity/ duration	Total cost[a]	Source
Completed IGRA: total cost, addition of **Scenario 12b**, with shipping/handling costed separately for PHU	MD: $137.51 PHU:	50%	—	Calculated, adjusted for the 50% share
Immigrants	$128.81		$133.16	
Contacts	$198.32		$167.91	
Test repeat Indeterminate IGRA result at MD's office	1	1	— $113.76	Estimated as the cost of 1 IGRA test without the initial MD visit
Indeterminate IGRA result at PHU:	1	1	—	
Immigrants			$122.78	
Contacts			$192.29	
Test repeat, total cost, adjusted for the 50% share, no additional shipping costs (**Scenario 12a**)	—	50%	—	Estimated as the cost of 1 IGRA test without the initial MD visit
Immigrants	$236.54		$118.27	
Contacts	$306.05		$153.025	
Test repeat, total cost, immigrants and contacts, additional scenario, with additional shipping costs to PHU (**Scenario 12b**)	MD: $113.76 PHU:	50%	—	Estimated as the cost of 1 IGRA test without the initial MD visit
Immigrants	$128.81		$121.285	
Contacts	$198.32		$156.04	
IGRA: immunocompromised populations, 100% by MDs				
Referral for LTBI	$23.75	1	$23.75	GP visit, minor assessment, Physician SoB[117]: A001
Blood sampling	$10.76	1	$10.76	L700, Ontario SoB: Laboratory Services
Test cost, includes all cost components, such as kits, consumables, and shipping and handling, done by personnel at the hospital laboratory	$103.00	1	$103.00	Cost, Sick Kids Hospital (email communication, M. Richard-Greenblatt, PhD, April 11, 2024)
Shipping and handling	$0	1	$0	Included in the list price (oral and email communications, E Rea, MD, R, Khan, RN, April 25, 2024; M. Richard-Greenblatt, PhD, April 15, 2024)
IGRA: total cost, immunocompromised	—	1	**$137.51**	Calculated
IGRA test repeat : total cost, immunocompromised	—	1	$113.76	Estimated as the cost of 1 IGRA test without the initial visit

Abbreviations: GP, general practitioner; IGRA, interferon-gamma release assay; LTBI, latent tuberculosis infection; NA, not applicable; PHU, Public Health Unit; SoB, Schedule of Benefits.

[a]All costs in 2024 CAD. The input parameters related to the physician fees, lab fees, and the list price of IGRA are treated as fixed and were not assigned the distribution in probabilistic analysis.

We conducted a set of one-way sensitivity analyses on the incremental cost of IGRA strategies versus TST alone to examine the influence of the following model inputs: screening participation, TST completion, prevalence of LTBI, the diagnostic accuracy of TST and IGRA, reactivation of LTBI into active TB in untreated patients, completion of LTBI and active TB treatment, and cost of shipping. These analyses were presented using tornado diagrams. We used a threshold parameter value for probability of reactivation of LTBI in the immunocompromised population to examine costs and budget impact in Scenario 13.

Results

Reference Case: Overall Budget Impact—All Subpopulations

Table 18 presents the overall budget impact of publicly funding IGRA to support the diagnosis of LTBI in 3 populations (immigrants, contacts, and immunocompromised people). These are overall estimates for the eligible populations, which were calculated altogether, and they are the result of averaging potential savings in some populations with additional costs in other populations.

In the current scenario (TST alone), the total costs ranged from $21.52 million in year 1 to about $24.32 million in year 5, with a total 5-year cost of $114.52 million. In the new scenario (IGRA alone as a single test), the total costs for the 3 populations were:

- In immigrants, between $15.66 million and 17.45 million per year, with a total 5-year cost of $82.73 million
- In contacts, about $0.73 million to $0.74 million per year, with a total 5-year cost of about $3.65 million
- In immunocompromised people, about $5.76 million to $6.64 million per year, with a total 5-year cost of about $31.12 million

In this analysis, for all populations, the budget impact of publicly funding IGRA alone (as a single test) was between $0.51 million and $0.65 million per year, for a total of about $2.99 million over the next 5 years. The cost associated with the IGRA test itself was $6.01 million. The overall budget impact is lower than the cost of testing alone because of the anticipated downstream savings (reductions in follow-up costs and treatment costs, see discussions of cost components, below).

Table 18: Budget Impact Analysis Results, Reference Case—IGRA Alone Versus TST Alone, All Populations

All populations	Total costs and budget Impact, in millions[a,b]					
Scenarios	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total 5-year cost**
Current scenario, TST alone, all populations	$21.52	$22.19	$22.89	$23.59	$24.32	$114.52
Cost of test	$4.04	$4.16	$4.29	$4.42	$4.55	$21.45
New scenario: IGRA alone, immigrants	$15.66	$16.09	$16.54	$16.99	$17.45	$82.73

Cost of test	$2.76	$2.92	$3.09	$3.27	$3.46	$15.49
New scenario: IGRA alone, contacts	$0.74	$0.73	$0.73	$0.73	$0.73	$3.65
BI: Cost of test	$0.28	$0.30	$0.31	$0.32	$0.33	$1.54
New scenario: IGRA alone, immunocompromised	$5.76	$6.04	$6.24	$6.44	$6.64	$31.12
BI: Cost of test	$1.85	$2.00	$2.10	$2.19	$2.29	$10.43
Total BI: IGRA alone vs. TST alone	**$0.65**	**$0.66**	**$0.62**	**$0.56**	**$0.51**	**$2.99**
BI: Cost of test	$0.86	$1.05	$1.21	$1.36	$1.53	$6.01

Abbreviations: BI, budget impact; IGRA, interferon-gamma release assay; TST, tuberculin skin test.

[a]In 2024 CAD.

[b]Results may appear inexact due to rounding.

Error! Reference source not found. presents the overall budget impact of publicly funding the new testing, including IGRA as a sequential test, to support the diagnosis of LTBI in all examined subpopulations (immigrants, contacts, and immunocompromised people). In our estimate, we included the costs of IGRA testing sequentially with TST as follow-up to TST-positive results in immigrant or contact populations and as follow-up to TST-negative results in immunocompromised people.

In the new scenario, with IGRA as part of sequential testing, the total cost depended on the population:

- In immigrants, the cost was between $15.55 million and 16.82 million per year, with a total 5-year cost of about $80.91 million
- In contacts, the cost was about $0.70 million to $0.72 million per year, with a total 5-year cost of about $3.52 million
- In immunocompromised people, the cost was between $7.86 million and $9.69 million per year, with a total 5-year cost of about $44.16 million

In our analysis for all populations, the total additional costs of IGRA as a sequential test with TST were between $2.61 million and $2.88 million per year, with an overall additional cost of about $14.07 million over the next 5 years. The total cost associated with the testing itself was about $8.28 million.

Table 19: Budget Impact Analysis Results, Reference Case—IGRA in Sequential Testing Versus TST Alone, All Populations

All populations	**Total costs and budget Impact, in millions[b,c]**					
Scenarios	Year 1	Year 2	Year 3	Year 4	Year 5	Total 5-year cost
Current scenario, TST alone, all populations	$21.52	$22.19	$22.89	$23.59	$24.32	$114.52
Cost of test	$4.04	$4.16	$4.29	$4.42	$4.55	$21.45
New scenario: SEQ,[a] immigrants	$15.55	$15.87	$16.18	$16.50	$16.82	$80.91
Cost of test	$2.75	$2.89	$3.05	$3.21	$3.38	$15.28
New scenario: SEQ,[a] contacts	$0.72	$0.70	$0.70	$0.70	$0.70	$3.52
Cost of test	$0.35	$0.37	$0.39	$0.41	$0.43	$1.95
New scenario: SEQ with initial TST, immunocompromised[d]	$7.86	$8.47	$8.87	$9.27	$9.69	$44.16
Cost of test	$2.19	$2.39	$2.52	$2.64	$2.78	$12.51
Total BI: SEQ– TST/IGRA vs. TST alone	**$2.61**	**$2.84**	**$2.86**	**$2.88**	**$2.88**	**$14.07**
BI: cost of test	$1.24	$1.49	$1.67	$1.85	$2.04	$8.28

Abbreviations: BI, budget impact; IGRA, interferon-gamma release assay; SEQ, sequential pathways; TST, tuberculin skin test.
[a]TST followed by IGRA, in TST-positive immigrant and contact populations.
[b]All costs are in 2024 CAD.
[c]Results may appear inexact due to rounding.
[d]TST followed by IGRA, in TST-negative immunocompromised people.

Table 20 presents the overall budget impact of publicly funding the new scenario with IGRA as a sequential test to support the diagnosis of LTBI in all examined subpopulations (immigrants, contacts, and immunocompromised people). In this scenario, we included the costs of IGRA testing sequentially with TST. In immigrants and contacts, IGRA is a follow-up test for TST-positive results. In immunocompromised populations, IGRA was the first-line test, with TST as a follow-up for IGRA-negative results. In the new scenario with IGRA in sequential testing, the total cost depended on the population:

- In immigrants, the cost was between $15.55 million and 16.82 million per year, with a total 5-year cost of about $80.91 million
- In contacts, the cost was about $0.70 million to $0.72 million per year, with a total 5-year cost of about $3.52 million
- In immunocompromised populations, the cost was between $8.62 million and $10.79 million per year, with a total 5-year cost of about $48.88 million

In our analysis for all populations, the total additional costs of testing with IGRA were between $3.37 million and $3.99 million per year, with an overall additional cost of about $18.80 million over the next 5 years. The total cost associated with the testing itself was about $10.12 million.

Table 20: Budget Impact Analysis Results, Reference Case—IGRA in Sequential Testing Versus TST Alone, All Populations

All populations	**Total costs and budget Impact, in millions[b,c]**					
Scenarios	Year 1	Year 2	Year 3	Year 4	Year 5	Total 5-year cost
Current scenario: TST alone	$21.52	$22.19	$22.89	$23.59	$24.32	$114.52
Cost of test	$4.04	$4.16	$4.29	$4.42	$4.55	$21.45
New scenario: SEQ, immigrants[a]	$15.55	$15.87	$16.18	$16.50	$16.82	$80.91
Cost of test	$2.75	$2.89	$3.05	$3.21	$3.38	$15.28
New scenario: SEQ, contacts[a]	$0.72	$0.70	$0.70	$0.70	$0.70	$3.52
Cost of test	$0.35	$0.37	$0.39	$0.41	$0.43	$1.95
New scenario: SEQ with initial IGRA, immunocompromised[d]	$8.62	$9.35	$9.82	$10.30	$10.79	$48.88
Cost of test	$2.48	$2.73	$2.89	$3.04	$3.21	$14.35
Total BI: SEQ TST/IGRA & IGRA/TST (immunocompromised) vs. TST alone	**$3.37**	**$3.72**	**$3.82**	**$3.91**	**$3.99**	**$18.80**
BI: cost of test	$1.54	$1.83	$2.04	$2.25	$2.47	$10.12

Abbreviations: BI, budget impact; IGRA, interferon-gamma release assay; TST, tuberculin skin test; SEQ, sequential pathways.
[a]TST followed by IGRA, in TST-positive immigrant and contact populations.
[b]All costs are in 2024 CAD.
[c]Results may appear inexact due to rounding.
[d]IGRA for all, then TST in IGRA-negative for immunocompromised people.

Reference Case: Budget Impact—By Subpopulation

Immigrant Populations

As shown in Table 21A, for the immigrant population, IGRA testing was associated with cost savings ranging from $1.63 million (IGRA alone) to $3.45 million (IGRA as a sequential test) over the 5-year time horizon. The total cost associated with the testing itself (IGRA or TST alone and sequentially) was an additional $1.09 million and $0.88 million, respectively.

Table 21A: Budget Impact Results, Reference Case—Immigrant Subpopulation

Immigrants	Total costs and budget impact, in millions[a-c]					
Scenarios	Year 1	Year 2	Year 3	Year 4	Year 5	Total 5-year cost
Current scenario: TST alone	$15.76	$16.30	$16.85	$17.43	$18.02	$84.37
Cost of test	$2.69	$2.78	$2.88	$2.98	$3.08	$14.41
New scenario: SEQ, TST/IGRA[d]	$15.55	$15.87	$16.18	$16.50	$16.82	$80.91
Cost of test	$2.75	$2.89	$3.05	$3.21	$3.38	$15.28
New scenario: IGRA alone	$15.66	$16.09	$16.54	$16.99	$17.45	$82.73
Cost of test	$2.76	$2.92	$3.09	$3.27	$3.46	$15.49
BI: IGRA alone vs. TST alone	**−$0.10**	**−$0.21**	**−$0.32**	**−$0.44**	**−$0.57**	**−$1.63**
BI: Cost of test	$0.07	$0.14	$0.21	$0.29	$0.38	$1.09
BI: SEQ, TST/IGRA[d] vs. TST alone	**−$0.21**	**−$0.44**	**−$0.67**	**−$0.93**	**−$1.20**	**−$3.45**
BI: Cost of test	$0.05	$0.11	$0.17	$0.24	$0.30	$0.88

Abbreviations: BI, budget impact; IGRA, interferon-gamma release assay; SEQ, sequential pathways; TST, tuberculin skin test.
[a]All costs are in 2024 CAD.
[b]Negative costs indicate savings.
[c]Results may appear inexact due to rounding.
[d]TST followed by IGRA, in TST-positive immigrant populations.

As shown in Table 21B, IGRA testing led to downstream savings from a reduction in follow-up costs (−$0.79 million to −$1.27 million over 5 years) and treatment costs (−$1.92 million to −$3.07 million over 5 years).

Table 21B: Budget Impact Results, Reference Case—Immigrant Subpopulation, by Cost Component

	Total costs and budget impact[a-c]					
Current scenario: TST	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total 5-year Cost**
Total costs, current scenario	$15.76	$16.30	$16.85	$17.43	$18.02	$84.37
Cost of test	$2.69	$2.78	$2.88	$2.98	$3.08	$14.41
Cost of FU	$3.78	$3.91	$4.05	$4.18	$4.33	$20.26
Cost of LTBI treatment	$9.17	$9.49	$9.81	$10.14	$10.49	$49.10
Cost of TB treatment	$0.11	$0.12	$0.12	$0.13	$0.13	$0.61
New scenario: IGRA alone						
Total costs, future scenario	$15.66	$16.09	$16.54	$16.99	$17.45	$82.73
Cost of test	$2.76	$2.92	$3.09	$3.27	$3.46	$15.49
Cost of FU	$3.74	$3.81	$3.89	$3.97	$4.05	$19.47
Cost of LTBI treatment	$9.06	$9.25	$9.43	$9.63	$9.82	$47.18
Cost of TB treatment	$0.11	$0.12	$0.12	$0.12	$0.12	$0.59
New scenario: SEQ: TST/IGRA[d]						
Total costs, future scenario	$15.55	$15.87	$16.18	$16.50	$16.82	$80.91
Cost of test	$2.75	$2.89	$3.05	$3.21	$3.38	$15.28
Cost of FU	$3.71	$3.75	$3.80	$3.84	$3.89	$18.99
Cost of LTBI treatment	$8.99	$9.10	$9.21	$9.32	$9.42	$46.03
Cost of TB treatment	$0.11	$0.12	$0.12	$0.13	$0.13	$0.61

Total costs and budget impact[a-c]						
BI: IGRA alone vs. TST						
Total Budget Impact	−$0.10	−$0.21	−$0.32	−$0.44	−$0.57	−$1.63
Cost of test	$0.07	$0.14	$0.21	$0.29	$0.38	$1.09
Cost of FU	−$0.05	−$0.10	−$0.15	−$0.21	−$0.28	−$0.79
Cost of LTBI treatment	−$0.12	−$0.24	−$0.37	−$0.52	−$0.67	−$1.92
Cost of TB treatment	$0.00	$0.00	$0.00	$0.00	$0.00	−$0.01
BI: SEQ (TST/IGRA)[d] vs. TST						
Total Budget Impact	−$0.21	−$0.44	−$0.67	−$0.93	−$1.20	−$3.45
Cost of test	$0.05	$0.11	$0.17	$0.24	$0.30	$0.88
Cost of FU	−$0.08	−$0.16	−$0.25	−$0.34	−$0.44	−$1.27
Cost of LTBI treatment	−$0.19	−$0.39	−$0.60	−$0.83	−$1.07	−$3.07
Cost of TB treatment	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00

Abbreviations: BI, budget impact; FU, follow-up; IGRA, interferon-gamma release assay; LTBI, latent tuberculosis infection; SEQ, sequential pathways; TB, tuberculosis; TST, tuberculin skin test.

[a]All costs are in 2024 CAD.

[b]Negative costs indicate savings.

[c]Results may appear inexact due to rounding.

[d]TST followed by IGRA, in TST-positive immigrant population.

Contacts

As shown in Table 22A, for contact investigations, IGRA testing was associated with cost savings ranging from $1.63 million (IGRA alone) to $1.76 million (IGRA as a sequential test) over the 5-year time horizon. The total cost associated with the testing itself (IGRA alone or sequentially) was $0.22 million and $0.62 million, respectively.

Table 22A: Budget Impact Analysis Results, Reference Case—Contacts Subpopulation

Contacts	Total costs and budget impact, in millions[a-c]					
Scenarios	Year 1	Year 2	Year 3	Year 4	Year 5	Total 5-year cost
Current scenario: TST alone	$0.99	$1.02	$1.05	$1.09	$1.12	$5.28
Cost of test	$0.25	$0.26	$0.26	$0.27	$0.28	$1.32
New scenario: IGRA alone	$0.74	$0.72	$0.73	$0.73	$0.73	$3.65
Cost of test	$0.28	$0.30	$0.31	$0.32	$0.33	$1.54
New scenario: SEQ, TST/IGRA[d]	$0.72	$0.70	$0.70	$0.70	$0.70	$3.52
Cost of test	$0.35	$0.37	$0.39	$0.41	$0.43	$1.95
Total BI: IGRA vs. TST alone	**−$0.26**	**−$0.30**	**−$0.33**	**−$0.36**	**−$0.39**	**−$1.63**
BI: cost of test	$0.03	$0.04	$0.04	$0.05	$0.05	$0.22
Total BI: SEQ, TST/IGRA[d] vs. TST alone	**−$0.28**	**−$0.32**	**−$0.35**	**−$0.38**	**−$0.42**	**−$1.76**
BI: cost of test	$0.10	$0.11	$0.13	$0.14	$0.15	$0.62

Abbreviations: BI, budget impact; IGRA, interferon-gamma release assay; SEQ, sequential pathways; TST, tuberculin skin test.

[a]All costs are in 2024 CAD.

[b]Negative costs indicate savings.

[c]Results may appear inexact due to rounding.

[d]TST followed by IGRA, in TST-positive contact population.

As shown in Table 22B, IGRA testing led to downstream savings from a reduction in follow-up costs (−$0.54 million to −$0.70 million over 5 years) and treatment costs (-$1.31 million to -$1.69 million over 5 years).

Table 22B: Budget Impact Results, Reference Case—Contact Subpopulation, by Cost Component

	Total costs and budget impact, in millions[a-c]					
Current scenario: TST	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total 5-year cost**
Total costs, current scenario	$0.99	$1.02	$1.05	$1.09	$1.12	$5.28
Cost of test	$0.25	$0.26	$0.26	$0.27	$0.28	$1.32
Cost of FU	$0.22	$0.22	$0.23	$0.24	$0.24	$1.15
Cost of LTBI treatment	$0.52	$0.54	$0.56	$0.57	$0.59	$2.78
Cost of TB treatment	$0.00	$0.01	$0.01	$0.01	$0.01	$0.03
New scenario: IGRA alone						
Total costs, future scenario	$0.74	$0.72	$0.73	$0.73	$0.73	$3.65
Cost of test	$0.28	$0.30	$0.31	$0.32	$0.33	$1.54
Cost of FU	$0.13	$0.12	$0.12	$0.12	$0.12	$0.61
Cost of LTBI treatment	$0.32	$0.30	$0.29	$0.29	$0.28	$1.48
Cost of TB treatment	$0.00	$0.00	$0.00	$0.00	$0.00	$0.02
New scenario: SEQ: TST/IGRA[d]						
Total costs, future scenario	$0.72	$0.70	$0.70	$0.70	$0.70	$3.52
Cost of test	$0.35	$0.37	$0.39	$0.41	$0.43	$1.95
Cost of FU	$0.11	$0.09	$0.09	$0.08	$0.08	$0.45
Cost of LTBI treatment	$0.26	$0.23	$0.22	$0.20	$0.19	$1.09
Cost of TB treatment	$0.01	$0.01	$0.01	$0.01	$0.01	$0.03
BI: IGRA alone vs. TST						
Total Budget Impact	−$0.26	−$0.30	−$0.33	−$0.36	−$0.39	−$1.63
Cost of test	$0.03	$0.04	$0.04	$0.05	$0.05	$0.22
Cost of FU	−$0.09	−$0.10	−$0.11	−$0.12	−$0.13	−$0.54
Cost of LTBI treatment	−$0.21	−$0.24	−$0.26	−$0.29	−$0.31	−$1.31
Cost of TB treatment	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
BI: SEQ (TST/IGRA)[d] vs. TST						
Total Budget Impact	−$0.28	−$0.32	−$0.35	−$0.38	−$0.42	−$1.76
Cost of test	$0.10	$0.11	$0.13	$0.14	$0.15	$0.62
Cost of FU	−$0.11	−$0.13	−$0.14	−$0.15	−$0.17	−$0.70
Cost of LTBI treatment	−$0.27	−$0.31	−$0.34	−$0.37	−$0.40	−$1.69
Cost of TB treatment	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00

Abbreviations: BI, budget impact; FU, follow-up; IGRA, interferon-gamma release assay; SEQ, sequential pathways; TB, tuberculosis; TST, tuberculin skin test.

[a]All costs are in 2024 CAD.

[b]Negative costs indicate savings.

[c]Results may appear inexact due to rounding.

[d]TST followed by IGRA, in TST-positive contact population.

Immunocompromised Populations

As shown in Table 23A, for the immunocompromised populations, IGRA testing was associated with additional costs ranging from $6.26 million (IGRA alone) to $19.29 million to $24.01 million (IGRA as sequential test) over the 5-year time horizon. The total cost associated with the testing itself (IGRA alone or sequentially) was $4.70 million and $8.62 million, respectively.

Table 23A: Budget Impact Results, Reference Case—Immunocompromised Populations

Immunocompromised	Total costs and budget impact, in millions[a,b]					
Scenarios	Year 1	Year 2	Year 3	Year 4	Year 5	Total 5-year cost
Current scenario: TST alone	$4.76	$4.87	$4.98	$5.08	$5.18	$24.87
Cost of test	$1.10	$1.12	$1.15	$1.17	$1.19	$5.73
New scenario: IGRA alone	$5.76	$6.04	$6.24	$6.44	$6.64	$31.12
Cost of test	$1.85	$2.00	$2.10	$2.19	$2.29	$10.43
New scenario: SEQ, TST/IGRA[c]	$7.86	$8.47	$8.87	$9.27	$9.69	$44.16
Cost of test	$2.19	$2.39	$2.52	$2.64	$2.78	$12.51
New scenario: SEQ, IGRA/TST[d]	$8.62	$9.35	$9.82	$10.30	$10.79	$48.88
Cost of test	$2.48	$2.73	$2.89	$3.04	$3.21	$14.35
Total BI: IGRA alone vs. TST alone	**$1.01**	**$1.17**	**$1.26**	**$1.36**	**$1.46**	**$6.26**
BI: cost of test	$0.76	$0.88	$0.95	$1.02	$1.10	$4.70
Total BI: SEQ, TST/IGRA[c] vs. TST alone	**$3.10**	**$3.60**	**$3.89**	**$4.19**	**$4.50**	**$19.29**
BI: cost of test	$1.09	$1.27	$1.37	$1.48	$1.58	$6.79
Total BI: SEQ, IGRA/TST[d] vs. TST alone	**$3.86**	**$4.48**	**$4.85**	**$5.22**	**$5.61**	**$24.01**
BI: Cost of test	$1.39	$1.61	$1.74	$1.87	$2.01	$8.62

Abbreviations: BI, budget impact; IGRA, interferon-gamma release assay; TST, tuberculin skin test; SEQ, sequential pathways.

[a]All costs are in 2024 CAD.

[b]Results may appear inexact due to rounding.

[c]TST followed by IGRA, in TST-negative immunocompromised population.

[d]IGRA followed by TST, in IGRA-negative immunocompromised population.

As shown in Table 23B, IGRA testing was associated with some downstream savings in the treatment costs (−$0.02 to −$0.07 million over 5 years, depending on the strategy).

Table 23B: Budget Impact Results, Reference Case—Immunocompromised Subpopulation, by Cost Component

	Total costs and budget Impact, in millions[a-c]					
Current scenario: TST	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total 5-year cost**
Total costs, current scenario	$4.76	$4.87	$4.98	$5.08	$5.18	$24.87
Cost of test	$1.10	$1.12	$1.15	$1.17	$1.19	$5.73
Cost of FU	$0.87	$0.89	$0.91	$0.93	$0.95	$4.56
Cost of LTBI treatment	$2.74	$2.80	$2.87	$2.93	$2.98	$14.32
Cost of TB treatment	$0.05	$0.05	$0.05	$0.05	$0.05	$0.26

Total costs and budget Impact, in millions[a-c]						
New scenario: IGRA alone						
Total costs, future scenario	$5.76	$6.04	$6.24	$6.44	$6.64	$31.12
Cost of test	$1.85	$2.00	$2.10	$2.19	$2.29	$10.43
Cost of FU	$0.93	$0.96	$0.99	$1.01	$1.04	$4.94
Cost of LTBI treatment	$2.93	$3.03	$3.11	$3.18	$3.26	$15.51
Cost of TB treatment	$0.05	$0.05	$0.05	$0.05	$0.05	$0.24
New scenario: SEQ, TST/IGRA[c]						
Total costs, future scenario	$7.86	$8.47	$8.87	$9.27	$9.69	$44.16
Cost of test	$2.19	$2.39	$2.52	$2.64	$2.78	$12.51
Cost of FU	$1.36	$1.46	$1.53	$1.59	$1.66	$7.60
Cost of LTBI treatment	$4.27	$4.58	$4.79	$5.00	$5.21	$23.84
Cost of TB treatment	$0.04	$0.04	$0.04	$0.04	$0.04	$0.21
New scenario: SEQ, IGRA/TST[d]						
Total costs, future scenario	$8.62	$9.35	$9.82	$10.30	$10.79	$48.88
Cost of test	$2.48	$2.73	$2.89	$3.04	$3.21	$14.35
Cost of FU	$1.47	$1.59	$1.67	$1.74	$1.82	$8.30
Cost of LTBI treatment	$4.62	$4.99	$5.23	$5.47	$5.72	$26.04
Cost of TB treatment	$0.04	$0.04	$0.04	$0.04	$0.04	$0.19
BI: IGRA alone vs. TST						
Total budget impact	$1.01	$1.17	$1.26	$1.36	$1.46	$6.26
Cost of test	$0.76	$0.88	$0.95	$1.02	$1.10	$4.70
Cost of FU	$0.06	$0.07	$0.08	$0.08	$0.09	$0.38
Cost of LTBI treatment	$0.19	$0.22	$0.24	$0.26	$0.28	$1.19
Cost of TB treatment	$0.00	$0.00	$0.00	−$0.01	−$0.01	−$0.02
BI: SEQ (TST/IGRA)[c] vs. TST						
Total budget impact	$3.10	$3.60	$3.89	$4.19	$4.50	$19.29
Cost of test	$1.09	$1.27	$1.37	$1.48	$1.58	$6.79
Cost of FU	$0.49	$0.57	$0.61	$0.66	$0.71	$3.03
Cost of LTBI treatment	$1.53	$1.78	$1.92	$2.07	$2.22	$9.52
Cost of TB treatment	−$0.01	−$0.01	−$0.01	−$0.01	−$0.01	−$0.06
BI: SEQ (IGRA/TST)[d] vs. TST						
Total budget impact	$3.86	$4.48	$4.85	$5.22	$5.61	$24.01
Cost of test	$1.39	$1.61	$1.74	$1.87	$2.01	$8.62
Cost of FU	$0.60	$0.70	$0.75	$0.81	$0.87	$3.74
Cost of LTBI treatment	$1.88	$2.19	$2.37	$2.55	$2.74	$11.72
Cost of TB treatment	−$0.01	−$0.01	−$0.01	−$0.02	−$0.02	−$0.07

Abbreviations: BI, budget impact; FU, follow-up; IGRA, interferon-gamma release assay; ; SEQ, sequential pathways; TB, tuberculosis; TST, tuberculin skin tests.

[a]In 2024 CAD.

[b]Negative costs indicate savings.

[c]Results may appear inexact due to rounding.

[c]TST followed by IGRA, in TST-negative immunocompromised population.

[d]IGRA followed by TST, in IGRA-negative immunocompromised population.

Sensitivity Analysis

Our scenario analyses showed that IGRA as a standalone test was the least costly of all IGRA testing options (Table 24). The results of sensitivity analyses by population are presented in Appendices 14 to 16. The total budget for all populations considered together was most affected by the uptake, size of populations of interest, lack of shared testing between PHU and MD settings, and the cost of the test:

- The largest savings in the total budget were seen in scenarios that assumed a large increase in the uptake of IGRA in immigrant populations, small uptakes of IGRA for all populations (5% per year), with 25% lower cost of IGRA test, or a large chance of reactivation of LTBI in immunocompromised populations
- The largest increase in the total budget was observed in scenarios that considered the testing for all people diagnosed with cancer in addition to those already indicated in the reference case population (e.g., selected non-solid cancers), and the testing setting (i.e., immigrant and immunocompromised people where testing was done at MD office, and assuming the wastage of PPD)

Table 24: Budget Impact Results—Sensitivity Analysis: All Populations

	Total 5-year budget impact(IGRA strategies vs. TST alone) in millions[a,b]		
Scenario	**IGRA alone**	**SEQ: TST/IGRA** (all subpopulations)	**SEQ: TST/IGRA & IGRA/TST[c]**
Reference case, total BI	**$2.99**	**$14.07**	**$18.80**
Reference case, BI, test cost	$6.01	$8.28	$10.12
Change in population size			
Scenario 1: number of people for testing in Ontario based on iPHIS LTBI data obtained from PHO, and published LTBI prevalence estimates, total BI	−$3.85	$7.63	$12.36
BI, test cost	$6.44	$10.76	$12.60
Scenario 2: all cancer types, total BI	$40.96	$131.15	$164.58
BI, test cost	$34.56	$49.48	$62.47
Change in the uptake of IGRA			
Scenario 3: large uptake for immigrants (75% Y1 to 100% Y5), total BI	−$11.24	−$16.03	−$11.30
BI, test cost	$15.49	$15.92	$17.75
Scenario 4: Low uptake for all (5% per year), total BI	−$1.93	−$2.77	−$1.96
BI, test cost	$2.65	$2.72	$3.04
Scenario 5: evenly spread uptake for immunocompromised people (20%/y), total BI	$1.00	$7.94	$11.16
BI, test cost	$4.51	$6.12	$7.38
Scenario 6: smaller uptake for immunocompromised people (10%/y), total BI	−$1.13	$1.36	$2.97

Scenario	Total 5-year budget impact(IGRA strategies vs. TST alone) in millions[a,b]		
	IGRA alone	**SEQ: TST/IGRA** (all subpopulations)	**SEQ: TST/IGRA & IGRA/TST[c]**
BI, test cost	$2.91	$3.81	$4.44
Change in the testing pathway			
Scenario 7: no cost of referral, total BI	$1.34	$11.15	$15.76
BI, test cost	$4.35	$5.36	$7.08
Scenario 8: all tests done by PHUs, total BI	$2.53	$14.11	$18.83
BI, test cost	$5.54	$8.32	$10.15
Scenario 9: tests done by MDs in immigrant/immunocompromised populations, total BI	$3.44	$14.14	$18.87
BI, test cost	$6.46	$8.35	$10.19
Scenario 10a: no waste of the PPD vial (no TST vial wastage at MD's office), total BI	$4.37	$14.07	$19.08
BI, test cost	$7.38	$8.28	$10.40
Scenario 10b: 80% waste of the PPD vial (most TST vial wastage at MD's office), total BI	−$2.36	$13.92	$17.55
BI, test cost	$1.19	$7.60	$8.33
Change in the cost of IGRA			
Scenario 11: IGRA cost 25% lower, total BI	$0.45	$12.53	$16.69
BI, test cost	$3.46	$6.74	$8.01
Scenario 12a: IGRA at hospital lab, cost of shipping and handling included in the test cost, total BI	$3.36	$14.28	$19.08
BI, test cost	$6.38	$8.49	$10.40
Scenario 12b: IGRA at hospital lab, cost of shipping and handling costed separately, total BI	$3.45	$14.32	$19.11
BI, test cost	$6.46	$8.53	$10.43
Change in the probability of reactivation of LTBI into active TB, immunocompromised			
Scenario 13: high probability of reactivation of LTBI (threshold value of 30%, hypothetical scenario), total BI	−$3.27	−$0.40	−$45.03
BI, test cost	$6.01	$10.12	$10.12

Abbreviations: BI, budget impact; IGRA, interferon-gamma release assay; iPHIS, Public Health Information System; LTBI, latent tuberculosis infection; PHO, Public Health Ontario; SEQ, sequential pathways; TST, tuberculin skin test.

[a]All costs are in 2024 CAD.

[b]Negative costs indicate savings.

[c]The IGRA/TST approach is used only for immunocompromised populations while TST/IGRA is for all 3 populations (immigrant, immunocompromised, and contacts). We calculated our estimates for all populations.

In additional one-way sensitivity analyses in immigrant and contact subpopulations, the incremental savings of IGRA alone compared with TST alone would be switched to incremental costs if there were substantial changes in the sensitivity and specificity of IGRA, specificity of TST, completion of TST, or prevalence of LTBI (See Figures 6 and 7).

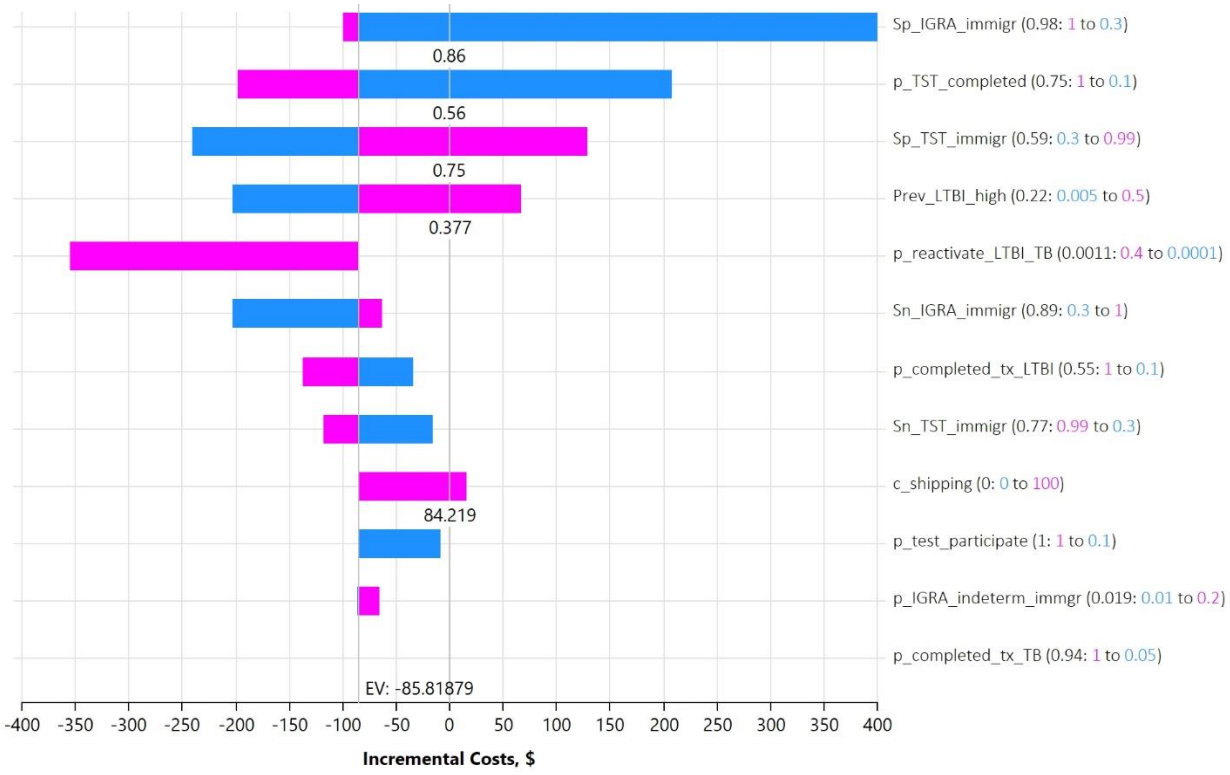

Figure 6. Tornado Diagram: Changes in Incremental Costs of IGRA Alone Versus TST Alone, Immigrant Populations

A tornado diagram showing changes in the incremental cost of IGRA alone versus TST alone, with changes in the initial values of clinical and cost parameters used for the reference case analysis in the BCG-vaccinated immigrant population. The y-axis represents changes in incremental cost because there is no difference in effectiveness outcomes between the compared interventions. Negative values indicate cost savings. EV is an expected value for the mean cost difference between IGRA and TST strategies for immigrant population and is presented per person (−$85.82 per person; in monetary terms, it represents savings; for more information on the cost outputs in section Cost Resources and Model Outputs, see Table 13A). Legend of the tornado diagram presents names and values of clinical and cost parameters; the values are presented in the brackets as follows: the reference case value (black font), low value (blue font), and high value (purple font); the bar colors—blue and purple—are cost differences associated with low or high parameter values (and their ranges). For example, incremental cost at the reference case value for the specificity of IGRA (Sp_IGRA_immigr = 0.98) is negative and equals to EV of about −$86 per person; this indicates cost savings per person; an incremental cost with a high specificity of IGRA (Sp_IGRA_immigr = 1) is even more negative or more favorable than the EV (more cost saving), while decreasing the specificity of IGRA to very low values (Sp_IGRA_immigr = 0.3) results in cost increases, which suggest that IGRA may not be a favorable option if the specificity is low. In addition, varying the value of participation in IGRA testing (the parameter labeled "accept testing") from 0.1 to 1.0 did not change the direction of the incremental cost estimates, while the budget impact estimates were sensitive to changes of diagnostic accuracy parameters (sensitivity and specificity) of IGRA, specificity of TST, completion of TST, and prevalence of LTBI.

Abbreviations: c_shipping, additional cost of IGRA shipping and handling; p_completed_tx_LTBI, probability of completion of preventative treatment for LTBI; p_completed_tx_TB, probability of completion of treatment for active TB; p_IGRA_indeterm_immigr, probability of IGRA indeterminate test; p_reactivate_LTBI_TB, probability of reactivation of LTBI into active TB; p_test_participate, probability of participation in testing; p_TST_completed, probability of completion of TST (both visits); Prev_LTBI_high, prevalence of LTBI ; Sn_IGRA_immigr, sensitivity of IGRA in immigrant population; Sn_TST_immigr, sensitivity of TST in immigrant population; Sp_IGRA_immigr, specificity of IGRA in immigrant population; Sp_TST_immigr, specificity of TST in immigrant population.

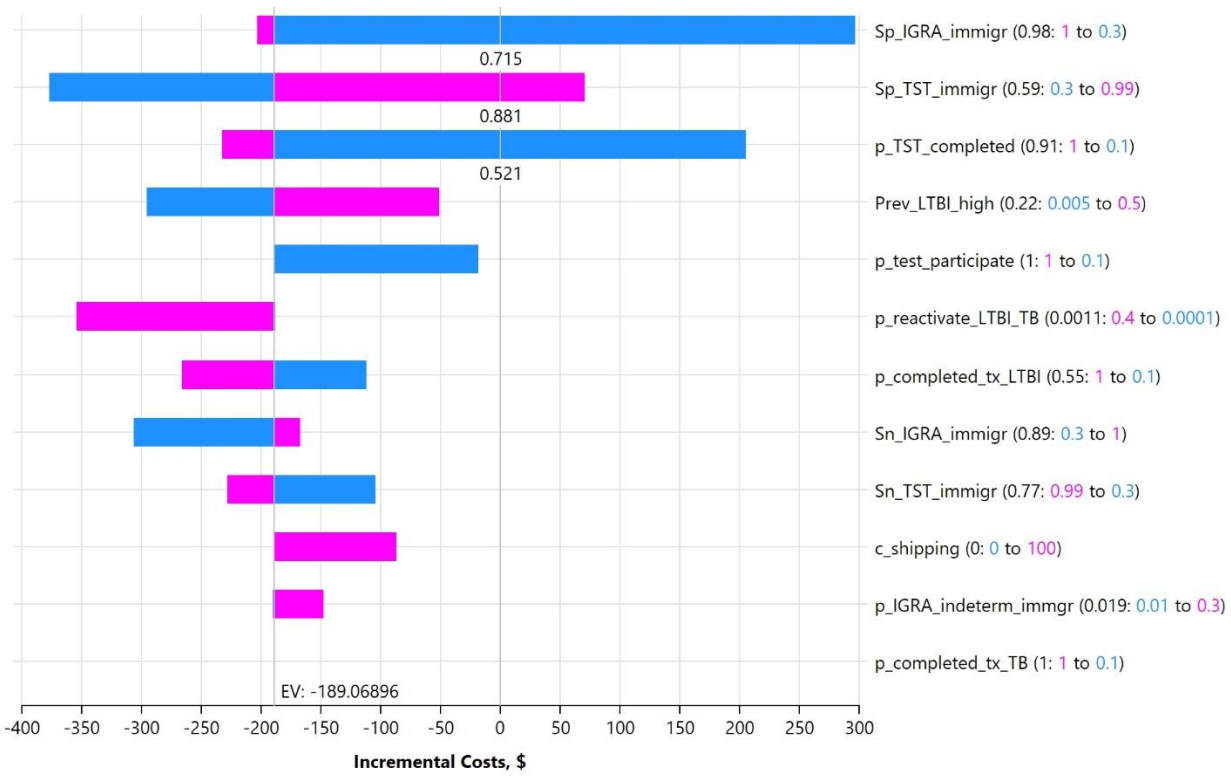

Figure 7. Tornado Diagram: Changes in Incremental Costs of IGRA Alone Versus TST Alone, People Identified Via Contact Investigation

A tornado diagram showing changes in the incremental cost of IGRA alone versus TST alone, with changes in the initial values of clinical and cost parameters used for the reference case analysis in the BCG-vaccinated people identified via contact investigations. The y-axis represents changes in incremental costs and negative values indicate cost savings. EV is an expected value for the mean cost difference between IGRA and TST strategies for contacts and is presented per person (−$189.07 per person; in monetary terms, it represents savings; for more information on the cost outputs in section Cost Resources and Model Outputs, see Table 13B). Legend of the tornado diagram presents names and values of clinical and cost parameters; the values are presented in brackets as follows: the reference case value (black font), low value (blue font), and high value (purple font); the bar colors—blue and purple—are cost differences associated with low or high parameter values (and their ranges). For example, an incremental cost with a high specificity of IGRA (Sp_IGRA_immigr = 1) is negative or more favorable than the EV (i.e., it is more cost saving), while decreasing the specificity of IGRA to very low values (Sp_IGRA_immigr = 0.3) results in cost increases with IGRA testing. Also, varying the value of participation in IGRA testing (the parameter labeled “accept testing”) from 0.1 to 1.0 did not change the direction of the incremental cost estimates, while the budget impact estimates were sensitive to the parameter estimates for the specificity of TST, and completion of TST.

Abbreviations: c_shipping, additional cost of IGRA shipping and handling; p_completed_tx_LTBI, probability of completion of preventative treatment for LTBI; p_completed_tx_TB, probability of completion of treatment for active TB; p_IGRA_indeterm_immigr, probability of IGRA indeterminate test; p_reactivate_LTBI_TB, probability of reactivation of LTBI into active TB; p_test_participate, probability of participation in testing; p_TST_completed, probability of completion of TST (both visits); Prev_LTBI_high, prevalence of LTBI; Sn_IGRA_immigr, sensitivity of IGRA, contacts; Sn_TST_immigr, sensitivity of TST, contacts; Sp_IGRA_immigr, specificity of IGRA, contacts; Sp_TST_immigr, specificity of TST, contacts.

In immunocompromised populations, the incremental costs of IGRA alone compared with TST alone would switch to savings with increasing sensitivity and specificity of TST (thresholds of 72% and 66%, respectively), specificity of IGRA (threshold of 90%), and probability of LTBI reactivation (threshold of 30%).

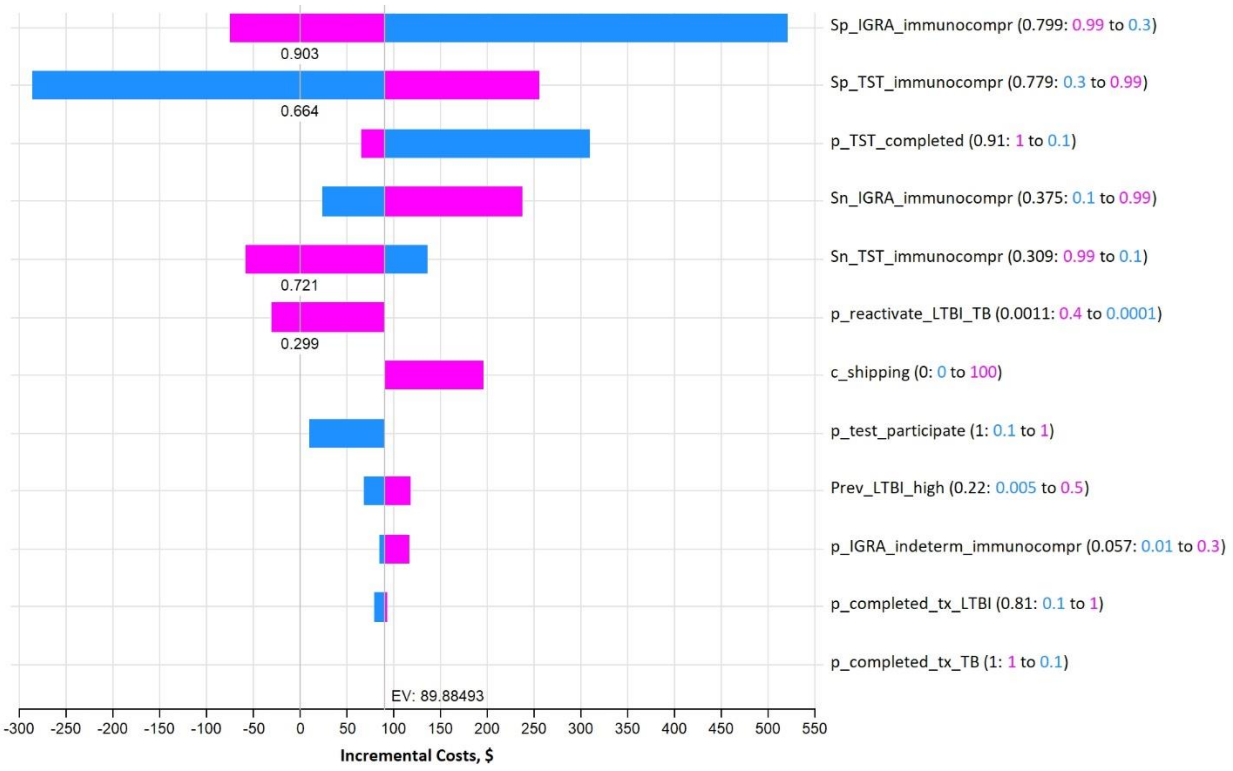

Figure 8. Tornado Diagram: Changes in Incremental Costs of IGRA Alone Versus TST Alone, Immunocompromised Populations

A tornado diagram showing changes in the incremental cost of IGRA alone versus TST alone, with changes in the initial values of clinical and cost parameters used for the reference case analysis in immunocompromised populations. The y-axis represents changes in incremental costs and negative values indicate cost savings. EV is an expected value for the mean cost difference between IGRA and TST strategies for immunocompromised populations and is presented per person ($89.87 per person; in monetary terms, it represents additional costs; for more information on the cost outputs in section Cost Resources and Model Outputs, see Table 13C). Legend of the tornado diagram presents names and values of clinical and cost parameters; the values are presented in the brackets as follows: the reference case value (black font), low value (blue font), and high value (purple font); the bar colors – blue and purple – are the cost differences associated with low or high parameter values. For example, an incremental cost with a high specificity of IGRA (0.99) is cost saving (negative) or more favorable than the EV, while decreasing the specificity of IGRA to very low values result in cost increases with IGRA (it is larger than EV). The threshold specificity of IGRA was found at 90%, at which point IGRA would become cost neutral, and with higher specificity values (> 90%) it would become cost saving. Varying the value of participation in IGRA testing (the parameter labeled "accept testing") from 0.1 to 1.0 did not change the direction of the incremental cost estimates, while the budget impact estimates were sensitive to the parameter estimates for the sensitivity and specificity of TST (the threshold values of 72% and 66%), and probability of LTBI reactivation (the threshold value of 30%).

Abbreviations: c_shipping, additional cost of IGRA shipping and handling; p_completed_tx_LTBI, probability of completion of preventative treatment for LTBI; p_completed_tx_TB, probability of completion of treatment for active TB; p_IGRA_indeterm_immunocompr, probability of IGRA indeterminate test, immunocompromised; p_reactivate_LTBI_TB, probability of reactivation of LTBI into active TB; p_test_participate, probability of participation in testing; p_TST_completed, probability of completion of TST (both visits); Prev_LTBI_high, prevalence of LTBI ; Sn_IGRA_immunocompr, sensitivity of IGRA in immunocompromised population; Sn_TST_immunocompr, sensitivity of TST in immunocompromised population; Sp_IGRA_immunocompr, specificity of IGRA in immunocompromised population; Sp_TST_immunocompr, specificity of TST in immunocompromised population.

Discussion

We conducted model-based budget impact analyses to estimate the total 5-year budget for publicly funding IGRA testing in Ontario for the eligible subgroups of people at high risk of LTBI[75] in whom IGRA would be the preferred test, as per the Standards.[75] We provided budget impact estimates for the overall population of interest and broken down by population subgroup (i.e., immigrant, contact, and immunocompromised populations, for simplicity of the calculations). We explored additional costs and

savings with IGRA as a standalone test and in sequential pathways with TST (serial testing), where the sequence of the tests depended on the population (as recommended by the Standards[75] and confirmed by experts). We did not examine the use of both IGRA and TST at the same time (parallel testing) because this is not considered good clinical practice and is not recommended by the Standards.[75]

In the reference case, considering all populations, the total additional costs of testing with IGRA as a single test, IGRA as the follow-up test to TST for all subgroups, and IGRA in various sequential pathways (follow-up test to TST in BCG-vaccinated immigrants and contacts and as an initial test in immunocompromised populations) were estimated at about $2.99 million, $14.07 million, and $18.80 million, respectively, over the next 5 years. The additional costs over 5 years associated solely with the testing was about $6.01 million, $8.28 million, and $10.12 million, respectively.

When we examined the budget impact by population, we found:

- Cost savings of over $1.63 million over 5 years with IGRA strategies in eligible BCG-vaccinated immigrant populations (assuming a 3% uptake of IGRA per year) and eligible BCG-vaccinated people identified via contact investigations (assuming a 75% uptake of IGRA in Year 1, rising to 100% in Year 5). The savings were result of reductions in unnecessary follow-up evaluations and unnecessary use of costly TB treatments in those incorrectly identified as positive (false positive) by TST
- Additional costs of over $6.26 million over 5 years with IGRA strategies in selected groups of immunocompromised people, including people with CKD, organ transplants, HIV-positive people, and investigations of people with non-solid cancers (assuming a 75% uptake of IGRA in Year 1, rising to 100% in Year 5). In these populations, IGRA was used to identify people at high risk of TB who were incorrectly identified as negative (false negative) by TST

We explored changes in the estimates of the budget in sensitivity analyses. The scenario analyses corroborated that IGRA as a standalone test was the least costly option of all IGRA testing strategies. The total budget estimate for all subgroups together was mostly affected by the uptake of IGRA, size of the population (estimated based on Ontario data), cost of the IGRA test, and the percentage-share of the testing between public health units and physicians. For instance:

- When we based our estimate of the eligible immigrant and contact populations on the iPHIS LTBI data obtained from Public Health Ontario[112] and published LTBI prevalence estimates,[14] we found a switch in the budget impact for IGRA as a standalone test from an additional cost of $2.99 million to a cost savings of $3.85 million. Lower additional costs were estimated for sequential strategies (see Scenario 1 in Table 24). This is because of the decreased estimate of the immigrant population and increased estimate of the contact population. However, our estimates of the population size based on the number of identified true positive results of TST testing in Ontario (i.e., LTBI episodes) have data limitations related to reporting and likely represent an underestimate of the true burden of LTBI in Ontario (oral and email communications, L. Macdonald, MD, A. Saunders, MSc, M. Whelan, MSc, E. Rea, MD, June 10–14, 2024). For example, positive TST results may be under-reported to local PHUs by those who administer the TST and interpret the results, data entry practices for LTBI diagnosed by a positive TST may vary across public health units and over time, and some LTBI episodes may be diagnosed via IGRA rather than TST, although to date this is expected to be a very

small proportion of reported LTBI episodes. As a result, we assume that the number of LTBI episodes reported in iPHIS annually underestimates the true burden of LTBI in Ontario. Our estimate is also limited by the data-related assumptions that we had to make to calculate an overall TST-screened population for Ontario (see Appendix 13).

- If the uptake of IGRA in the immigrant population changed from small (3% per year) to very high (75% in year 1), then the cost savings in immigrant and contact populations together would be larger than the cost increases in immunocompromised populations so that the overall budget savings would be between $11.24 million (IGRA alone) and $16.03 million (sequential strategies) over 5 years (see Scenario 3 in Table 24).
- Interestingly, if the increase in uptake of IGRA remained small and constant (5% per year) for all populations, then we would see overall cost savings for all strategies across all populations (Table 24). This is because of the savings in BCG-vaccinated populations and small additional costs in immunocompromised populations. The savings would be larger than the additional costs in our budget estimates for all populations (see Scenario 4 in Table 24). Overall, the 5-year budget impact for IGRA alone would be a savings of $2.72 million, $0.28 million, and an additional $1.07 million for immigrant, contact, and immunocompromised populations, respectively, for a total budget impact of $1.93 million in savings (see data in Appendices 14–16).
- The total additional costs of IGRA testing could be lowered by $2 million to $7 million if a slower evenly spread roll-out of IGRA testing was used in a relatively large immunocompromised population (see Scenario 5 in Table 24: uptake of 20% per year in immunocompromised populations).

We did not separately estimate the size of population of people who are unlikely to return for their second TST visit because their reasons could vary widely. However, these populations still need to have an indication for testing and are thus already included within the estimated immigrant and contact populations (and therefore are considered in our analyses; oral and email communications, E. Rea, MD, April 10–25).

Last, funding of TST in Indigenous populations (First Nations) in Ontario would likely combine federal and provincial sources (e.g., PPD vials are provided by the Infectious Diseases Policy and Programs Unit, email and oral communications, Ontario Ministry of Health, April 10, 2024). Until 2014, many Indigenous communities offered universal BCG vaccination for their populations, thus making them more likely to be BCG-vaccinated than other Canadian-born people, because of their high risk of LTBI and high incidence of TB. Therefore, testing with IGRA could be a more sensible approach for this population. In addition, estimated costs for these populations are likely to be greater due to the need for timely couriers, the limited access to facilities for blood draw, and insufficient laboratories capable of processing IGRA tests. The cost of IGRA is currently very high due to the lack of nearby hospitals with labs that can process IGRA tests. In our scenario analyses (Scenarios 12a and 12b), we estimated the additional costs of IGRA testing (with or without shipping costs) assuming that the test was done at a local hospital with established equipment and trained personnel.

Equity Considerations

There is inequity in access to IGRA testing in Ontario because it is only available to those who can pay for it out of pocket or can access laboratories offering this testing. Our budget impact analyses addressed inequity in access for people who are considered eligible and at high-risk by the Standards.[75] The additional personal costs incurred by the 2 visits for a TST versus the single visit for IGRA, such as additional (often unpaid) time off work and travel costs, are also significant equity considerations, as the burden of these personal costs falls more heavily on the population most likely to need LTBI diagnosis and treatment (i.e., immigrants and contacts). However, they have not been included in this provincial budget impact analysis (which estimates costs from a public payer perspective). Moreover, we examined various assumptions related to IGRA testing and provided insight into how much investment the province would need to make to enable full (100%) access to IGRA testing over the next 5 years or conduct IGRA in an established Ontario-based hospital lab. Overall, publicly funding IGRA would address and mitigate the issues around unequal access to IGRA testing.

Strengths and Limitations

Our analysis had several strengths:

- Our estimates were calculated from the outputs of our probabilistic model, which accounted for the diagnostic accuracy of IGRA and TST, follow-up and treatment costs associated with LTBI and future active TB, and completion of the testing and therapy
- We examined the use of IGRA as a single test and in a sequential pathway with TST, which are the testing strategies recommended by the current Standards[75]
- Our model parameter inputs were informed by our up-to-date clinical evidence review, which considered the most recent systematic reviews of the highest quality
- We derived the costs associated with TST and IGRA testing through expert consultation from Ontario sources and established the costs related to follow-up medical evaluations and treatment of LTBI and active TB from the relevant Canadian and Ontario-based economic studies
- We validated our assumptions and estimates with clinical experts with expertise in the use of IGRA and TST in support of a diagnosis of LTBI
- The findings of our reference case and sensitivity analyses are generally aligned with the results of the published Canadian economic studies included in our economic evidence review.[77-81] They are generalizable to all populations currently recommended for IGRA testing as an alternative or preferred test to TST by the Standards[75]

Our analysis also had some limitations:

- We were restricted by uncertainty in the overall population size, particularly the immunocompromised population
- In addition, the Standards[75] distinguish recommendations for BCG-vaccinated population by their age when vaccinated, information that was not always available. Thus, we considered previously vaccinated individuals together

- The uptake of IGRA testing in contact investigations and immunocompromised populations may be smaller than estimated because of limited system capacity to rapidly implement the new technology
- The downstream treatment costs could be much higher in exposed immunocompromised populations due to their higher chance of reactivation of LTBI (Table 24, scenario 13). Therefore, it is possible that we overestimated the budget impact for this subpopulation in the reference case
- Finally, because of uncertainty in the test settings for the populations of interest, we made a simplifying assumption regarding the share of testing between PHUs and MDs (50%/50% in the reference case). However, it is more likely that a small proportion of selected immigrants could be tested by designated physicians (MDs) and not by PHUs. In a scenario analysis, we showed that this assumption slightly affected the budget impact because the test costs assumed for immigrant population in the reference case (adjusted for the 50/50 share) are not substantially different from those used in a scenario that assumed no share (100% of tests done by MDs, Table A14, Appendix 12, and Scenarios 8 and 9)

Our analyses provide rough cost estimates of possible pathways. We conducted sensitivity analyses to address the implications of important assumptions or parameter values and explore changes in the budget estimates, including several scenarios related to changes in the population size, uptake of IGRA, and test settings. In the implementation stage, further work would be needed to establish a clinically inclusive and fiscally reasonable approach to IGRA testing if it is recommended for public funding.

Conclusions

Over the next 5 years, the total additional costs of publicly funding testing with IGRA in Ontario for all examined population subgroups ranged between $2.99 million (IGRA as a standalone test) and $14.07 to $18.80 million (IGRA in sequential pathways with TST). In the population-specific analyses, we estimated cost savings of $1.63 million or higher with publicly funded testing with IGRA in eligible BCG-vaccinated immigrant populations or BCG-vaccinated people identified via contact investigations. We found additional costs of $6.26 million or higher with publicly funded testing with IGRA in immunocompromised people.

Preferences and Values Evidence

Objective

The objective of this analysis was to explore the preferences and values of patients who have experience with the tuberculosis skin test (TST) and the interferon-gamma release assay (IGRA) testing for latent tuberculosis infection (LTBI).

Background

Exploring patient preferences and values provides a unique source of information about people's experiences of a health condition and the health technologies or interventions used to manage or treat that health condition. It includes the impact of the condition and its treatment on the person with the health condition, their family and other care partners, and the person's personal environment. Engagement also provides insights into how a health condition is managed by the province's health system.

Information shared from lived experience can also identify gaps or limitations in published research (e.g., outcomes important to those with lived experience that are not reflected in the literature).[121-123] Additionally, lived experience can provide information and perspectives on the ethical and social values implications of health technologies or interventions.

Because the needs, preferences, priorities, and values of those with lived experience in Ontario are important to consider to understand the impact of a technology or intervention in people's lives, we may speak directly with people who live with a given health condition, including those with experience of the technology or intervention we are exploring.

For this analysis, we examined the preferences and values of health care providers regarding TST and IGRA.

Partnership Plan

The partnership plan for this health technology assessment focused on engagements to examine the experiences of people who have experience with TST and/or IGRA testing for LTBI.

Participant Outreach

We used an approach called purposive sampling,[124-127] which involves actively reaching out to people with direct experience of the health condition and health technology or intervention being reviewed. [124-127] We also used snowball sampling to identify additional contacts from interview participants and Ontario Health. We distributed our recruitment poster through 15 clinicians and 1 public health contact who serve the community with testing for LTBI. We also reached out to tuberculosis (TB) awareness and support groups to further facilitate patient recruitment.

Inclusion Criteria

We sought to interview people with direct experience with TST and/or IGRA.

Exclusion Criteria

We did not set exclusion criteria for participants who otherwise met the inclusion criteria.

Participants

Despite our recruitment efforts, we did not hear back from interested patients by the deadline for recruitment. The clinician contacts we reached out to for recruitment explained that this could be due to language barriers in the typical populations for LTBI testing (immigrants, refugees, etc.).

Next we sought to capture the preferences and values of patients indirectly through provider engagement via an online survey. We engaged with health care providers across clinical sites in Ontario who have experience with TST and/or IGRA for LTBI. Our survey was completed by 53 providers, including primary care physicians, nurse practitioners, respirologists, pediatricians, and public health personnel. All participants were familiar and had direct experience with TST and/or IGRA.

Approach

At the beginning of the survey, we included a written description of the role of our organization and the purpose of this health technology assessment. Questions focused on the pros and cons of TST and IGRA, as well as on provider preference and the perceived impact on patients of using these tests for LTBI. See Appendix 18 for our interview guide.

Data Extraction and Analysis

We used a modified version of a grounded-theory methodology to analyze survey results. The grounded-theory approach allowed us to organize and compare information on experiences across participants. This method consists of a repetitive process of obtaining, documenting, and analyzing responses while simultaneously collecting, analyzing, and comparing information.[128,129] We used the qualitative data analysis software program NVivo[130] to identify and interpret patterns in the data. The patterns we identified allowed us to describe the impact of IGRA testing for LTBI.

Results

Patient Population for LTBI Testing

Providers described the populations that they serve for LTBI testing. Recently arrived immigrants and immunocompromised patients were mentioned by most participants. In addition, health care workers who need LTBI testing for work/study purposes, as well as persons living in congregate settings, such as shelters, long term care, and correction facilities, were mentioned as a group highly susceptible for LTBI, and therefore required testing. Participants also mentioned that they refer multiple patients at their clinic for TST or IGRA.

Tuberculin Skin Test

The TST is the conventional method for LTBI testing and the only publicly funded test in Ontario. It involves the injection of a derivative protein under the patient's skin on their forearm. This spot is then checked by a health care provider during a second appointment 48–72 hours later. Participants commented on the challenges of TST, including delayed care caused by missed appointments for the second/follow-up visit, inter-reader variability of results, and the risk for false positives in patients who

have received a BCG vaccination, which is common in newcomer populations (immigrants and refugees). Administration difficulties in young children and those with comorbidities was also highlighted as a challenge by providers.

Delayed care

Participants reported significant delays in care due to missed follow up visits for the second TST reading. The requirement of a second visit for TST was also highlighted as a challenge for health care resource utilization.

> *TST has a high rate of nonreturn for the second reading.*
>
> *[TST] is inefficient for clinic workflow (leads to more work for clinic admin staff, waiting room crowding, low-value use of precious [nursing] resource).*
>
> *Client needs to come back for reading, causing substantial delay [in care].*

Subjective Reading

Participants mentioned that TST is difficult to interpret and is often dependent on the user for an accurate reading, especially in immunocompromised patients, leading to misdiagnoses.

> *TST is difficult to interpret and [is] frequently interpreted incorrectly.*
>
> *Dependent on the clinician's visual inspection. Not all clinicians can accurately read the test.*
>
> *Some challenges with interpreting TST [include] inconsistency about reading between providers, especially in immunocompromised / HIV patients.*
>
> *I have also seen many patients misdiagnosed with LTBI based on false positive results and the clinician's experience with planting [administering] and reading the TST.*

False Positives and Negatives (BCG-Vaccinated and Immunocompromised Populations)

Participants explained that TST is not as sensitive with people who have received the BCG vaccine, which most people who get tested for LTBI have. This leads to a high rate of false positives. In addition, people who are immunocompromised have a higher likelihood of receiving a false negative result.

> *[TST] not as sensitive with BCG vaccine (which most patients have had).*
>
> *It is difficult to interpret positive results in the context of prior BCG vaccination, which most patients have had.*
>
> *Have high false positive [for BCG vaccinated].*
>
> *Risk of false negatives in immunocompromised patients.*

Administrative Challenges

Participants reported various administrative challenges with TST, including the difficulty of scheduling 2 appointments within a short period of time (1 for administering the test and a second for reading the test results), high health care resource use, as well as difficulty with administering the test in children and people with comorbidities such as ADHD (attention deficit hyperactivity disorder).

> *TST can be difficult to schedule, especially for transient populations (e.g., underhoused)…if we could use an IGRA we could test more opportunistically.*

> *Difficulty in test administration, especially if [the patient is] very young or has other comorbidities; e.g., ADHD.*

> *Education lacking in the community about appropriate TST administration and reading (measuring induration correctly and providing that in the referral) leads to unnecessary referrals.*

> *More resources for staff [are] required.*

Interferon-Gamma Release Assay

All participants highlighted the advantages of IGRA over TST, citing multiple reasons, such as the streamlining of care, determinate results in BCG-vaccinated populations, patient and provider preference, and improved equity.

Streamlining of Care

Providers explained that IGRA improves clinical workflow as it is performed through bloodwork. They mentioned that IGRA could be performed as part of the routine initial intake of bloodwork for newcomers (immigrants or refugees), leading to a streamlining of care and avoidance of delays. Moreover, participants noted that IGRA requires only a single visit to the clinic, allowing for better patient adherence and health care resource use.

> *All the newcomer clients seen at the clinic have some screening blood tests. If this test [were] covered, we could add it to the screening tests. [It is] less invasive for the clients and improves workflow.*

> *It would ideal if IGRA could be covered for our client group. This would expedite the screening process (not have to wait for next nursing appointment, which can take up to 6–12 months based on our wait list), allow better compliance with screening by patients doing bloodwork versus waiting for an appointment.*

> *IGRA is much better than TST. We do bloodwork for all newly arrived refugees, so it's easy to add on.*

> *IGRA also improves compliance significantly since it's 1 blood test; many patients are lost to follow-up to read the TST.*

Determinate Results in BCG-Vaccinated Populations

Participants explained that IGRA is not reliant on the user for an accurate reading. Furthermore, it eliminates the risk of false positive results in people who have received a BCG vaccination. This is particularly important in populations that are susceptible for LTBI as they may not be aware of their vaccination status, and for newcomers who often are BCG vaccinated.

> *[IGRA is a] simple blood test without inter reader variability.*
>
> *Removal of biases and inter-readability concerns.*
>
> *IGRA is more accurate and would give better picture/numbers of those at risk of TB.*
>
> *IGRA iso not affected by prior vaccination, which is very important as many clients are completely unsure of their vaccine records from childhood.*
>
> *IGRA is especially useful [for people] who have been BCG-vaccinated, which is a majority of patients seen in our TB clinic.*

Provider Preferences

All providers emphasized their preference towards IGRA for the diagnosis of LTBI. They explained that IGRA should be the standard of care and be offered to patients without cost. They also implied that having IGRA as an accessible test would increase accurate diagnoses of LTBI and reduce inequities in healthcare.

> *[IGRA] needs to be the gold standard for TB screening and testing and needs to be publicly funded.*
>
> *This [IGRA] is the standard of care; [it] should be offered as an insured test to all who need it.*
>
> *IGRA is the standard of care for screening for LTBI and is the most appropriate test for use in certain populations and in certain clinical/logistical circumstances. IGRA is the preferred test over TST in a number of clinical situations….*
>
> *IGRA is the expected standard of care, but yet is not available to patients who cannot afford it.*

Some participants also mentioned that IGRA is the preferred test for children under the age of 10.

> *[IGRA] can be drawn with other bloodwork as part of a workup, leading to fewer painful procedures for children.*
>
> *We see a lot of children under 10 years old where IGRA is the preferred test.*
>
> *[IGRA is] reliable in children.*

Perceived Impact on Patients

Interferon-gamma release assay is preferred by most patients, according to providers who shared their insights from their interactions with their patients. This was mainly due to the convenience of IGRA, such as not requiring multiple visits to the clinic.

> *[IGRA] is an extremely valuable tool/test to have for our patient population. I have spoken informally to many patients, and they would agree with this statement.*
>
> *Most patients prefer IGRA as [there is] no need for a return visit.*
>
> *This is an important equity issue, particularly for immigrants and refugees. IGRA is a preferred option by many patients.*

Participants also explained that IGRA testing is especially important when considering treatment for LTBI.

> *We have had situations where, should we have had an IGRA available, we would have been able to diagnose LTBI much earlier…and possibly start therapy and prevent negative health outcomes.*
>
> *IGRA is more accurate, [it] helps in a much more robust way in decision making [regarding] management of LTBI. It would make life easier for patients, providers, and the system.*
>
> *IGRA [is] preferred, especially if considering treatment for LTBI.*
>
> *IGRA tests would allow us to more accurately counsel patients on the importance of treating latent TB [infection].*

Challenges With IGRA

Participants explained the challenges with IGRA, including implementation challenges and risk of false negative results in immunocompromised patients. Implementation challenges included delays in lab shipment and collection process of blood samples, leading to indeterminate results.

> *[There are] problems in collecting and transporting blood, especially if batched and processed at an outside facility.*
>
> *[IGRA results in] objective measurement; but I've seen issues with discordant results and lab shipment/collection problems.*
>
> *Time constraints lead to indeterminate results.*
>
> *[IGRA is] dependent on lab hours.*

One participant mentioned that both IGRA and TST pose a risk of false negative results in immunocompromised patients.

> *[IGRA has] false negatives in immunocompromised patients (same as for TST).*

Equity

Participants highlighted that having IGRA as an accessible diagnostic test would improve equity for newcomer populations and people with lower incomes, as they are a common group to be affected by LTBI. They mentioned that these patients face difficulties traveling to the clinic for the multiple appointments required by TST.

> *This [IGRA] would improve equity for migrant populations and those who are lower income.*
>
> *[IGRA] would be of great benefit to those in shelters, street involved people who may have difficulty with that second visit [for TST].*
>
> *Thinking about the families and children that are most affected by having IGRA available, this is an issue of equity. Perpetuation of harm by not being able to complete the workup that is recommended for these children is real.*

Patients who are not able to afford IGRA experience delays in diagnosis and treatment.

> *IGRA is currently only available to those who can afford it, but often would be most useful [to people] who cannot afford such a costly test.*
>
> *Many of my immigrant and refugee [patients] find the cost of IGRA a barrier.*
>
> *Expensive test to do, especially for vulnerable, marginalized populations, who are the ones at [greatest] risk of TB.*
>
> *The cost is prohibitive for many patients.*

Patients receiving a TST face barriers such as childcare arrangements, having to take time off from work, transportation, and language barriers, which can result in non-adherence and delayed care.

> *TST is very inefficient for patients (second visit for skin test reading is disruptive, expensive; and difficult parking, transportation, kids out of school); patients often do not show up, leading to need for repeat testing.*
>
> *[TST] entails 2 visits, sometimes more...with a vulnerable population with poor access to transportation, health literacy, and other barriers. This testing often is not completed.*
>
> *Multiple visits are a burden for patients (take time off work, travel distances, childcare), [which is a] more significant burden for people in lower paid jobs or*

with other financial strains, and a burden for health care workers (takes up precious appointment time that can delay care for other patients).

Discussion

Outreach for our summary of provider perspectives yielded engagement with 53 health care providers who had expertise with IGRA and/or TST. Participants reported the strengths of IGRA testing for LTBI, including the streamlining of care and improved accuracy. They also explained the perceived positive impact of IGRA on patients, including improved equity and access to care. Cost was highlighted as a major barrier for accessing IGRA. Participants also commented on the challenges that patients face with TST due to the multiple visits needed. Barriers include transportation, language, childcare arrangements, and taking time off from work, which results in non-adherence and delayed care.

Limitation

There is a lack of direct patient engagement. The patient populations that get tested for LTBI commonly include newcomers and people living in congregate settings (e.g., shelters, long-term care homes, correctional facilities). Our clinical experts advised that it would be difficult to directly engage with this population due to language barriers. During our recruitment stage, we reached out to 14 clinicians and 1 public health contact, as well as 2 TB awareness organizations, to distribute our recruitment posters; however, by the deadline for recruitment, we did not hear back from interested participants. To mitigate this limitation, we engaged with health care providers who gave us insight into the perceived impact of IGRA on patients' lives as well as patients' preferences and decision-making factors for LTBI testing.

Conclusions

Overall, participants had positive comments about IGRA testing for LTBI. They expressed that IGRA is their preferred test for LTBI; however, they highlighted cost as a barrier to accessing the test. Furthermore, participants reflected on the downsides of TST related to perceived impact on patients and equity.

Conclusions of the Health Technology Assessment

The interferon-gamma release assay was found to have good evidence as a rule-in test for LTBI due to consistently high specificity. Compared to TST, IGRA appears to have fewer false-positives among those who tested positive on both LTBI tests in head-to-head comparisons, which was particularly notable in the population that has had the BCG vaccine. Additionally, IGRA may be informative for people with immunocompromising conditions, who are at risk for a false-negative from a TST, as it yields indeterminate findings, signaling that further clinical investigation may be needed.

Based on our review of the 5 economic studies from Canada, IGRA (either as a stand alone or in sequence with TST) is cost-effective compared with TST alone for supporting the diagnosis of LTBI in high-risk populations that are aligned with the Canadian TB Standards, published in 2022. All reviewed studies were of good quality and 3 studies were directly applicable to the Ontario context and our research question. Therefore, we did not conduct a primary economic evaluation.

Over the next 5 years, the total additional costs of publicly funding testing with IGRA in Ontario for all examined population subgroups ranged between $2.99 million (IGRA as a stand-alone test) and $14.07 to $18.80 million (IGRA in sequential pathways with TST). In the population-specific analyses, we estimated cost savings of $1.63 million or higher with publicly funded testing with IGRA in eligible BCG-vaccinated immigrant populations or in BCG-vaccinated people identified via contact investigations. We found additional costs of $6.26 million or higher with publicly funded testing with IGRA in immunocompromised people.

Health care professionals who we spoke with expressed that IGRA is patients' preferred test for LTBI; however, they highlighted cost as a barrier to access the test. Furthermore, participants reflected on the downsides of TST related to perceived impact on patients and equity, particularly the need for a second office visit to read the test results.

Abbreviations

BCG: Bacille Calmette-Guérin

CCO: Ontario Health (Cancer Care Ontario)

CI: confidence interval

CKD: chronic kidney disease

CrI: credible interval

DES: discrete event simulation

GRADE: Grading of Recommendations Assessment, Development, and Evaluation

HIV: human immunodeficiency virus

ICER: incremental cost-effectiveness ratio

IGRA: interferon-gamma release assay

iPHIS: integrated Public Health Information System

LTBI: Latent TB infection

NICE: National Institute for Health and Care Excellence

NPV: negative predictive value

OR: odds ratio

PHO: Public Health Ontario

PHU: Public Health Unit

PPD: purified protein derivative (derived from tuberculin, it is injected under the skin)

PPV: positive predictive value

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses

QALY: quality-adjusted life-year

QFT: QuantiFERON Gold (IGRA test)

RR: relative risk

SD: standard deviation

TB: Tuberculosis

TST: tuberculin skin test

WTP: willingness-to-pay

Glossary

Adverse event: An adverse event is an unexpected medical problem that happens during treatment for a health condition. Adverse events may be caused by something other than the treatment.

Base case: In economic evaluations, the base case is the "best guess" scenario, including any assumptions, considered most likely to be accurate. In health technology assessments conducted by Ontario Health, the reference case is used as the base case.

Budget impact analysis: A budget impact analysis estimates the financial impact of adopting a new health care intervention on the current budget (i.e., the affordability of the new intervention). It is based on predictions of how changes in the intervention mix will impact the level of health care spending for a specific population. Budget impact analyses are typically conducted for a short-term period (e.g., 5 years). The budget impact, sometimes referred to as the net budget impact, is the estimated cost difference between the current scenario (i.e., the anticipated amount of spending for a specific population without using the new intervention) and the new scenario (i.e., the anticipated amount of spending for a specific population following the introduction of the new intervention).

Cohort model: In economic evaluations, a cohort model is used to simulate what happens to a homogeneous cohort (group) of patients after receiving a specific health care intervention. The proportion of the cohort who experiences certain health outcomes or events is estimated, along with the relevant costs and benefits. In contrast, a microsimulation model follows the course of individual patients.

Cost–benefit analysis: A cost–benefit analysis is a type of economic evaluation that expresses the effects of a health care intervention in terms of a monetary value so that these effects can be compared with costs. Results can be reported either as a ratio of costs to benefits or as a simple sum that represents the net benefit (or net loss) of one intervention over another. The monetary valuation of the different intervention effects is based on either prices that are revealed by markets or an individual or societal willingness-to-pay value.

Cost–consequence analysis: A cost–consequence analysis is a type of economic evaluation that estimates the costs and consequences (i.e., the health outcomes) of two or more health care interventions. In this type of analysis, the costs are presented separately from the consequences.

Cost-effective: A health care intervention is considered cost-effective when it provides additional benefits, compared with relevant alternatives, at an additional cost that is acceptable to a decision-maker based on the maximum willingness-to-pay value.

Cost-effectiveness analysis: Used broadly, "cost-effectiveness analysis" may refer to an economic evaluation used to compare the benefits of two or more health care interventions with their costs. It may encompass several types of analysis (e.g., cost-effectiveness analysis, cost–utility analysis). Used more specifically, "cost-effectiveness analysis" may refer to a type of economic evaluation in which the main outcome measure is the incremental cost per natural unit of health (e.g., life-year, symptom-free day) gained.

Cost–utility analysis: A cost–utility analysis is a type of economic evaluation used to compare the benefits of two or more health care interventions with their costs. The benefits are measured using

quality-adjusted life-years, which capture both the quality and quantity of life. In a cost–utility analysis, the main outcome measure is the incremental cost per quality-adjusted life-year gained.

Decision tree: A decision tree is a type of economic model used to assess the costs and benefits of two or more alternative health care interventions. Each intervention may be associated with different outcomes, which are represented by distinct branches in the tree. Each outcome may have a different probability of occurring and may lead to different costs and benefits.

Deterministic sensitivity analysis: Deterministic sensitivity analysis is an approach used to explore uncertainty in the results of an economic evaluation by varying parameter values to observe the potential impact on the cost-effectiveness of the health care intervention of interest. One-way sensitivity analysis accounts for uncertainty in parameter values one at a time, whereas multiway sensitivity analysis accounts for uncertainty in a combination of parameter values simultaneously.

Discounting: Discounting is a method used in economic evaluations to adjust for the differential timing of the costs incurred and the benefits generated by a health care intervention over time. Discounting reflects the concept of positive time preference, whereby future costs and benefits are reduced to reflect their present value. The health technology assessments conducted by Ontario Health use an annual discount rate of 1.5% for both future costs and future benefits.

Dominant: A health care intervention is considered dominant when it is more effective and less costly than its comparator(s).

EQ-5D: The EQ-5D is a generic health-related quality-of-life classification system widely used in clinical studies. In economic evaluations, it is used as an indirect method of obtaining health state preferences (i.e., utility values). The EQ-5D questionnaire consists of five questions relating to different domains of quality of life: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. For each domain, there are three response options: no problems, some problems, or severe problems. A newer instrument, the EQ-5D-5L, includes five response options for each domain. A scoring table is used to convert EQ-5D scores to utility values.

Equity: Unlike the notion of equality, equity is not about treating everyone the same way.[131] It denotes fairness and justice in process and in results. Equitable outcomes often require differential treatment and resource redistribution to achieve a level playing field among all individuals and communities. This requires recognizing and addressing barriers to opportunities for all to thrive in our society.

Health-related quality of life: Health-related quality of life is a measure of the impact of a health care intervention on a person's health. It includes the dimensions of physiology, function, social life, cognition, emotions, sleep and rest, energy and vitality, health perception, and general life satisfaction.

Health state: A health state is a particular status of health (e.g., sick, well, dead). A health state is associated with some amount of benefit and may be associated with specific costs. Benefit is captured through individual or societal preferences for the time spent in each health state and is expressed in quality-adjusted weights called utility values. In a Markov model, a finite number of mutually exclusive health states are used to represent discrete states of health.

Incremental cost: The incremental cost is the additional cost, typically per person, of a health care intervention versus a comparator.

Incremental cost-effectiveness ratio (ICER): The incremental cost-effectiveness ratio (ICER) is a summary measure that indicates, for a given health care intervention, how much more a health care consumer must pay to get an additional unit of benefit relative to an alternative intervention. It is obtained by dividing the incremental cost by the incremental effectiveness. Incremental cost-effectiveness ratios are typically presented as the cost per life-year gained or the cost per quality-adjusted life-year gained.

Markov model: A Markov model is a type of decision-analytic model used in economic evaluations to estimate the costs and health outcomes (e.g., quality-adjusted life-years gained) associated with using a particular health care intervention. Markov models are useful for clinical problems that involve events of interest that may recur over time (e.g., stroke). A Markov model consists of mutually exclusive, exhaustive health states. Patients remain in a given health state for a certain period of time before moving to another health state based on transition probabilities. The health states and events modelled may be associated with specific costs and health outcomes.

Ministry of Health perspective: The perspective adopted in economic evaluations determines the types of costs and health benefits to include. Ontario Health develops health technology assessment reports from the perspective of the Ontario Ministry of Health. This perspective includes all costs and health benefits attributable to the Ministry, such as treatment costs (e.g., drugs, administration, monitoring, hospital stays) and costs associated with managing adverse events caused by treatments. This perspective does not include out-of-pocket costs incurred by patients related to obtaining care (e.g., transportation) or loss of productivity (e.g., absenteeism).

One-way sensitivity analysis: A one-way sensitivity analysis is used to explore uncertainty in the results of an economic evaluation. It is done by varying one model input (i.e., a parameter) at a time between its minimum and maximum values to observe the potential impact on the cost-effectiveness of the health care intervention of interest.

Probabilistic analysis: A probabilistic analysis (also known as a probabilistic sensitivity analysis) is used in economic models to explore uncertainty in several parameters simultaneously and is done using Monte Carlo simulation. Model inputs are defined as a distribution of possible values. In each iteration, model inputs are obtained by randomly sampling from each distribution, and a single estimate of cost and effectiveness is generated. This process is repeated many times (e.g., 10,000 times) to estimate the number of times (i.e., the probability) that the health care intervention of interest is cost-effective.

Quality-adjusted life-year (QALY): The quality-adjusted life-year (QALY) is a generic health outcome measure commonly used in cost–utility analyses to reflect the quantity and quality of life-years lived. The life-years lived are adjusted for quality of life using individual or societal preferences (i.e., utility values) for being in a particular health state. One year of perfect health is represented by one quality-adjusted life-year.

Reference case: The reference case is a preferred set of methods and principles that provide the guidelines for economic evaluations. Its purpose is to standardize the approach of conducting and reporting economic evaluations, so that results can be compared across studies.

Risk difference: Risk difference is the difference in the risk of an outcome occurring between one health care intervention and an alternative intervention.

Scenario analysis: A scenario analysis is used to explore uncertainty in the results of an economic evaluation. It is done by observing the potential impact of different scenarios on the cost-effectiveness of a health care intervention. Scenario analyses involve varying structural assumptions from the reference case.

Sensitivity analysis: Every economic evaluation contains some degree of uncertainty, and results can vary depending on the values taken by key parameters and the assumptions made. Sensitivity analysis allows these factors to be varied and shows the impact of these variations on the results of the evaluation. There are various types of sensitivity analysis, including deterministic, probabilistic, and scenario.

Short-Form–Six Dimensions (SF-6D): The SF-6D is a generic health-related quality-of-life classification system widely used in clinical studies. In economic evaluations, it is used as an indirect method of obtaining health state preferences (i.e., utility values). The classification system consists of six attributes (physical functioning, role limitations, social functioning, pain, mental health, and vitality), each associated with four to six levels, thus producing a total of 18,000 possible unique health states. A scoring table is used to convert SF-6D scores to health state values.

Social capital: Social capital refers to the connections among people's social networks and the reciprocity and trust arise from them. More social capital is generally seen as better than less, but some kinds are more societally productive (for example, bridging) and others are more valuable for individuals (for example, bonding). It is also important to note that the effects of social capital are not always positive. For example, some communities' social bonding can make them exclusionary, wealth concentrated, and restrictive of freedoms.

Societal perspective: The perspective adopted in an economic evaluation determines the types of costs and health benefits to include. The societal perspective reflects the broader economy and is the aggregation of all perspectives (e.g., health care payer and patient perspectives). It considers the full effect of a health condition on society, including all costs (regardless of who pays) and all benefits (regardless of who benefits).

Time horizon: In economic evaluations, the time horizon is the time frame over which costs and benefits are examined and calculated. The relevant time horizon is chosen based on the nature of the disease and health care intervention being assessed, as well as the purpose of the analysis. For instance, a lifetime horizon would be chosen to capture the long-term health and cost consequences over a patient's lifetime.

Tornado diagram: In economic evaluations, a tornado diagram is used to determine which model parameters have the greatest influence on results. Tornado diagrams present the results of multiple one-way sensitivity analyses in a single graph.

Uptake rate: In instances where two technologies are being compared, the uptake rate is the rate at which a new technology is adopted. When a new technology is adopted, it may be used in addition to an existing technology, or it may replace an existing technology.

Utility: A utility is a value that represents a person's preference for various health states. Typically, utility values are anchored at 0 (death) and 1 (perfect health). In some scoring systems, a negative utility value indicates a state of health valued as being worse than death. Utility values can be aggregated over time to derive quality-adjusted life-years, a common outcome measure in economic evaluations.

Willingness-to-pay value: A willingness-to-pay value is the monetary value a health care consumer is willing to pay for added health benefits. When conducting a cost–utility analysis, the willingness-to-pay value represents the cost a consumer is willing to pay for an additional quality-adjusted life-year. If the incremental cost-effectiveness ratio is less than the willingness-to-pay value, the health care intervention of interest is considered cost-effective. If the incremental cost-effectiveness ratio is more than the willingness-to-pay value, the intervention is considered not to be cost-effective.

Appendices

Appendix 1: Literature Search Strategies

Clinical Evidence Search

Search Date: January 9, 2024

Databases searched: Ovid MEDLINE, Embase, Cochrane Database of Systematic Reviews, NHS Economic Evaluation Database; and EBSCO Cumulative Index to Nursing and Allied Health Literature

Database segments: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to January 3, 2024>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2024 Week 01>, Ovid MEDLINE(R) ALL <1946 to January 08, 2024>
Search Strategy:
---
1 Tuberculosis/ (239899)
2 tuberculo*.ti,ab,kf. (481399)
3 Mycobacterium tuberculosis/ (132231)
4 Latent Tuberculosis/ (12300)
5 Tuberculosis, Pulmonary/ (98534)
6 (((mycobacteri* or bacteri* or laten* or active or disease* or infection*) adj3 TB) or LTB or LTBI or koch*).ti,ab,kf. (67013)
7 or/1-6 (576360)
8 Interferon-gamma Release Tests/ (7433)
9 (((interferon* or IFN) adj3 gamma* adj3 (release* or test* or assay* or diagnos* or screen*)) or ((interferon-y or y-interferon*) adj3 (release or test* or assay*)) or IGRA or IGRAs).ti,ab,kf. (20757)
10 (quantiferon* or QFT* or gold plus* or "gold in tube*").ti,ab,kf. (7987)
11 (tspot* or t spot* or "t-spot.tb*" or tb assay* or tb blood test*).ti,ab,kf. (2616)
12 (QIAreach* or standard e TB feron* or "T-cell select*").ti,ab,kf. (1256)
13 (qiagen gmbh* or oxford immunotec* or diasorin inc*).ti,ab,kf. (449)
14 or/8-13 (30103)
15 7 and 14 (15430)
16 exp Animals/ not Humans/ (16422933)
17 15 not 16 (11293)
18 Congress.pt. (67511)
19 17 not 18 (11289)
20 limit 19 to english language [Limit not valid in CDSR; records were retained] (10575)
21 20 use coch (0)
22 (Systematic Reviews or Meta Analysis).pt. (192867)
23 Systematic Review/ or Systematic Reviews as Topic/ or Meta-Analysis/ or exp Meta-Analysis as Topic/ or exp Technology Assessment, Biomedical/ (1025393)
24 ((systematic* or methodologic*) adj3 (review* or overview*)).ti,ab,kf. (764529)
25 (meta analy* or metaanaly* or met analy* or metanaly* or meta review* or metareview* or health technolog* assess* or HTA or HTAs or (technolog* adj (assessment* or overview* or appraisal*))).ti,ab,kf. (700186)

26 (evidence adj2 (review* or overview* or synthes#s)).ti,ab,kf. (104994)
27 (review of reviews or overview of reviews).ti,ab,kf. (2705)
28 umbrella review*.ti,ab,kf. (3606)
29 GRADE Approach/ (3796)
30 ((pool* adj3 analy*) or published studies or published literature or hand search* or handsearch* or manual search* or ((database* or systematic*) adj2 search*) or reference list* or bibliograph* or relevant journals or data synthes* or data extraction* or data abstraction*).ti,ab,kf. (669376)
31 (medline or pubmed or medlars or embase or cinahl or web of science or ovid or ebsco* or scopus).ab. (800250)
32 cochrane.ti,ab,kf. (336370)
33 (meta regress* or metaregress*).ti,ab,kf. (34648)
34 (((integrative or collaborative or quantitative) adj3 (review* or overview* or synthes*)) or (research adj3 overview*)).ti,ab,kf. (41688)
35 (cochrane or (health adj2 technology assessment) or evidence report or systematic review*).jw. (77778)
36 ((comparative adj3 (efficacy or effectiveness)) or relative effectiveness or ((indirect or indirect treatment or mixed-treatment) adj comparison*)).ti,ab,kf. (60629)
37 or/22-36 (1927703)
38 20 and 37 (618)
39 38 use medall,cleed (274)
40 or/21,39 (274)
41 tuberculosis/ (239899)
42 tuberculo*.tw,kw,kf. (481755)
43 Mycobacterium tuberculosis/ (132231)
44 latent tuberculosis/ (12300)
45 (((mycobacteri* or bacteri* or laten* or active or disease* or infection*) adj3 TB) or LTB or LTBI or koch*).tw,kw,kf. (67691)
46 or/41-45 (563934)
47 interferon gamma release assay/ (7417)
48 (((interferon* or IFN) adj3 gamma* adj3 (release* or test* or assay* or diagnos* or screen*)) or ((interferon-y or y-interferon*) adj3 (release or test* or assay*)) or IGRA or IGRAs).tw,kw,kf,dv. (20794)
49 (tspot* or t spot* or "t-spot.tb*" or tb assay* or tb blood test*).tw,kw,kf,dv. (2958)
50 (QIAreach* or standard e TB feron* or "T-cell select*").tw,kw,kf,dv. (1269)
51 (qiagen gmbh* or oxford immunotec* or diasorin inc*).tw,kw,kf,dv. (779)
52 or/47-51 (26148)
53 46 and 52 (12625)
54 (exp animal/ or nonhuman/) not exp human/ (12005527)
55 53 not 54 (11738)
56 conference abstract.pt. (5013227)
57 55 not 56 (10080)
58 limit 57 to english language [Limit not valid in CDSR; records were retained] (9350)
59 Systematic review/ or "systematic review (topic)"/ or exp Meta Analysis/ or "Meta Analysis (Topic)"/ or Biomedical Technology Assessment/ (996097)
60 (meta analy* or metaanaly* or health technolog* assess* or systematic review*).hw. (1000098)
61 ((systematic* or methodologic*) adj3 (review* or overview*)).tw,kw,kf. (775173)
62 (meta analy* or metaanaly* or met analy* or metanaly* or meta review* or metareview* or health technolog* assess* or HTA or HTAs or (technolog* adj (assessment* or overview* or appraisal*))).tw,kw,kf. (708173)

63 (evidence adj2 (review* or overview* or synthes#s)).tw,kw,kf. (107391)
64 (review of reviews or overview of reviews).tw,kw,kf. (2926)
65 umbrella review*.tw,kw,kf. (3637)
66 ((pool* adj3 analy*) or published studies or published literature or hand search* or handsearch* or manual search* or ((database* or systematic*) adj2 search*) or reference list* or bibliograph* or relevant journals or data synthes* or data extraction* or data abstraction*).tw,kw,kf. (678847)
67 (medline or pubmed or medlars or embase or cinahl or web of science or ovid or ebsco* or scopus).ab. (800250)
68 cochrane.tw,kw,kf. (339807)
69 (meta regress* or metaregress*).tw,kw,kf. (35638)
70 (((integrative or collaborative or quantitative) adj3 (review* or overview* or synthes*)) or (research adj3 overview*)).tw,kw,kf. (42780)
71 (cochrane or (health adj2 technology assessment) or evidence report or systematic review*).jw. (77778)
72 ((comparative adj3 (efficacy or effectiveness)) or relative effectiveness or ((indirect or indirect treatment or mixed-treatment) adj comparison*)).tw,kw,kf. (61968)
73 or/59-72 (1931962)
74 58 and 73 (698)
75 74 use emez (410)
76 40 or 75 (684)
77 76 use medall (274)
78 76 use coch (0)
79 76 use cleed (0)
80 76 use emez (410)
81 remove duplicates from 76 (451)

CINAHL

#	Query	Results
S1	(MH "	") 17,678
S2	TI tuberculo* OR AB tuberculo*	28,056
S3	(MH "Mycobacterium Tuberculosis")	4,404
S4	(MH "Latent Tuberculosis")	86
S5	(MH "Tuberculosis, Pulmonary")	5,813
S6	TI (((mycobacteri* or bacteri* or laten* or active or disease* or infection*) N3 TB) or LTB or LTBI or koch*) OR AB (((mycobacteri* or bacteri* or laten* or active or disease* or infection*) N3 TB) or LTB or LTBI or koch*)	4,960
S7	S1 OR S2 OR S3 OR S4 OR S5 OR S6	35,509
S8	(MH "Interferon-Gamma Release Tests")	0
S9	TI (((interferon* or IFN) N3 gamma* N3 (release* or test* or assay* or diagnos* or screen*)) or ((interferon-y or y-interferon*) N3 (release or test* or assay*)) or IGRA or IGRAs) OR AB (((interferon* or IFN) N3 gamma* N3 (release* or test* or assay* or diagnos* or screen*)) or ((interferon-y or y-interferon*) N3 (release or test* or assay*)) or IGRA or IGRAs)	884
S10	TI (quantiferon* or QFT* or gold plus* or "gold in tube*") OR AB (quantiferon* or QFT* or gold plus* or "gold in tube*")	577
S11	TI (tspot* or t spot* or "t-spot.tb*" or tb assay* or tb blood test*) OR AB (tspot* or t spot* or "t-spot.tb*" or tb assay* or tb blood test*)	303

S12	TI (QIAreach* or standard e TB feron* or "T-cell select*") OR AB (QIAreach* or standard e TB feron* or "T-cell select*")	22
S13	TI (qiagen gmbh* or oxford immunotec* or diasorin inc*) OR AB (qiagen gmbh* or oxford immunotec* or diasorin inc*)	30
S14	S8 OR S9 OR S10 OR S11 OR S12 OR S13	1,413
S15	S7 AND S14	1,118
S16	(PT "Meta Analysis") or (PT "Systematic Review")	169,900
S17	(MH "Systematic Review") OR (MH "Meta Analysis")	160,941
S18	((systematic* or methodologic*) N3 (review* or overview*))	211,094
S19	(meta analy* or metaanaly* or met analy* or metanaly* or meta review* or metareview* or health technolog* assess* or HTA or HTAs or (technolog* N1 (assessment* or overview* or appraisal*)))	133,276
S20	(evidence N2 (review* or overview* or synthes#s)))	28,737
S21	((review or overview) N2 reviews)	9,325
S22	umbrella review*	817
S23	((pool* N3 analy*) or published studies or published literature or hand search* or handsearch* or manual search* or ((database* or systematic*) N2 search*) or reference list* or bibliograph* or relevant journals or data synthes* or data extraction* or data abstraction*)	131,349
S24	AB(medline or pubmed or medlars or embase or cinahl or web of science or ovid or ebsco* or scopus)	127,553
S25	cochrane	73,494
S26	(meta regress* or metaregress*)	5,329
S27	(((integrative or collaborative or quantitative) N3 (review* or overview* or synthes*)) or (research N3 overview*))	14,011
S28	SO(cochrane or (health N2 technology assessment) or evidence report or systematic review*)	12,464
S29	((comparative N3 (efficacy or effectiveness)) or relative effectiveness or ((indirect or indirect treatment or mixed-treatment) N1 comparison*))	10,291
S30	S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29	370,831
S31	S15 AND S30	80
S32	PT Proceedings	76,098
S33	S31 NOT S32	80
S34	S31 NOT S32 Limiters - English Language	80

Economic Evidence Search

Search Date: January 10, 2024

Databases searched: Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, NHS Economic Evaluation Database; and EBSCO Cumulative Index to Nursing and Allied Health Literature

Database segments: EBM Reviews - Cochrane Central Register of Controlled Trials <December 2023>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to January 3, 2024>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2024 Week 01>, Ovid MEDLINE(R) ALL <1946 to January 09, 2024>
Search Strategy:
---
1 Tuberculosis/ (241779)
2 tuberculo*.ti,ab,kf. (488390)
3 Mycobacterium tuberculosis/ (132680)
4 Latent Tuberculosis/ (12491)
5 Tuberculosis, Pulmonary/ (99758)
6 (((mycobacteri* or bacteri* or laten* or active or disease* or infection*) adj3 TB) or LTB or LTBI or koch*).ti,ab,kf. (68489)
7 or/1-6 (584407)
8 Interferon-gamma Release Tests/ (7464)
9 (((interferon* or IFN) adj3 gamma* adj3 (release* or test* or assay* or diagnos* or screen*)) or ((interferon-y or y-interferon*) adj3 (release or test* or assay*)) or IGRA or IGRAs).ti,ab,kf. (21102)
10 (quantiferon* or QFT* or gold plus* or "gold in tube*").ti,ab,kf. (8200)
11 (tspot* or t spot* or "t-spot.tb*" or tb assay* or tb blood test*).ti,ab,kf. (2661)
12 (QIAreach* or standard e TB feron* or "T-cell select*").ti,ab,kf. (1256)
13 (qiagen gmbh* or oxford immunotec* or diasorin inc*).ti,ab,kf. (474)
14 or/8-13 (30655)
15 7 and 14 (15698)
16 exp Animals/ not Humans/ (16426259)
17 15 not 16 (11561)
18 Case Reports/ or Comment.pt. or Editorial.pt. or (Letter not (Letter and Randomized Controlled Trial)).pt. or Congress.pt. (6595888)
19 17 not 18 (10407)
20 limit 19 to english language [Limit not valid in CDSR; records were retained] (9778)
21 20 use cleed,coch (29)
22 economics/ (265027)
23 economics, medical/ or economics, pharmaceutical/ or exp economics, hospital/ or economics, nursing/ or economics, dental/ (1077454)
24 economics.fs. (470475)
25 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).ti,ab,kf. (1321816)
26 exp "costs and cost analysis"/ (701070)
27 (cost or costs or costing or costly).ti. (340597)
28 cost effective*.ti,ab,kf. (467555)

29 (cost* adj2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog* or increment*)).ab,kf. (319787)
30 models, economic/ (16214)
31 markov chains/ or monte carlo method/ (110219)
32 (decision adj1 (tree* or analy* or model*)).ti,ab,kf. (70391)
33 (markov or markow or monte carlo).ti,ab,kf. (184752)
34 quality-adjusted life years/ (57484)
35 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).ti,ab,kf. (116403)
36 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).ti,ab,kf. (204003)
37 or/22-36 (3475185)
38 20 and 37 (638)
39 38 use medall,cctr (274)
40 21 or 39 (303)
41 tuberculosis/ (241779)
42 tuberculo*.tw,kw,kf. (489148)
43 Mycobacterium tuberculosis/ (132680)
44 latent tuberculosis/ (12491)
45 (((mycobacteri* or bacteri* or laten* or active or disease* or infection*) adj3 TB) or LTB or LTBI or koch*).tw,kw,kf. (69167)
46 or/41-45 (572234)
47 interferon gamma release assay/ (7424)
48 (((interferon* or IFN) adj3 gamma* adj3 (release* or test* or assay* or diagnos* or screen*)) or ((interferon-y or y-interferon*) adj3 (release or test* or assay*)) or IGRA or IGRAs).tw,kw,kf,dv. (21157)
49 (tspot* or t spot* or "t-spot.tb*" or tb assay* or tb blood test*).tw,kw,kf,dv. (3003)
50 (QIAreach* or standard e TB feron* or "T-cell select*").tw,kw,kf,dv. (1269)
51 (qiagen gmbh* or oxford immunotec* or diasorin inc*).tw,kw,kf,dv. (804)
52 or/47-51 (26555)
53 46 and 52 (12792)
54 (exp animal/ or nonhuman/) not exp human/ (12011811)
55 53 not 54 (11905)
56 Case Report/ or Comment/ or Editorial/ or (letter.pt. not (letter.pt. and randomized controlled trial/)) or conference abstract.pt. or conference review.pt. (11529012)
57 55 not 56 (8785)
58 limit 57 to english language [Limit not valid in CDSR; records were retained] (8114)
59 Economics/ (265027)
60 Health Economics/ or Pharmacoeconomics/ or Drug Cost/ or Drug Formulary/ (150591)
61 Economic Aspect/ or exp Economic Evaluation/ (563928)
62 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw,kw,kf. (1342226)
63 exp "Cost"/ (701070)
64 (cost or costs or costing or costly).ti. (340597)
65 cost effective*.tw,kw,kf. (476420)
66 (cost* adj2 (util* or efficac* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog* or increment*)).ab,kw,kf. (329680)
67 Monte Carlo Method/ (85478)
68 (decision adj1 (tree* or analy* or model*)).tw,kw,kf. (73811)
69 (markov or markow or monte carlo).tw,kw,kf. (188224)
70 Quality-Adjusted Life Years/ (57484)

71 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw,kw,kf. (119757)
72 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw,kw,kf. (224844)
73 or/59-72 (2987441)
74 58 and 73 (595)
75 74 use emez (330)
76 40 or 75 (633)
77 76 use medall (252)
78 76 use coch (0)
79 76 use cctr (22)
80 76 use cleed (29)
81 76 use emez (330)
82 remove duplicates from 76 (449)

CINAHL

#	Query	Results
S1	(MH "	") 17,680
S2	TI tuberculo* OR AB tuberculo*	28,062
S3	(MH "Mycobacterium Tuberculosis")	4,404
S4	(MH "Latent Tuberculosis")	86
S5	(MH "Tuberculosis, Pulmonary")	5,814
S6	TI (((mycobacteri* or bacteri* or laten* or active or disease* or infection*) N3 TB) or LTB or LTBI or koch*) OR AB (((mycobacteri* or bacteri* or laten* or active or disease* or infection*) N3 TB) or LTB or LTBI or koch*)	4,962
S7	S1 OR S2 OR S3 OR S4 OR S5 OR S6	35,517
S8	(MH "Interferon-Gamma Release Tests")	0
S9	TI (((interferon* or IFN) N3 gamma* N3 (release* or test* or assay* or diagnos* or screen*)) or ((interferon-y or y-interferon*) N3 (release or test* or assay*)) or IGRA or IGRAs) OR AB (((interferon* or IFN) N3 gamma* N3 (release* or test* or assay* or diagnos* or screen*)) or ((interferon-y or y-interferon*) N3 (release or test* or assay*)) or IGRA or IGRAs)	884
S10	TI (quantiferon* or QFT* or gold plus* or "gold in tube*") OR AB (quantiferon* or QFT* or gold plus* or "gold in tube*")	577
S11	TI (tspot* or t spot* or "t-spot.tb*" or tb assay* or tb blood test*) OR AB (tspot* or t spot* or "t-spot.tb*" or tb assay* or tb blood test*)	303
S12	TI (QIAreach* or standard e TB feron* or "T-cell select*") OR AB (QIAreach* or standard e TB feron* or "T-cell select*")	22
S13	TI (qiagen gmbh* or oxford immunotec* or diasorin inc*) OR AB (qiagen gmbh* or oxford immunotec* or diasorin inc*)	30
S14	S8 OR S9 OR S10 OR S11 OR S12 OR S13	1,413
S15	S7 AND S14	1,118
S16	(MH "Economics")	14,117
S17	(MH "Economic Aspects of Illness")	11,218
S18	(MH "Economic Value of Life")	666
S19	MH "Economics, Dental"	153
S20	MH "Economics, Pharmaceutical"	2,414
S21	MW "ec"	193,215
S22	(econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*)	347,734

S23	(MH "Costs and Cost Analysis+")	135,962
S24	TI cost*	63,755
S25	(cost effective*)	52,246
S26	AB (cost* N2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*))	40,804
S27	(decision N1 (tree* or analy* or model*))	11,983
S28	(markov or markow or monte carlo)	7,950
S29	(MH "Quality-Adjusted Life Years")	6,090
S30	(QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs)	15,569
S31	((adjusted N1 (quality or life)) or (willing* N2 pay) or sensitivity analysis or sensitivity analyses)	25,991
S32	S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31	481,999
S33	S15 AND S32	88
S34	PT (Case Study or Commentary or Editorial or Letter or Proceedings)	1,281,856
S35	S33 NOT S34	85
S36	S33 NOT S34 Limiters - English Language	85

Grey Literature Search

Performed on: January 10 – 17, 2024

Websites searched:
Alberta Health Evidence Reviews, BC Health Technology Assessments, Canadian Agency for Drugs and Technologies in Health (CADTH), Institut national d'excellence en santé et en services sociaux (INESSS), Institute of Health Economics (IHE), University Of Calgary Health Technology Assessment Unit, Ontario Health Technology Assessment Committee (OHTAC), McGill University Health Centre Health Technology Assessment Unit, Centre Hospitalier de l'Universite de Quebec-Universite Laval, Contextualized Health Research Synthesis Program of Newfoundland (CHRSP), Health Canada Medical Device Database, International HTA Database (INAHTA), Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers, Centers for Medicare & Medicaid Services Technology Assessments, Veterans Affairs Health Services Research and Development, Institute for Clinical and Economic Review, Oregon Health Authority Health Evidence Review Commission, Washington State Health Care Authority Health Technology Reviews, National Institute for Health and Care Excellence (NICE), National Health Service England (NHS), Healthcare Improvement Scotland, Health Technology Wales, Ireland Health Information and Quality Authority Health Technology Assessments, Adelaide Health Technology Assessment, Australian Government Medical Services Advisory Committee, Monash Health Centre for Clinical Effectiveness, The Sax Institute, Australian Government Department of Health and Aged Care, Australian Safety and Efficacy Register of New Interventional Procedures - Surgical (ASERNIP-S), Pharmac, Italian National Agency for Regional Health Services (Aegnas), Belgian Health Care Knowledge Centre, Ludwig Boltzmann Institute for Health Technology Assessment (Austria), The Regional Health Technology Assessment Centre (HTA-centrum), Swedish Agency for Health Technology Assessment and Assessment of Social Services, Norwegian Institute of Public Health - Health Technology Assessments, The Danish Health Technology Council, Ministry of Health Malaysia - Health Technology Assessment Section, Tuft's Cost-Effectiveness Analysis Registry, Sick Kids PEDE Database, PROSPERO, EUnetHTA, clinicaltrials.gov

Keywords used:

tuberculosis, TB, latent, LTBI, LTB, interferon gamma, interferon gamma release assay, IGRA, IFN, quantiferon, QFT, gold plus, gold in tube, t.spot, tspot, t spot, tuberculose

Clinical results (included in PRISMA): 17
Economic results (included in PRISMA): 33
Ongoing HTAs (PROSPERO/EUnetHTA/NICE/MSAC): 38
Ongoing clinical trials: 0

Appendix 2: Critical Appraisal of Clinical Evidence

Table A1: Risk of Bias[a] Among Systematic Reviews (ROBIS Tool)

	Phase 2				Phase 3
Author, year	Study eligibility criteria	Identification and selection of studies	Data collection and study appraisal	Synthesis and findings	Risk of bias in the review
Volkman et al, 2024[56]	Low	Low	Low[b]	Low	Low
Zhou et al, 2023[57]	Low	Low	Low	Low	Low
Yahav et al, 2023[58]	Low	Low	Low	Low	Low
Jonas et al, 2023[55]	Low	Low	Low	Low	Low
Zhou et al, 2022[59]	Low	Low	Low	Low	Low
Park et al, 2022[60]	Low	Low	Low	Low	Low
Chen et al, 2022[61]	Low[c]	Low	Low	Low	Low
Oh et al, 2021[62]	Low	Low	Low	Low	Low
Zhou et al, 2020[63]	Low	Low	Low[d]	Low[d]	Low
Yamasue et al, 2020[64]	Low	Low	Low	Low	Low
Campbell et al, 2020[65]	Low	Low	Low	Low	Low
Alrajhi et al 2020[66]	Low	Low[e]	Low	Low	Low

[a]Possible risk-of-bias levels: low, high, unclear.

[b]Unclear if 2 reviewers were involved in the extraction, but based on overall reporting of study methodology, we considered the risk of bias to be low.

[c]Included conference abstracts and briefs.

[d]Unclear if duplicate data extract and quality assessment; used 'we' in description.

[e]Sensitivity analyses were conducted to assess the inclusion of studies published as abstracts and letter to the editor.

Appendix 3: Other Measures to Compare Findings

Campbell et al, 2020[65] reported differences in incidence rate ratio by level of agreement between IGRA and TST positive and negative findings. Zhou et al, 2020[63] reported rates of progression to TB disease based on alignments in IGRA and TST. Alrajhi et al, 2020[66] reported the odds ratio of testing positive when on an immunosuppressant versus not on an immunosuppressant. Four studies reported concordance as a rate of agreement between IGRA and TST test results.[56,60,62,66]

Table A2: Other Measures Comparing IGRA and TST Findings

Author, year	Population	Test agreement scenario Group 1 and Group 2 descriptions of scenarios	Results Incidence rate ratio of progressing to TB disease (95% CI)
Campbell et al, 2020[65]	Higher risk for TB	Group 1: IGRA and TST both positive Group 2: IGRA and TST both negative	19.1 (2.9–127.3)
		Group 1: IGRA and TST both positive Group 2: IGRA positive and TST negative	3.0 (0.2–40.7)
		Group 1: IGRA and TST both positive Group 2: IGRA negative and TST positive	7.6 (1.6–36.7)
		Group 1: IGRA positive and TST negative Group 2: IGRA and TST both negative	5.1 (2.4–10.8)
		Group 1: IGRA negative and TST positive Group 2: IGRA and TST both negative	3.6 (1.8–7.2)
		Scenarios	**Proportion progress to TB disease (95% CI)**
Zhou et al, 2020[63]	High risk population for TB	IGRA and TST both positive	6.1% (2.3–11.5)
		IGRA and TST both negative	0.5% (0.2–1.1)
		IGRA negative and TST positive	0.8% (0.2–1.6)
		IGRA positive and TST negative	1.7% (0.3–4.2)
		LTBI test	**Odds ratio of testing positive when on immunosuppressants, vs. not on an immunosuppressant (95% CI)**
Alrajhi et al, 2020[66]	Adults with inflammatory bowel disease	With IGRA	0.57 (0.31 – 1.03); *P* = 0.006
		With TST	1.14 (061–2.12)
		Scenarios	**Rate of agreement occurrence (95% CI)**
Volkman et al, 2024[56]	Children < 5, with no underlying immunosuppression	IGRA and TST both positive or both negative	50% (17–80)

Park et al, 2022[60]	Adults with inflammatory bowel disease	IGRA and TST both positive or both negative	83.3% (78.5–88.1)
		IGRA negative and TST positive	9.5% (5.8–13.2)
		IGRA positive and TST negative	5.8% (4.0-7.7)
Oh et al, 2021[62]	Adults at higher risk for TB	IGRA and TST both positive or both negative	46% (38–54)
Alrajhi et al, 2020[66]	Adults with inflammatory bowel disease	IGRA and TST both positive or both negative	84.8% (81.4–88.3)

Appendix 4: Selected Excluded Studies – Clinical Evidence

For transparency, we provide an example list of studies that readers might have expected to see but that did not meet the inclusion criteria, along with the primary reason for exclusion.

Citation	Primary reason for exclusion
Brett K, Severn M. Interferon gamma release assay for the identification of latent tuberculosis infection in rural and remote settings. Canadian Agency for Drugs and Technologies in Health CADTH Health Technology Review. 2021;04:04.	Wrong study design. This publication is a dive into relevant primary studies from a systematic review that was identified during a rapid review
Ghosh S, Dronavalli M, Raman S. Tuberculosis infection in under-2-year-old refugees: should we be screening? A systematic review and meta-regression analysis. J Paediatr Child Health. 2020;56(4):622-9.	Wrong study design. Had high risk of bias according to ROBIS assessment and did not report quality assessment of primary studies
Hamada Y, Gupta RK, Quartagno M, Izzard A, Acuna-Villaorduna C, Altet N, et al. Predictive performance of interferon-gamma release assays and the tuberculin skin test for incident tuberculosis: an individual participant data meta-analysis. EClin Med. 2023;56:101815.	Population not specific to our population of interest
Krutikov M, Faust L, Nikolayevskyy V, Hamada Y, Gupta RK, Cirillo D, et al. The diagnostic performance of novel skin-based in-vivo tests for tuberculosis infection compared with purified protein derivative tuberculin skin tests and blood-based in vitro interferon-gamma release assays: a systematic review and meta-analysis. Lancet Infect Dis. 2022;22(2):250-64.	Wrong intervention
Ortiz-Brizuela E, Apriani L, Mukherjee T, Lachapelle-Chisholm S, Miedy M, Lan Z, et al. Assessing the diagnostic performance of new commercial interferon-gamma release assays for mycobacterium tuberculosis infection: a systematic review and meta-analysis. Clin Infect Dis. 2023;76(11):1989-99.	Results for population of interest could not be extracted.
Saag LA, LaValley MP, Hochberg NS, Cegielski JP, Pleskunas JA, Linas BP, et al. Low body mass index and latent tuberculous infection: a systematic review and meta-analysis. Int J Tuberc Lung Dis. 2018;22(4):358-65.	Population outside of scope

Appendix 5: Systematic Reviews That Met the Inclusion Criteria, but Were Published Before 2020

For transparency, we provide a list of systematic reviews that met the inclusion criteria, but were not included in the core results of this overview of reviews.

Citation
Al-Ghafli H, Al-Hajoj S. QuantiFERON-TB Gold In-Tube in Saudi Arabia benchmarked with other sites of the Middle East: a meta-analysis review. J Infect Dev Ctries. 2018;12(9):687-99.
World Health Organization. Use of tuberculosis interferon-gamma release assays (IGRAs) in low- and middle-income countries: policy statement. WHO Guidelines Approved by the Guidelines Review Committee. 2011.
Auguste P, Madan J, Tsertsvadze A, Court R, McCarthy N, Sutcliffe P, et al. Identifying latent tuberculosis in high-risk populations: systematic review and meta-analysis of test accuracy. Int J Tuberculosis Lung Dis. 2019;23(11):1178-90.
Auguste P, Tsertsvadze A, Pink J, Court R, McCarthy N, Sutcliffe P, 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.
Auguste P, Tsertsvadze A, Pink J, Court R, Seedat F, Gurung T, 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.
Ayubi E, Doosti-Irani A, Mostafavi E. Do the tuberculin skin test and the QuantiFERON-TB Gold in-tube test agree in detecting latent tuberculosis among high-risk contacts? A systematic review and meta-analysis. Epidemiol Health. 2015;37:e2015043.
Ayubi E, Doosti-Irani A, Sanjari Moghaddam A, Khazaei S, Mansori K, Safiri S, et al. Comparison of QuantiFERON-TB Gold In-Tube (QFT-GIT) and tuberculin skin test (TST) for diagnosis of latent tuberculosis in haemodialysis (HD) patients: a meta-analysis of kappa estimates. Epidemiol Infect. 2017;145(9):1824-33.
Ayubi E, Doosti-Irani A, Sanjari Moghaddam A, Sani M, Nazarzadeh M, Mostafavi E. The Clinical usefulness of tuberculin skin test versus interferon-gamma release assays for diagnosis of latent tuberculosis in HIV patients: a meta-analysis. PLoS ONE [Electronic Resource]. 2016;11(9):e0161983.
Campbell JR, Chen W, Johnston J, Cook V, Elwood K, Krot J, et al. Latent tuberculosis infection screening in immigrants to low-incidence countries: a meta-analysis. Mol Diagn Ther. 2015;19(2):107-17.
Campbell JR, Krot J, Elwood K, Cook V, Marra F. A systematic review on TST and IGRA tests used for diagnosis of LTBI in immigrants. Mol Diagn Ther. 2015;19(1):9-24.
Cattamanchi A, Smith R, Steingart KR, Metcalfe JZ, Date A, Coleman C, et al. Interferon-gamma release assays for the diagnosis of latent tuberculosis infection in HIV-infected individuals: a systematic review and meta-analysis. J Acquire Immune Defic Syndr. 2011;56(3):230-8.
Chang KC, Leung CC. Systematic review of interferon-gamma release assays in tuberculosis: focus on likelihood ratios. Thorax. 2010;65(3):271-6.
Chang KC, Leung ECC, Leung CC. Interferon-gamma release assays in childhood tuberculosis: a systematic review. Hong Kong J Paediatr. 2009;14(2):86-95.
Diel R, Goletti D, Ferrara G, Bothamley G, Cirillo D, Kampmann B, et al. Interferon-gamma release assays for the diagnosis of latent Mycobacterium tuberculosis infection: a systematic review and meta-analysis. Eur Respir J. 2011;37(1):88-99.
Diel R, Loddenkemper R, Nienhaus A. Predictive value of interferon-gamma release assays and tuberculin skin testing for progression from latent TB infection to disease state: a meta-analysis. Chest. 2012;142(1):63-75.
Dinnes J, Deeks J, Kunst H, Gibson A, Cummins E, Waugh N, et al. A systematic review of rapid diagnostic tests for the detection of tuberculosis infection. Health Technol Assess. 2007;11(3):1-196.
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 [Electronic Resource]. 2017;12(11):e0188631.
Doosti-Irani A, Ayubi E, Mostafavi E. Tuberculin and QuantiFERON-TB-Gold tests for latent tuberculosis: a meta-analysis. Occup Med (Oxford). 2016;66(6):437-45.
Eisenhut M, Fidler K. Performance of tuberculin skin test measured against interferon gamma release assay as reference standard in children. Tuberculosis Res Treat Print. 2014;2014:413459.
Ferguson TW, Tangri N, Macdonald K, Hiebert B, Rigatto C, Sood MM, et al. The diagnostic accuracy of tests for latent tuberculosis infection in hemodialysis patients: a systematic review and meta-analysis. Transplantation. 2015;99(5):1084-91.

Citation
Ge L, Ma JC, Han M, Li JL, Tian JH. Interferon-gamma release assay for the diagnosis of latent Mycobacterium tuberculosis infection in children younger than 5 years: a meta-analysis. Clin Pediatr. 2014;53(13):1255-63.
Greveson K. Can ELISpot replace the tuberculin skin test for latent tuberculosis? Br J Nursing. 2009;18(20):1248-54.
Jonas DE, Riley S, Lee L, Coffey C, Wang SH, Asher GN, et al. Screening for latent tuberculosis infection in adults: an evidence review for the U.S. Preventive Services Task Force. Agency for Healthcare Research and Quality. 2023:05.
Kahwati LC, Feltner C, Halpern M, Woodell CL, Boland E, Amick HR, et al. Screening for latent tuberculosis infection in adults: an evidence review for the U.S. Preventive Services Task Force. Agency for Healthcare Research and Quality. 2016:09.
Lu P, Chen X, Zhu LM, Yang HT. Interferon-Gamma release assays for the diagnosis of tuberculosis: a systematic review and meta-analysis. Lung. 2016;194(3):447-58.
Machingaidze S, Wiysonge CS, Gonzalez-Angulo Y, Hatherill M, Moyo S, Hanekom W, et al. The utility of an interferon gamma release assay for diagnosis of latent tuberculosis infection and disease in children: a systematic review and meta-analysis. Pediatr Infect Dis J. 2011;30(8):694-700.
Mamishi S, Pourakbari B, Marjani M, Mahmoudi S. Diagnosis of latent tuberculosis infection among immunodeficient individuals: review of concordance between interferon-gamma release assays and the tuberculin skin test. Br J Biomed Sci. 2014;71(3):115-24.
Maung Myint T, Rogerson TE, Noble K, Craig JC, Webster AC. Tests for latent tuberculosis in candidates for solid organ transplantation: a systematic review and meta-analysis. Clin Transplant. 2019;33(8):e13643.
Menzies D, Pai M, Comstock G. Meta-analysis: new tests for the diagnosis of latent tuberculosis infection: areas of uncertainty and recommendations for research. Ann Intern Med. 2007;146(5):340-54.
Munoz L, Santin M. Interferon-gamma release assays versus tuberculin skin test for targeting people for tuberculosis preventive treatment: an evidence-based review. J Infect. 2013;66(4):381-7.
Nasiri MJ, Pormohammad A, Goudarzi H, Mardani M, Zamani S, Migliori GB, et al. Latent tuberculosis infection in transplant candidates: a systematic review and meta-analysis on TST and IGRA. Infection. 2019;47(3):353-61.
Overton K, Varma R, Post JJ. Comparison of interferon-gamma release assays and the tuberculin skin test for diagnosis of tuberculosis in human immunodeficiency virus: a systematic review. Tuberc Respir Dis. 2018;81(1):59-72.
Pyo J, Cho SK, Kim D, Sung YK. Systematic review: agreement between the latent tuberculosis screening tests among patients with rheumatic diseases. Korean J Intern Med. 2018;33(6):1241-51.
Rogerson TE, Chen S, Kok J, Hayen A, Craig JC, Sud K, et al. Tests for latent tuberculosis in people with ESRD: a systematic review. Am J Kidney Dis. 2013;61(1):33-43.
Ruan Q, Zhang S, Ai J, Shao L, Zhang W. Screening of latent tuberculosis infection by interferon-gamma release assays in rheumatic patients: a systemic review and meta-analysis. Clin Rheumat. 2016;35(2):417-25.
Sadatsafavi M, Shahidi N, Marra F, FitzGerald MJ, Elwood KR, Guo N, et al. A statistical method was used for the meta-analysis of tests for latent TB in the absence of a gold standard, combining random-effect and latent-class methods to estimate test accuracy. J Clin Epidemiol. 2010;63(3):257-69.
Shahidi N, Fu YT, Qian H, Bressler B. Performance of interferon-gamma release assays in patients with inflammatory bowel disease: a systematic review and meta-analysis. Inflammatory Bowel Dis. 2012;18(11):2034-42.

Appendix 6: Selected Excluded Studies – Economic Evidence

For transparency, we provide an example list of studies that readers might have expected to see but that did not meet the inclusion criteria, along with the primary reason for exclusion.

Citation	Primary reason for exclusion
Gosce L, Allel K, Hamada Y, Korobitsyn A, Ismail N, Bashir S. Economic evaluation of novel Mycobacterium tuberculosis specific antigen-based skin tests for detection of TB infection: A modelling study. 2023.	Wrong intervention/comparator
Deuffic-Burban S, Atsou K, Viget N, Melliez, H, Bouvet E, Yazdanpanah Y. Cost-effectiveness of QuantiFERON-TB test vs. tuberculin skin test in the diagnosis of latent tuberculosis infection. 2010.	Wrong setting: non-Canadian economic evaluation
Auguste P E, Mistry H, McCarthy ND, Sutcliffe PA, Clarke AE. Cost-effectiveness of testing for latent tuberculosis infection in people with HIV. 2022.	Wrong setting: non-Canadian economic evaluation
Kowada, A. Interferon-gamma release assay for tuberculosis screening of solid-organ transplant recipients is cost-effective. 2019.	Wrong setting: non-Canadian economic evaluation
Campbell JR, Sasitharan T, Marra FA. Systematic review of studies evaluating the cost utility of screening high-risk populations for latent tuberculosis infection. 2015.	Wrong study type: systematic review
Brett K, Severn M. Interferon gamma release assay for identifying latent tuberculosis infection in people with bacillus Calmette-Guerin vaccination. 2021.	Wrong study type: not economic study
Brett K, Severn M. Interferon gamma release assay for identifying latent tuberculosis infection in people with Bacillus Calmette-Guerin vaccination. 2021.	Wrong study type: not economic study

Appendix 7: Economic Literature Review – Cost-Effectiveness of IGRA Versus TST for LTBI

Table A3: Characteristics of Studies Included in the Economic Literature Review: Summary of Methods

Author, year, country	Study and analysis characteristics	Interventions and comparator	Populations	Model description and main inputs
Oxlade et al, 2007 [81] Canada	Cost-effectiveness analysis, Markov (state-transition) model	1) Interventions for immigration entry screening:	1) Immigrants at entry to Canada (mean age 35 years) 2) Close and causal contacts (mean age 35 years)	—State transition model, 4 health states: non-infected, recent LTBI, long-standing LTBI, and active TB —Prevalence of LTBI different between 2 screened cohorts, and dependent on the incidence of TB —Diagnostic and treatment activities completed at the end of the first year
	Perspective: not clearly reported[a]	• CXR (chest x-rays)	Both populations stratified by: • Incidence of TB in the home country, divided into 3 subcohorts: low, intermediate, and high incidence of TB (with 2/60/120 active TB cases per 100,000 persons, respectively) • BCG vaccination status	—Medical evaluation for positive results (TST, cut-off > 10 mm or QFT) included: initial clinic visit, consultation, chest x-ray, and blood test —People with active TB or LTBI received full or preventative TB therapy with INH —Costs of treating TB (active or infection) included
	Time horizon: 20 y Discount rate: 3%	• TST • QFT (IGRA)[b] • TST followed by QFT [b] if TST-positive	All cohorts assumed to be HIV-negative	Test accuracy, TST/QFT: • Sn, TST/QFT: 0.95 • Sp, TST by BCG-vaccination status: 1) non-BCG vaccinated: 0.98 2) vaccinated in infancy: 0.92 3) vaccinated in older age: 0.60 • Sp, QFT: 0.98, regardless of BCG vaccination status
		2) Interventions for contact screening: • TST • QFT (IGRA)[b]		Test, unit cost (CAD 2004) • CXR: $25.74 • TST: $12.73 • QFT: $41.32[b]
		3) Comparator for both cohorts: • No screening		

Author, year, country	Study and analysis characteristics	Interventions and comparator	Populations	Model description and main inputs
Marra et al, 2008[80] Canada	Cost-effectiveness analysis, Markov (state-transition) model	1) Interventions[c]:	Contacts (age ≥ 20 y) with undiagnosed LTBI exposed to confirmed or suspected cases of active TB Population divided in subgroups by: 1) BCG vaccination status: positive, negative, and unknown 2) Ethnicity: foreign-born, non-aboriginal Canadian-born, and Aboriginal	–Diagnostic tree followed by state-transition model with several Markov submodels: reactivation of TB (describes 4 health states: at-risk of reactivation, active TB, previous TB, and dead), active TB (health states not described), healthy (health states not described) –Accounted for secondary spread of TB from each active TB case, diagnostic assessments, and treatment of active TB or LTBI with INH: compliance, costs, and side effects –Most data inputs based on BC CDC registry
	Perspective: third party payer (British Columbia) Time horizon: 20 y Discount rate: 3%	• *QFT-G (IGRA)*[d] • Medical evaluation same as for TST alone (second test is QFT) • Sequential TST/QFT-G: TST followed by QFT-G[d] • Medical evaluation: TST-positive further testing with QFT-G and begin the treatment for LTBI if positive result confirmed TST-negative at first TST, then a second TST after 8 to 12 wk TST is positive and QFT-G is negative or QFT-G indeterminate (2%): QFT-G was the second test, done 8 to 12 wk later 2) Comparator: • TST alone (current practice): • Medical evaluation: TST-positive (cut-off > 5 mm) included: clinic visits, CXR, additional follow-up and workup if CXR+ (active TB case) TST negative: second TST test after 8 to 12 wk	Population assumed to be HIV-negative Close and casual contacts were not separately modeled (weighted proportion average used, based on BC data)	Test accuracy, TST/QFT by ethnicity, and BCG-vaccination status: • Sn, TST or QFT-G: 0.99 • Sp, TST: ○ Canadian-born, BCG- (+): 0.685 ○ Foreign-born, BCG (+): 0.608 ○ Aboriginal, BCG (+): 0.608 ○ Canadian-born, BCG (-): 0.999 ○ Foreign-born, BCG (-): 0.990 ○ Aboriginal, BCG (-): 0.999 Sp, QFT-G: 0.96, regardless of BCG-vaccination status or ethnicity Test, unit cost (2005 CAD): • TST: $25.41 • QFT-G[d]: $45.32

Author, year, country	Study and analysis characteristics	Interventions and comparator	Populations	Model description and main inputs
Campbell et al, 2017[79] Canada	Cost-effectiveness analysis, discrete-event simulation model	1) Interventions[e]:	Two populations: 1) Flagged for post-landing medical surveillance: a subgroup of the whole 2014 cohort of new permanent residents of Canada (n = 6,100, ~2.4% of the total; mean age: NR) –Flagging for surveillance based on age and TB incidence in the country of origin and BCG vaccination status (numbers derived from Ontario data) 2) Whole cohort: all new permanent residents of Canada who immigrated in 2014 (N = 260,600, mean age: NR) (this group was examined in sensitivity analysis and the results between the 2 cohorts were compared)	–Discrete-event simulation model simulating individual event pathways for immigrants after arrival to Canada; part of the full cohort was being flagged for surveillance (2.4%) –Initial part of the model accounted for the completion of screening for LTBI with TST or IGRA –4 health states after the screening: either healthy or with LTBI (considered healthy), transitioning from these states to: • active TB (from LTBI or healthy) • healthy (from TB) • dead (due to TB, adverse event of therapy [hepatotoxicity] or background mortality) –The model accounted for adherence to screening, incompletion of TST, treatment of LTBI (medical evaluation, treatment with INH or RIF—the medication effectiveness, side effects, and costs) –The model accounted for reactivation of LTBI, relapse from active TB, and people and secondary transmission
	Perspective: Third party payer (British Columbia [BC]) Time horizon: 10 y Discount rate: 1.5%	• *IGRA/INH*[f]: IGRA • IGRA-positive followed by 9 months of treatment with INH • IGRA/RIF: IGRA • IGRA-positive followed by 4 mo of treatment with RIF • Sequential TST/IGRA/INH (SEQ/INH): sequential testing, TST first, followed by IGRA for confirmation of TST-positive test • Test-positive: 9 mo of INH		–LTBI prevalence estimated by the TB incidence in the country of origin (4 categories) for people under surveillance (flagged cohort) and those who were not flagged –The model accounted for the probability of BCG vaccination depending on LTBI prevalence and number of cases: 93.8% if > 30 cases, or 0.605 if < 30 cases Test accuracy, TST and IGRA • Sn, TST: 0.78 ○ Completion of TST: 72% • Sn IGRA: 0.89

Author, year, country	Study and analysis characteristics	Interventions and comparator	Populations	Model description and main inputs
		• Sequential TST/IGRA/RIF (SEQ/RIF): sequential testing, TST followed by IGRA in TST-positive • Test-positive: 4 mo of RIF • TST/RIF: TST alone • TST-positive (≥ 10 mm) followed by 4 mo of RIF • No intervention: no testing 2) Comparator: • TST/INH: TST alone • TST-positive (≥ 10 mm) followed by 9 mo of INH		• Sp, TST: ○ BCG−(+): 0.602 ○ BCG− (−): 0.974 • Sp, IGRA: 0.957 • IGRA, indeterminate: 6% Test, unit cost (2016 CAD) • TST, completed: $31 ○ $11 tuberosol ○ $20 (2 visits by nurses) • TST, incomplete: $21 • IGRA[f]: $54.00
Campbell et al, 2019[77] Canada	Cost-effectiveness analysis, discrete-event simulation model	1) Interventions (same as in the 2017 study): • IGRA/INH • IGRA/RIF • Sequential TST/IGRA/INH (SEQ/INH) • Sequential TST/IGRA/RIF (SEQ/RIF) • TST/RIF • TST/INH	Prospective migrants with permanent resident status coming from countries (mean age: NR; assumed age distribution of permanent residents to Ontario/Canada in 2014)	–Similar discrete-event simulation model as in the prior 2017 study, some model inputs updated
	Perspective: third party payer (British Columbia) Time horizon: 25 y Discount rate: 3%	2) Comparator: no intervention (no testing) –Only CXR and treatment if needed For our review, we estimated ICER/INB for TST options vs. IGRA options and we could not use sn results because the comparator was different	Classified into 4 categories (n of cases of active TB/100,000/y), same as in prior 2017 study: • low TB incidence: < 30 • moderate TB incidence: > 30 and < 100 • high TB incidence: > 100 and < 200 • very high TB incidence: > 200 Populations of interest were further adjusted for patient age, BCG vaccination status, chest radiograph results, and LTBI prevalence	–Estimated LTBI prevalence by country of origin for 4 populations: same estimates as reported in prior paper for the whole cohort of interest Same input estimates as in the 2017 study for: –Test accuracies: Sn and Sp of TST/IGRA –Test costs –Costs of treatments (INH/RIF) –Utility values Updated inputs: 1) 4 types of populations, their characteristics further adjusted to the prevalence of abnormal CXR results based on a reference cohort of permanent residents who came to Ontario during the period 2002–2011

Author, year, country	Study and analysis characteristics	Interventions and comparator	Populations	Model description and main inputs
				2) TST completion assumed to be 100% 3) Higher efficacy of LTBI treatment with INH and RIF 4) Different discount rate 5) Longer time horizon
Campbell et al, 2019 [78] Canada	Cost-effectiveness analysis, discrete-event simulation model	1) Interventions:	People who migrated to Canada who have had 1) diagnosed late-stage CKD and/or 2) initiated dialysis therapy	–Discrete-event simulation model accommodated modeling of multiple competing events for each individual alongside the clinical pathway. Individuals were screened for LTBI with TST or IGRA, and then treated for LTBI with INH if they tested positive. The model accounted for acceptance of screening (0.77), adherence to INH therapy and medical evaluation, INH effectiveness, side effects, and its costs –4 health states after screening: late-stage CKD, dialysis, active TB, and dead (all-cause or TB-specific [active TB alone or hepatotoxicity because of INH therapy])
	Perspective: third party payer (British Columbia)	• IGRA/INH[f]: IGRA • IGRA-positive followed by 9 mo of treatment with INH (INH is the best treatment option for CKD population)	Mean age was not reported, but patients were stratified into 2 age groups: < 60 y and ≥ 60 y	–Inputs related to patient characteristics and treatment were obtained from BC admin data (competing-risk analysis applied to administrative data, with 3 outcomes: active TB, dialysis [in the case of those with late-stage CKD], and death)
	Time horizon: 5 y Discount rate: 1.5%	• TST/INH: TST alone • TST-positive (≥ 10 mm) followed by 9 mo of INH	Classified into 4 categories (n of cases of active TB/100,000/y): • low TB incidence: < 30 • moderate TB incidence: > 30 and < 100 • high TB incidence: > 100 and < 200 • very high TB incidence: > 200	–Multi-state utilities: CKD (0.66), dialysis (0.62), and event of hospitalization (0.4) adjusted for the diagnosis of LTBI (1) and treatment of LTBI (side-effects of INH: 0.8) or active TB (0.75)

Author, year, country	Study and analysis characteristics	Interventions and comparator	Populations	Model description and main inputs
		2) Comparator: no intervention (no testing) Only CXR and treatment if needed –For our review, we estimated ICER/INB for TST options vs IGRA options and we could not use sn results because the comparator was different	Admin database linkages were used to identify the patient cohort and their characteristics Further adjustment made for diagnosis of diabetes, use of immunosuppressants, or diagnosis of HIV (immunocompromised effects), BCG vaccination status, and LTBI prevalence	Test accuracy: IGRA or TST • Sn, TST (specific to CKD/dialysis): 0.651/0.519 ○ Completion of TST: *P* = .913 • Sp, TST: ○ BCG−(+): 0.602 ○ BCG− (−): 0.974 • Sn, IGRA (specific to CKD/dialysis): 0.780/0.670 • IGRA indeterminate (specific to CKD/dialysis): 4.1%/6.7% • Sp, IGRA: 0.957 Tests, unit cost, CAD (2016): same as in 2017 study

Abbreviations: BCG, bacillus Calmette-Guérin; CXR, x-ray; IGRA, interferon-gamma release assay; INH, isoniazid; LTBI, latent tuberculosis infection; NR, not reported; QFT, QuantiFERON-TB Gold; RIF, rifampin; Sn, sensitivity; Sp, specificity; TB, tuberculosis; TST, tuberculin skin test.

[a]Oxlade et al[81] did not clearly define and report the perspective: costs included government, health system costs (relevant to Ontario), and out of pocket costs (type of cost not clearly reported).

[b]Oxlade et al[81]: IGRA test was QuantiFERON-TB Gold, the test cost included the manufacturer's current unit cost for the test plus tax ($19.00; 2004 CAD), and costs for clinical personnel, transportation, laboratory personnel, and reporting ($22.32; 2004 CAD).

[c]Marra et al[80]: strategies were further categorized by population subgroups (BCG vaccination status) and ethnicity (foreign-born, non-aboriginal Canadian-born, and Aboriginal). Results were reported by the subgroup, and per strategy.

[d]Marra et al[80]: IGRA test was QuantiFERON-TB Gold, the test costs included staff time, equipment, consumables, and commercial kits (a total of $45.32, 2005 CAD).

[e]Campbell et al[79]: IGRA and TST diagnostic strategies followed by treatment with INH or RIF. In the original paper, no testing strategy included as an intervention strategy and compared with TST/INH. We focused on reporting the results for the comparison between IGRA and TST strategies.

[f]Campbell et al[79]: IGRA test was not specified (QFT or T-SPOT). The test accuracy based on the source including both types of IGRA tests. The test cost was based on the cost of QuantiFERON-TB Gold. It was referenced back to Marra et al[80] (BC CDC) and it included the cost of kit and labor ($47) and nurse visits ($7), for a total of $54 (2016 CAD).

Table A4: Characteristics of Studies Included in the Economic Literature Review: Results

Author, year, country	Results		
	Health outcomes	**Costs**	**Cost-effectiveness**
Oxlade et al, 2007[81] Canada	Incremental effectiveness, TST vs. QFT: future active TB cases prevented with (reported only for immigrant entry screening):	Total mean cost and incremental cost (estimated from reported data, only for IGRA and TST strategies, immigrant entry screening by BCG status) per 1,000 people; CAD (2004)	**1) Immigrant entry screening** (reporting only results relevant to TST and QFT): compared to TST alone, QFT alone was equally effective and associated with cost savings in people who were BCG-vaccinated in older ages (TST specificity: 60%), regardless of incidence of TB from various countries. For people who were BCG vaccinated in infancy or not vaccinated, QFT was more expensive. Incremental costs ranged from $16,110 to $35,790.
	QFT or TST screening, country with low/intermediate/high TB incidence: 0.05/1.3/2.1, respectively; incremental effectiveness = 0; same values for both strategies]	TST alone, country with low/intermediate/high TB incidence (BCG non-vaccinated, Sp: 0.98), total mean cost: $30,320/$267,250/$423,250	**Sequential screening with TST followed by QFT vs. TST** alone was equally effective in low-incidence countries, but less effective in countries with intermediate or high incidence of TB: intermediate, 1.3 (TST) and0.05 (IGRA/SEQ) = 12.5 active TB cases averted with TST; high: 2.1–0.05 = 2.05 active TB cases averted with TST.
	TST, followed by QFT if TST is positive All countries reported as 0.05	TST alone, country with low/intermediate/high TB incidence (BCG vaccinated in infancy, Sp: 0.92), total mean cost: $48,810/$279,390/$431,060	**Sequential testing (QFT only in people who were TST-positive)** would result in savings in populations with a low prevalence of TB infection and in those who were BCG-vaccinated when older (TST specificity low, 60%); in these populations, ICER was cost saving (low),$49,498/12.5 = $3,959.84 per active TB case averted (intermediate), and $14,598/12.5 = $7,120.97 per active TB case averted (high).
		TST alone, country with low/intermediate/high TB incidence (BCG vaccinated, older ages, Sp: 0.60), total mean cost: $129,660/$332,520/$465,260	**2) Contact screening**: no mean cost data was reported for TST and QFT strategies, so we were unable to estimate the difference of QFT vs. TST, compared to no screening. Close contact testing, QFT or TST, was cost saving (smaller savings among contacts originally from high-incidence TB countries [high prevalence of prior LTBI associated with protective effect against disease following re-infection]). QFT was more cost-effective than TST in close and casual contacts who had received BCG vaccination after infancy because of reduced TST specificity.
		QFT alone, country with low/intermediate/high TB incidence (Sp: 0.98), total mean cost: $64,920/$303,020/$459,040	Additional deterministic analyses varied the QFT sensitivity for active disease (0.70–0.90) and the discount rate (0%–6%) and found no impact on the findings and no change in relative order of the screening strategies in any of the populations or scenarios.
		TST followed by QFT in people who are TST-positive, country with low/intermediate/high TB incidence (non-vaccinated, TST Sp: 0.98), total mean cost: $27,369/$283,022/$450,662	Probabilistic sensitivity analysis: not done.
		TST followed by QFT in people who are TST-positive, country with low/intermediate/high TB incidence (vaccinated in infancy, TST Sp: 0.92), total mean cost: $30,793/$285,281/$452,115	

Author, year, country	Results		
	Health outcomes	**Costs**	**Cost-effectiveness**
		TST followed by QFT if TST-positive, country with low/intermediate/high TB incidence (vaccinated, older ages, TST Sp: 0.60), total mean cost: $45,827/$295,164/$458,475 QFT alone vs. TST alone, country with low/intermediate/high TB incidence (non-vaccinated, TST Sp: 0.98), incremental cost: $34,600/$35,770/$35,790 QFT alone vs. TST alone, country with low/intermediate/high TB incidence (BCG-vaccinated in infancy, TST Sp: 0.92), incremental cost: $16,110/$23,630/$27,980 QFT alone vs. TST alone, country with low/intermediate/high TB incidence (BCG vaccinated, older ages, TST Sp: 0.60), incremental cost: savings (−$64,740/−$29,500,−$6,220) TST/QFT vs. TST alone, country with low/intermediate/high TB incidence (non-vaccinated, TST Sp: 0.98), incremental cost: −$2,951/$15,772/$27,412 TST/QFT vs. TST alone, country with low/intermediate/high TB incidence (BCG-vaccinated in infancy, TST Sp: 0.92), incremental cost: −$21,441/$3,632/$19,602 TST/QFT vs. TST alone, country with low/intermediate/high TB incidence (BCG vaccinated, older ages, TST Sp: 0.60), incremental cost: savings (−$102,291/−$49,498/(−$14,598)	
Marra et al, 2008[80] Canada	Incremental effectiveness of 8 QFT-G interventions, QALYs (active TB cases averted) compared with TST alone (15.1143 QALYs [0.012 active TB cases averted])	Incremental cost (compared with TST alone: $442.6), per person (2005 CAD)	ICER and incremental net monetary benefit (INMB at WTP of $50,000/QALY gained): best option is QFT-G in BCG-positive contacts, TST for others; ICER is cost saving (dominant), INMB = $3.70 (the highest value of all).
	QFT-G in BCG-positive contacts, TST for others: 0.0001 QALYs (No. of active TB cases averted not reported clearly)	QFT-G in BCG-positive contacts, TST for others: –$0.61	QFT-G for all: ICER: $79,443 per QALY and INMB= –$11.15 (negative value indicates not cost-effective at $50,000/QALY).

Author, year, country	Results		
	Health outcomes	**Costs**	**Cost-effectiveness**
	TST/QFT-G in BCG-positive contacts, TST for others: 0.0000 QALY	TST/QFT-G in BCG-positive contacts, TST for others: –$2.54	Authors conclusions: the most economically attractive strategy is to administer QFT-G in BCG-vaccinated contacts and to reserve TST for all others (INMB = $3.70 CAD/contact). The least cost-effective strategy was QFT-G for all contacts.
	QFT-G in foreign born, aboriginal, and BCG-positive contacts, TST in others: 0.0002 QALYs	QFT-G in foreign born, aboriginal, and BCG-positive contacts, TST in others: $5.00	Deterministic sensitivity analysis/scenarios: QFT-G for all with positive INMB (cost-effective) if prevalence of LTBI up to 30% (vs. 10% in reference case), single-step QFT-G (fast-conversion), higher rate of start and completion of LTBI treatment (75% vs. 61%), a higher rate of TB reactivation (0.24–0.60% vs. 0.18–0.55% in base case), higher WTP (> $100,000/QALY vs. $50,000/QALY).
	QFT-G in foreign-born and aboriginal, TST for Canadian-born: 0.0001 QALYs	QFT-G in foreign-born and aboriginal, TST for Canadian-born: $5.58	The cost of QFT-G on the INMB of the optimal strategy: below the threshold price of QFT-G of $57, none of QFT-G interventions was cost-effective.
	TST/QFT-G in foreign-born, aboriginal, and BCG-positive contacts, TST in others: 0.0000 QALY	TST/QFT-G in foreign-born, aboriginal, and BCG-positive contacts, TST in others: –$1.67	Diagnostic accuracy of QFT-G: as long as Sn was >80%, the optimal strategy remained cost-effective even if Sp of QFT-G = 90%.
	TST/QFT-G in foreign-born and aboriginal, TST for Canadian-born: 0.0000 QALY	TST/QFT-G in foreign-born and aboriginal, TST for Canadian-born: –$0.67	Probabilistic sensitivity analysis: not done.
	TST/QFT-G for all: −0.0001 QALYs	TST/QFT-G for all: $5.34	
	QFT-G for all: 0.0004 QALYs	QFT-G for all: $30.08	
Campbell et al, 2017[79] Canada	Mean and incremental effectiveness of IGRA interventions (compared with TST/INH), expressed as QALYs or active TB cases averted (per population) for “flagged” cohort for immigration TB medical surveillance (n = 6,100)	Mean and incremental cost (compared with TST/INH), per population (flagged cohort, n = 6,100); CAD (2016)	ICER: flagged cohort: best options, IGRA/INH and IGRA/RIF, ICER: cost saving (dominant vs. TST/INH); INMB higher with IGRA/RIF than with IGRA/INH ($753,658 vs. $676,330); SEQ/INH or SEQ/RIF less effective and less costly. ICERs, $1.06 million/QALY and $308,919/QALY; WTP assumed for any intervention being cost-effective: $100,000/QALY or $20,000/TB case averted (mean cost of treating TB).
	TST/RIF, flagged cohort: total TB cases (and change in TB cases vs. TST/INH) and total QALYs (change in QALY): TB cases: 100.58 (1.17); QALYs: 45,025.4 (−0.7)	TST/RIF, flagged cohort: total mean cost (change in cost vs. TST/INH): $2,914,913 (−$222,762)	In analysis for the whole cohort (N = 260,600), none of the interventions were less costly, or cost-effective compared with the reference case with TST/INF for those flagged for TB medical surveillance: ICERS > $100,000/QALY.
	IGRA/INH, flagged cohort: total TB cases (and change in TB cases vs. TST/INH) and total QALYs (change in QALY): TB cases −92.70 (−6.71); QALYs 45,030.9 (4.8)	IGRA/INH, flagged cohort: total mean cost (change in cost vs. TST/INH): $2,946,383 (−$191,292)	If completion of treatment improved by 30% and there were 100% adherence to surveillance after screening, then INMb would be higher (adding more QALYs), but there would be added costs of screening and treatment with IHN as compared to treatment with RIF so that there would be no cost saving seen with IGRA/INH and only with IGRA/RIF. Thus, IGRA/RIF would remain as most cost-effective.

Author, year, country	Results		
	Health outcomes	**Costs**	**Cost-effectiveness**
	IGRA/RIF, flagged cohort: total TB cases (and change in TB cases vs. TST/INH) and total QALYs (change in QALY): TB cases 94.51 (−4.90); QALYs 45,030.1 (4.0)	IGRA/RIF, flagged cohort: total mean cost (change in cost vs. TST/INH): $2,784,661 (−$353,014)	Deterministic sensitivity analysis: IGRA/RIF would have negative INMB (not cost-effective at WTP of $100,000/QALY) if TST Sn and Sp increased to 0.95 (vs. 0.78 in the reference case) and 1 (vs. 0.60 in the ref case), respectively, or if TST completion was 100% (vs. 0.72 in the reference case); same if cost of IGRA was assumed to be $62 (vs. $54 in the reference case) or cost of treatment with RIF was assumed to be $686 (vs. $575 in the reference case), when healthy HSU was 1.0 (vs. 0.81 in the reference case, assumed to be the same as for LTBI), probability of dying from TB was twice as high (reference case: 4.7% vs. 8%), probability of indeterminate IGRA was higher (reference case: 6% vs. 18%), completion of medical evaluation after screening lower (reference case: 78% vs. 60%); completion of therapy with RIF was lower (reference case: 81.4% vs. 70%), proportion of BCG-vaccinated was lower in people at high-risk of LTBI (prevalence ≥ 30 cases/100,000): reference case: 94% vs. 50%
	SEQ/INH, flagged cohort: total TB cases (and change in TB cases vs. TST/INH) and total QALYs (change in QALY): TB cases 100.58 (1.17); QALYs 45,025.8 (−0.3)	SEQ/INH, flagged cohort: total mean cost (change in cost vs. TST/INH): $2,853,649 (−$284,026)	Probabilistic sensitivity analysis: 1) flagged cohort analysis: best option, IGRA/RIF had a probability of being cost-effective of 99.4% at a WTP of $10,000/QALY gained, lowering to about 97% at $40,000/QALY gained, and to 64.9% at $100,000/QALY gained
	SEQ/RIF, flagged cohort: total TB cases (and change in TB cases vs. TST/INH) and total QALYs (change in QALY): TB cases 101.73 (2.32); QALYs 45,016.0 (−1.3)	SEQ/RIF, flagged cohort: total mean cost (change in cost vs. TST/INH): $2,756,316 (−$381,359)	The whole cohort: in efficiency frontier analysis, IGRA/RIF for all immigrants maximized QALYs. In migrants from countries ≥ 30 cases/100,000, IGRA/RIF was the most cost-effective option in deterministic analysis with a probability of being cost-effective of 43.3% at a WTP of $100,000 per QALY; however, use of SEQ/RIF in migrants from countries ≥ 200 cases per 100,000 had the highest probability of being cost-effective at a threshold of 47.8%
	TST/INH, flagged cohort: total TB cases and total QALYs (change: NA), comparator: TB cases 99.41 (NA, 0); QALYs 45,026.1 (NA, 0)	TST/INH, flagged cohort: total mean cost (change in cost NA), comparator : $3,137,675 (NA, 0)	
Campbell et al, 2019[77] Canada	Mean and incremental effectiveness of IGRA interventions (compared with TST/RIF estimated by us), expressed as QALYs per 1,000 persons; categorized by 4 population subgroups based on incidence of TB in migrants'/backhome countries: 1) low TB incidence; 2) moderate TB incidence; 3) high TB incidence; and 4) very high TB incidence	Mean and incremental cost (compared with TST/RIF, estimated), per 1,000 persons; CAD (2016)	Our best estimates when comparing vs. TST/RIF, for migrants coming from countries with: 1) low TB incidence: all IGRA options with more QALYs and less costly than TST, but SEQ/RIF offers the most QALYs and most savings; 2) moderate TB incidence: all IGRA options with less QALYs and less costly than TST, but cost-effective because the INBs for all comparisons were positive (at WTP of $50,000/QALY); SEQ/RIF, and IGRA/RIF with the highest cost savings and the highest INBs; 3) high TB incidence: all IGRA options were cost-effective vs. TST, with SEQ/RIF, IGRA/RIF, and SEQ/INH with more QALYs and cost savings and IGRA/INH, with more QALYs and additional costs (INB > 0; ICER: ~$27,000/QALY); 4) very high TB incidence: all IGRA options were cost-

Author, year, country	Results		
	Health outcomes	Costs	Cost-effectiveness
			effective (INB > 0); only IGRA/RIF with additional QALYs and cost savings.
	Low TB incidence: total QALYs (change in QALYs vs. TST/RIF, estimated) for SEQ/RIF, −13,761.3 (0.65); SEQ/INH, 13,761.08 (0.43); IGRA/RIF, 13,761.22 (0.57); and IGRA/INH, 13,761.07 (0.42)	Low TB incidence, total mean costs (change in costs vs. TST/RIF, estimated) for: SEQ/RIF, 60,996 (−59,914); SEQ/INH, 67,309 (−53,601); IGRA/RIF, 80,107 (−40,803); and IGRA/INH, 91,056 (−29,854)	Based on our own estimation, the most cost-effective options when sequentially comparing IGRA options for migrants coming from countries with: 1) low TB incidence: SEQ/RIF; 2) moderate TB incidence: SEQ/RIF; ICER of IGRA/RIF vs. SEQ/RIF = $23,620/QALY); 3) high TB incidence: SEQ/RIF and IGRA/RIF, ICER of IGRA/RIF vs. SEQ/RIF = $10,161/QALY; and 4) very high TB incidence: IGRA/RIF.
	Moderate TB incidence: total QALYs (change in QALYs vs. TST/RIF, estimated) for: SEQ/RIF, −13,736.36 (−0.48); SEQ/INH, 13735.71 (−1.13); IGRA/RIF, 13736.66 (−0.18); and IGRA/INH, 13736.69 (−0.15)	Moderate TB incidence, total mean costs (change in costs vs. TST/RIF, estimated) for: SEQ/RIF, 121,950 (−84,195); SEQ/INH, 142,739 (−63,406); IGRA/RIF, 129,036 (−77,109); and IGRA/INH, 154,804 (−51,341)	Results of deterministic or PSA presented vs. no intervention (no testing), based on reported data unable to explore drivers of cost-effectiveness of IGRA strategies vs. TST strategies.
	High TB incidence: total QALYs (change in QALYs vs. TST/RIF, estimated) for: SEQ/RIF, 13,704.93 (0.58); SEQ/INH, 13,704.38 (0.03); IGRA/RIF, −13,705.48 (1.13); and IGRA/INH, 13,704.93 (0.58)	High TB incidence, total mean costs (change in costs vs. TST/RIF, estimated) for: SEQ/RIF, 194,289 (−53,199); SEQ/INH, 231,835 (−15,653); IGRA/RIF, 199,878 (−47,610); and IGRA/INH, 263,572 (16,084)	
	Very high TB incidence: total QALYs (change in QALYs vs. TST/RIF, estimated) for: SEQ/RIF, −13,670.25 (−0.07); SEQ/INH, 13,671.23 (0.91); IGRA/RIF, 13,671.50 (1.18); and IGRA/INH, -13,671.02 (0.70)	Very high TB incidence, total mean costs (change in costs vs. TST/RIF, estimated) for: SEQ/RIF, 263,628 (−54,394); SEQ/INH, 318,435 (410); IGRA/RIF, 268,840 (−49,185); and IGRA/INH, 337,716 (19,691)	
	TST/RIF, comparator of interest for our evaluation (TST/INH was dominated by TST/RIF in all for populations: higher costs and lower QALYs), mean QALYs: 1) low incidence: 13,760.65; 2) moderate TB incidence: 13,736.84; 3) high TB incidence: 13,704.35; 4) very high TB incidence: 13,670.32	TST/RIF, total mean costs (change in costs: NA) for: 1) low TB incidence: 120,910; 2) moderate TB incidence: 206,145; 3) high TB incidence: 247,488; 4) very high TB incidence: 318,025	
	TST/INH, comparator of interest for our evaluation (TST/INH was dominated by TST/RIF in all for populations), mean QALYs: low incidence: 13,760.59; moderate TB incidence: 13,735.98; high incidence:13,704.15; very high incidence: 13,669.91	TST/INH, total mean costs (change in costs: NA) for: 1) low TB incidence: 162, 233; 2) moderate TB incidence: 277,998; 3) high TB incidence: 348,686; 4) very high TB incidence: 415,877	

Author, year, country	Results		
	Health outcomes	**Costs**	**Cost-effectiveness**
Campbell et al, 2019[78] Canada	Mean effectiveness, expressed as QALYs per person, 1) people starting with dialysis, and 2) those with late-stage CKD; categorized by 2 age groups and 4 population subgroups (low, moderate, high, and very high) based on incidence of TB	Mean cost, per person; CAD (2016)	When compared to TST for all people < 60 y, and those people ≥ 60 y who have late-stage CKD or who are initiating dialysis, IGRA was associated with more QALYs (small increments) and lower costs, and, therefore was cost saving (the original analysis compared TST and IGRA vs. no screening only).
	IGRA/INH, in dialysis, age < 60 y, total mean QALY: low TB incidence: 2.79946; moderate TB incidence: 2.77393; high TB incidence: 2.79260; and very high TB incidence: 2.78464	**IGRA/INH**, in dialysis, age < 60 y, total mean cost: low TB incidence: $148.22; moderate TB incidence: $555.95; high TB incidence: $656.54; very high TB incidence: $1,063.92	PSA, cost-efficiency frontier for IGRA, people in dialysis: IGRA screening at a willingness-to-pay threshold of $100,000 was highly probable to be the most cost-effective option, with probabilities > 79% among those > 60 y from countries with moderate, high, or very high TB incidence
	TST/INH, in dialysis, age < 60 y, total mean QALY: low TB incidence: 2.79932; moderate TB incidence: 2.77337; high TB incidence: 2.79189; very high TB incidence: 2.78347	**TST/INH**, in dialysis, age < 60 y, total mean cost: low TB incidence: $203.50; moderate TB incidence: $663.30; high TB incidence: $759.94; very high TB incidence: $1,165.36	PSA, cost-efficiency frontier for IGRA, people in late-stage CKD: IGRA screening at a willingness-to-pay threshold of $50,000 was highly probable to be the most cost-effective option, with probabilities > 75%–80% for both groups coming from countries with moderate, high, or very high TB incidence
	IGRA/INH, in dialysis, age ≥ 60 y, total mean QALY: low TB incidence: 2.30436; moderate TB incidence: 2.23593; high TB incidence: 2.25267; very high TB incidence: 2.22301	**IGRA/INH**, in dialysis, age ≥ 60 y, total mean cost ($): low TB incidence: 122.96; moderate TB incidence: 477.11; high TB incidence: 561.89; very high TB incidence: 973.03	Results of deterministic or PSA presented vs. no intervention (no testing); based on reported data; unable to explore drivers of cost-effectiveness of IGRA strategies vs. TST strategies.
	TST/INH, in dialysis, age ≥ 60 y, total mean QALY: low TB incidence: 2.30425; moderate TB incidence: 2.23534; high TB incidence: 2.25197; very high TB incidence: 2.22163	**TST/INH**, in dialysis, age ≥ 60 y, total mean cost: low TB incidence: $176.00; moderate TB incidence: $585.22; high TB incidence: $666.85; very high TB incidence: $1,085.25	
	IGRA/INH, late-stage CKD, age < 60 y, total mean QALY: low TB incidence: 2.99247; moderate TB incidence: 2.98910; high TB incidence: 2.98710; very high TB incidence: 2.98398	**IGRA/INH**, late-stage CKD, age < 60 y, total mean: low TB incidence: $90.04; moderate TB incidence: $206.61; high TB incidence: $245.65; very high TB incidence: $364.77	
	TST/INH, late-stage CKD, age < 60 y, total mean QALY: low TB incidence: 2.99243; moderate TB incidence: 2.98893; high TB incidence: 2.98684; very high TB incidence: 2.98352	**TST/INH**, late-stage CKD, age < 60 y, total mean cost: low TB incidence: $140.95; moderate TB incidence: $285.93; high TB incidence: $317.05; very high TB incidence: $410.82	

Author, year, country	Results		
	Health outcomes	**Costs**	**Cost-effectiveness**
	IGRA/INH, late-stage CKD, age ≥ 60 y, total mean QALY: low TB incidence: 2.55380; moderate TB incidence: 2.51397; high TB incidence: 2.53277; very high TB incidence: 2.51147	**IGRA/INH**, late-stage CKD, age ≥ 60 y, total mean cost: low TB incidence: $98.81; moderate TB incidence: $271.95; high TB incidence: $321.74; very high TB incidence: $507.19	
	TST/INH, late-stage CKD, age ≥ 60 y, total mean QALY: low TB incidence: 2.55371; moderate TB incidence: 2.51347; high TB incidence: 2.53229; very high TB incidence: 2.51061	**TST/INH**, late-stage CKD, age ≥ 60 y, total mean cost: low TB incidence: $147.60; moderate TB incidence: $351.18; high TB incidence: $394.09; very high TB incidence: $558.75	

Abbreviations: BCG, bacillus Calmette-Guérin; CKD, chronic kidney disease; IGRA, interferon-gamma release assay; INH, isoniazid; LTBI, latent tuberculosis infection; PSA, probabilistic analysis; QALY, quality-adjusted life year; QFT, QuantiFERON-TB Gold; RIF, rifampin; Sn, sensitivity; Sp, specificity; TB, tuberculosis; TST, tuberculin skin test; WTP, willingness to pay.

Appendix 8: Results of Applicability and Limitation Checklists for Studies Included in the Economic Literature Review

Table A5: Assessment of the Applicability of Studies Evaluating the Cost-Effectiveness of IGRA Versus TST for LTBI

Author, year, country	Is the study population appropriate for the review question?	Are the interventions appropriate for the review question?	Is the system in which the study was conducted sufficiently like the current Ontario context?	Is the perspective of the costs appropriate for the review question (e.g., Canadian public payer)?	Is the perspective of the outcomes appropriate for the review question?	Are all future costs and outcomes discounted appropriately (as per current CADTH guidelines)?	Are QALYs derived using CADTH's preferred methods, or is an appropriate social care–related equivalent used as an outcome? (If not, describe rationale and outcomes used in line with the analytical perspective taken)	Overall judgment[a]
Oxlade et al, 2007[81] Canada	Yes	Yes	Yes	Yes, Canada and Ontario government and limited societal	Yes	Yes, 3% (ranged from 0% to 6%)	No, case prevented	Partially applicable
Marra et al, 2008[80] Canada	Yes	Yes	Yes	Yes, third party payer (BC)	Yes	Yes, 3%	Yes	Directly applicable
Campbell et al, 2017[79] Canada	Yes	Yes	Yes	Yes, third party payer (BC)	Yes	Yes, 1.5%	Yes	Directly applicable
Campbell et al, 2019[77] Canada	Yes	Yes (IGRA could be compared with TST given broken down results)	yes	Yes, third party payer (BC)	Yes	Yes, 3%	Yes	Partially applicable

Author, year, country	Is the study population appropriate for the review question?	Are the interventions appropriate for the review question?	Is the system in which the study was conducted sufficiently like the current Ontario context?	Is the perspective of the costs appropriate for the review question (e.g., Canadian public payer)?	Is the perspective of the outcomes appropriate for the review question?	Are all future costs and outcomes discounted appropriately (as per current CADTH guidelines)?	Are QALYs derived using CADTH's preferred methods, or is an appropriate social care–related equivalent used as an outcome? (If not, describe rationale and outcomes used in line with the analytical perspective taken)	Overall judgment[a]
Campbell et al, 2019[78] Canada	Yes (immunocompromised)	Yes (IGRA could be compared with TST given broken down results)	Yes	Yes, third party payer (BC)	Yes	Yes, 1.5%	Yes	Directly applicable

Abbreviations: CADTH, Canadian Agency for Drugs and Technologies in Health; IGRA, interferon-gamma release assay; QALY, quality-adjusted life-year; TST, tuberculin skin test.

Note: Response options for all items were "yes," "partially," "no," "unclear," and "NA" (not applicable).

[a]Overall judgment may be "directly applicable," "partially applicable," or "not applicable."

Table A6: Assessment of the Limitations of Studies Evaluating the Cost-Effectiveness of IGRA Versus TST for LTBI

Author, year, country	Does the model structure adequately reflect the nature of the health condition under evaluation ?	Is the time horizon sufficientl y long to reflect all important differences in costs and outcomes ?	Are all important and relevant health outcomes included?	Are the clinical inputs[a] obtained from the best available sources?	Do the clinical inputs[a] match the estimates contained in the clinical sources?	Are all important and relevant (direct) costs included in the analysis?	Are the estimates of resource use obtained from the best available sources?	Are the unit costs of resources obtained from the best available sources?	Is an appropriate incremental analysis presented, or can it be calculated from the reported data?	Are all important and uncertain parameters subjected to appropriate sensitivity analysis?	Is there a potential conflict of interest ?	Overall judgment [b]
Oxlade et al, 2007[81] Canada	Yes	Yes	Partially, QALYs not included, but the effectiveness is the same between the TST and IGRA (QFT) strategies	Yes, Sn of TST (cut-off > 10 mm) and IGRA same	Yes	Yes	Yes	Yes	Yes, for migrants - recalculated for contacts not able	Partially, PSA not done	Not reported	Minor Limitations
Marra et al, 2008[80] Canada	Yes	Yes	Yes	Yes, Sn of TST (cut-off > 5 mm, not clearly reported) and IGRA same	Yes	Yes	Yes	Yes	Yes	Yes, PSA not done	No	Minor limitations
Campbell et al, 2017[79] Canada	Yes	Yes	Yes	Yes, Sn of TST (cut-off: > 10 mm) smaller than Sn of IGRA, IGRA/QFT test type not specified	Yes	Yes	Yes	Yes	Yes	Yes, PSA done	No	Minor Limitations
Campbell et al, 2019[77] Canada	Yes	Yes	Yes	Yes, Sn of TST (cut-off: > 10 mm) smaller than Sn of IGRA, IGRA/QFT test type not specified	Yes	Yes	Yes	Yes	Yes, estimated from data (IGRA vs. TST)	Yes, PSA	No	Minor limitations
Campbell et al, 2019[78] Canada	Yes	Yes	Yes	Yes, Sn of TST (cut-off: > 10 mm) smaller than Sn of IGRA	Yes	Yes	Yes	Yes	Yes, estimated from data (IGRA vs. TST)	Yes, PSA done	No	Minor limitations

Abbreviations: Sn, sensitivity; IGRA, interferon-gamma release assay; LTBI, latent tuberculosis infection; PSA, probabilistic analysis, Sn, sensitivity, QALY, quality-adjusted life-year; QFT, QuantiFERON; TST, tuberculin skin test.

Note: Response options for all items were “yes,” “partially,” “no,” “unclear,” and “NA” (not applicable).

[a]Clinical inputs include relative treatment effects, natural history, and utilities.

[b]Overall judgment may be “minor limitations,” “potentially serious limitations,” or “very serious limitations.”

Appendix 9: Economic Evidence—GRADE

Table A7: GRADE Evidence Profile for the Comparison of IGRA and TST—Directly Applicable Economic Studies

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
3 economic studies[78-80] deemed to be directly applicable	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected		⨁⨁⨁⨁ High

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; IGRA, interferon-gamma release assay; NICE, National Institute for Health and Care Excellence; TST, tuberculin skin test.

Note: Assessments done by a single reviewer for directly applicable studies. We used the NICE quality appraisal checklist for economic evaluations, which consists of two sections (Tables A5 and A6, Appendix 8). The quality assessment (Table A6) was used to assess the methodological quality or risk of bias (credibility of the published models and their limitations, including modeling [structural], method, and parameter assumptions), inconsistency, and imprecision of the reported cost-effectiveness estimates (variability in probabilistic and other sensitivity analyses). The applicability assessment (Table A5) was used to examine indirectness (applicability of the study findings to the Ontario context/our question). Study details are described in the main text of the report.

Appendix 10: Estimation of Immunocompromised Population

Table A8: Annual Estimates for Number of People With HIV in Ontario[109]

HIV positive	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	Year 1	Year 2	Year 3	Year 4	Year 5
Actual, first time HIV diagnosis[109]	834	707	666	696	686	716	697	738	683	515					
Actual, past HIV diagnosis[109]	107	113	87	100	112	113	157	201	239	146					
Actual, overall	941	820	753	796	798	829	854	939	922	661					
Forecast	—	—	—	—	—	—	—	—	—	—	797	793	789	785	780

Abbreviation: HIV, human immunodeficiency virus.

Table A9: Annual Estimates for Incident Number of People With End-Stage CKD in Ontario[110]

End-stage CKD	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	Year 1	Year 2	Year 3	Year 4	Year 5
Actual[110]	2,828	2,912	3,039	3,071	3,102	3,285	3,300	3,376	3,308	3,252					
Forecast	—	—	—	—	—	—	—	—	—	—	3,507	3,563	3,618	3,674	3,729

Abbreviation: CKD, chronic kidney disease.

Table A10: Annual Estimates for Number of People With Kidney Transplants in Ontario[110]

Kidney transplants (pediatric and adult recepients)	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	Year 1	Year 2	Year 3	Year 4	Year 5
Actual [110]	521	604	597	730	696	673	747	609	652	699					
Forecast	—	—	—	—	—	—	—	—	—	—	733	745	757	769	782

Table A11: Annual Estimates for Number of People With Cancers in Ontario[111]

Cancer, all sexes and all ages, Ontario	2023	2024	2025	2026	2027	2028
Projection, all non-solid tumors (reference case)	**8,781**	**9,032**	**9,291**	**9,538**	**9,766**	**9,997**
Leukemia	2,872	2,934	3,000	3,057	3,115	3,179
Hodgkin lymphoma	451	458	469	473	483	492
Non-Hodgkin lymphoma	5,458	5,640	5,822	6,008	6,168	6,326
Myeloma	1,844	1,915	1,986	2,056	2,126	2,195
Projection, all cancers combined (Scenario 2)	97,586	99,832	102,080	104,272	106,554	108,823

Appendix 11: Costing Components, Contact and Immigrant Populations: TST and IGRA

The cost and cost components were based on consultations with experts (email and oral expert consultations, E. Rea, MD, R. Khan, RN, P. Galange, MD, January 12 to April 25, 2024). We made a simplifying assumption regarding the share of testing between PHUs and MDs (50%/50% in the reference case). This was tested in sensitivity analysis (see Table A14, Appendix 12, and Scenarios 8 and 9).

Table A12. Costing Components When the Tests Are Requested and Done at an MD's Office

Test	Referral	Blood sampling	Test fee	Test supplies	Need for incubators to transport samples	Transportation of specimens (shipping cost)	Travel time (nurse)
TST	Yes (fee first visit: applied)	No	• First visit, OHIP fee (nurse labour included in the fee) • Second visit: fee for TST reading (2nd visit, OHIP fee, no nurse time)	Yes	NA	No	No
IGRA	Yes (fee applied)	Yes (lab fee)	Yes (list price) Includes all costs: equipment, tubes, supplies, transportation (shipping/ handling)	No (included in test fee)	No	No	No

Abbreviations: IGRA, IGRA, interferon-gamma release assay; NA, not applicable; OHIP, Ontario Health Insurance Plan; TST, tuberculin skin test.

Table A13. Costing components when the tests are requested and done at Public Health Unit (PHU)

Test	Referral	Blood sampling	Test fee	Test supplies	Need for incubators to transport samples	Transportation of specimens (shipping cost)	Travel time (nurse)
TST	No: billing not allowed because of the Medical Act (no physician's fee)	No	• First visit: nurse plants the test (nurse labour time) • Second visit: nurse reads the test (nurse labour time)	Yes	NA	No	Yes, full cost for nurse's time
IGRA	No	Yes (nurse's time)	Yes (list price) Includes all costs: equipment, tubes, supplies, transportation (shipping/handling)	No (included in test fee)	No (already available across the majority of PHU units)	No (established workflow system at PHUs), Shipping/handling separately costed in Scenario 12b	Smaller, half cost assumed

Abbreviations: IGRA, interferon-gamma release assay; NA, not applicable; PHU, public health unit; TST, tuberculin skin test.

Appendix 12: Sensitivity Analysis—Description of Scenarios

Table A14: Summary of Changes in Parameter Input Values or Assumptions in Scenario Analyses Compared With Reference Case

Scenarios	Reference Case	Description of changes (vs. reference case)
Change in population size		
Scenario 1: Number of people in Ontario for testing in immigrant and contact populations estimated from PHO data	Initial population for immigrant and contact populations based on reported demographic data, expected population growth, and expected number of contact investigations (Tables 8A and 8B), details described in the main report Model parameter values and uptakes described in Tables 10–12 and Tables 14A–14C	• Estimate of the initial population size and assumptions described in Appendix 13 • No changes to the model parameter values • No changes to the uptake rates
Scenario 2: Inclusion of all types of cancers in immunocompromised population	Non-solid cancer types included in estimation of immunocompromised population (Table 8C)	• All cancer types included in the estimate (Table 16 and Appendix 10, Table A11) • No changes to the model parameter values • No changes to the uptake rates
Change in uptake rates for IGRA		
Scenario 3: Large uptake in immigrant population (same large uptake for all)	Uptake of IGRA strategies in immigrant population: 3 % per year (3% in Year 1 to 15% in Year 5, Table 14A)	• Change in the uptake of IGRA for immigrant population from 75% in Year 1 to 100% in Year 5, and same uptake as in the reference case for the rest (contacts/ immunocompromised populations: 75%–100%, Tables 14B and 14C) • No change in the population size No changes to the model parameter values
Scenario 4: Same low uptake in all populations	Uptake of IGRA strategies in: • Immigrant population: 3% in Year 1 to 15% in Year 5 (Table 14A) • Contact/immunocompromised populations: 75% in Year 1 to 100% in Year 5 (Tables 14B and 14C)	• Low uptake (5% per year) of IGRA in all populations: 5% in Year 1 to 25% in Year 5 • No change in the population size • No changes to the model parameter values
Scenario 5: Evenly spread uptake for immunocompromised populations	Uptake of IGRA strategies in immunocompromised populations: 75% in Year 1 to 100% in Year 5 (Table 14C)	• Evenly spread uptake (20% per year) of IGRA in immunocompromised populations: 20% in Year 1 to 100% in Year 5, no changes to the uptakes of IGRA for the rest • No change in the population size • No changes to the model parameter values
Scenario 6: Smaller uptake of IGRA for immunocompromised populations	Uptake of IGRA strategies in immunocompromised populations: 75% in Year 1 to 100% in Year 5 (Table 14C)	• Smaller uptake (10% per year) of IGRA in immunocompromised populations: 10% in Year 1 to 50% in Year 5, no changes to the uptake of IGRA for the rest • No change in the population size • No changes to the model parameter values

Scenarios	Reference Case	Description of changes (vs. reference case)
Changes in the testing pathway		
Scenario 7: No cost of referral	If testing is done by MDs, the cost of referral visit included ($23.75, Tables 11A and 11B)	• Parameter value change, referral visit cost: $0 for the referral visit regardless of the setting (MD or PHU) • No changes to other model parameter values • No changes in the population size • No changes to the uptake rates
Scenario 8: Share of TST/IGRA testing between MDs and PHUs	• Immigrant and contact populations: Simplifying assumption of the share—50%/50% between MDs and PHUs; we estimated and adjusted the overall costs of testing (Tables 11A and 11B; reference case: complete TST in immigrants and contacts: $71.23 and $140.74, respectively; IGRA in immigrants and contacts: $124.83 and $159.59, respectively) • Immunocompromised population: no share, 100% done by MDs	• Parameter value change for immigrants and contacts; no share, 100% testing done by PHUs: we used unadjusted costs estimated for PHU setting (Table 11A: TST in immigrants and contacts by PHUs: $68.52 and $207.54, respectively; and Table 11B: IGRA in immigrants and contacts by PHUs: $115.15 and $184.66, respectively) • No change of setting for immunocompromised populations • No changes to other model parameter values • No changes in the population size • No changes to the uptake rates
Scenario 9: All testing for immigrants done by MDs	Immigrant population: simplifying assumption of the share: 50%/50% between MDs and PHUs; we adjusted the overall costs of testing (Tables 11A and 11B; reference case in immigrants: complete TST: $71.23 and IGRA: $124.83)	• Parameter value change for immigrants only, no share between MDs and PHUs, 100% testing done by MDs; we used unadjusted cost estimates for MD setting (Table 11A: TST in immigrants by MDs, $73.94; Table 11B: IGRA in immigrants by MDs, $134.51) • No change of the setting for contact and immunocompromised populations • No changes to other model parameter values • No changes in the population size • No changes to the uptake rates
Scenarios 10: No waste of PPD (no TST vial wastage, consumables, Scenario 10a) or large wastage (80% of the doses in the vial wasted, Scenario 10b) when testing done by MDs	TST cost-adjusted for the wastage of the TST vial if testing done at MDs (Table 11A: TST consumable cost related to PPD: $37.08, 44.4% wastage of the vial)	• Parameter value change for the TST vial wastage (i.e., consumable cost related to PPD): Scenario 10a, no wastage of the vial (Table 11A: TST consumable cost related to PPD: $20.60); Scenario 10b, large (80%) wastage of the vial (TST consumable cost per dose: $103) • No changes to other model parameter values • No changes in the population size • No changes to the uptake rates
Changes in the cost of IGRA		
Scenario 11: Lower cost of IGRA test	Cost of IGRA (list price): $100 per test, the test cost includes all cost components such as equipment, overheads, labour, kits, consumables and shipping and handling	• Parameter value change for the cost of IGRA: the cost decreased by 25% ($75 per test) • No changes to other model parameter values • No changes in the population size • No changes to the uptake rates

Scenarios	Reference Case	Description of changes (vs. reference case)
Scenario 12a: IGRA provided by a hospital lab, with shipping and handling included in the hospital lab IGRA test price	Cost of IGRA (list price): $100 per test, the test cost includes all cost components, such as equipment, overhead, labour, kits, consumables, and shipping and handling	• Parameter value change for the cost of IGRA if done at a hospital lab: $103 per test, the test cost includes all cost components, such as equipment, overhead, labour, kits, consumables, and shipping and handling (Table 17) • No changes to other model parameter values • No changes in the population size • No changes to the uptake rates

Scenario 12b: IGRA provided by a hospital lab, with shipping and handling in PHUs costed separately, and listed in addition to the hospital lab IGRA test price	Cost of IGRA (list price): $100 per test, the test cost includes all cost components, such as equipment, overheads, labour, kits, consumables, and shipping and handling	• Parameter value change for the cost of IGRA if done at a hospital lab with additional inclusion of the cost of shipping and handling:
		  ○ Cost of IGRA: $103 per test, the test cost includes all cost components such as equipment, overheads, labour, kits, consumables, but it does not cover shipping and handling, may be applicable to remote areas (Table 17)
		  ○ Assumed additional cost of shipping and handling for PHUs (Table 17: $6.025 per test)
		• No changes to other model parameter values
		• No changes in the population size
		• No changes to the uptake rates

Change in the probability of reactivation of LTBI into active TB, immunocompromised population		
Scenario 13: high probability of reactivation of LTBI into active TB in immunocompromised populations	Probability of reactivation of LTBI same for all populations and based on the inputs from the literature[79] (Table 10A: 0.0011)	• Parameter value change for the probability of reactivation of LTBI into active TB in immunocompromised populations only • Hypothetical threshold value of 0.30 used in this scenario (Figure 8) • No changes to other model parameter values • No changes in the population size • No changes to the uptake rates

Abbreviations: IGRA, interferon-gamma release assay; LTBI, latent tuberculosis infection; MD, medical doctor (physician); PHU, public health unit; PPD, purified protein derivative; TST, tuberculin skin test.

Appendix 13: Estimation of Immigrant and Contact Subpopulations from Reported LTBI Episodes in Ontario

To estimate the populations of interest, we used unpublished aggregate, non-identifiable data on the number of reported LTBI episodes per year recorded in iPHIS and extracted by and obtained from Public Health Ontario (email communication, A. Saunders, MSc, 01 Apr 2024), PHO Data Request #2024-011,[112] and expert oral and email communications (L. Macdonald, MD, A. Saunders, MSc, M. Whelan, MSc and E. Rea, MD, June 10-14, 2024).

Estimate of Number of People Eligible for LTBI Testing in Ontario

Based on the PHO data (Table A15; as presented in the unpublished report,[112] the annual number of LTBI episodes in Ontario between January 1, 2015 and December 31, 2023 ranged from 4,307 (in 2020) to 7,995 (in 2015). Data reported between 2020 and 2022 should be interpreted with caution because these were pandemic years and access to care, including for TB infection testing and treatment, as well as iPHIS data entry practices were likely impacted by the COVID-19 pandemic response.

For the purpose of estimating the size of immigrant and contact subpopulations in a scenario analysis (sensitivity analysis: Scenario 1), we used the largest estimated annual number of LTBI episodes reported for people born outside of Canada (4,884 LTBIs in 2019). We assumed that this estimate was a true positive estimate for LTBI in Ontario for these populations and used it as a starting point to calculate the overall number of tested immigrants and contacts annually.

Next, we applied the Bayesian approach to diagnostic assessment with TST, and used the published sensitivity and specificity of TST[114] and modelled the prevalence of LTBI in Ontario (among those born outside of Canada)[14] to estimate the number of false-positives and number of test-negative as following:

- The Bayesian formulas for estimation of the test-positive and test-negative results:
    - True positive = (prevalence × sensitivity of TST)/(prevalence × sensitivity of TST) + ([1 – prevalence] × [1 − specificity of TST])
    - False positive = (1 − prevalence) × (1 − specificity of TST)/(prevalence × sensitivity of TST) + ([1 – prevalence] × [1 − specificity of TST])
    - Test positive = (prevalence × sensitivity of TST) + ([1 – prevalence] × [1 − specificity of TST])
    - Test negative = (prevalence × [1 − sensitivity of TST]) + ([1 − prevalence] × specificity of TST)

  where sensitivity of TST (10 mm) was 0.77, specificity of TST was 0.59,[114] and prevalence of LTBI was 0.22.[14]

  Using these formulas, we estimated proportions of true positives (0.346), false positives (0.654), test positives (0.49), and test negatives (0.51). Assuming there would be 4,884 true-positive test results (LTBI episodes for people born outside of Canada in 2019) as the largest reported estimate (excluding missing data; Table A15):

- We estimated 9,232 people with false-positive results and a total of 14,116 people who were testing positive
- We then estimated that 14,692 people tested negative (from the number of people who tested positive: 14,116 × 0.51/0.49)

- Thus, the overall size of tested foreign-born immigrant and contact populations was about 28,808 people

Next, we assumed that the proportion of incomplete TST tests was about 10% (n = 2,881), which increased the total estimate to 31,689 screened people (immigrant and contacts, foreign born):

- For the purpose of estimating the budget impact by subpopulation (immigrant and contact), we assumed that about 37.6% of screened people were identified via contact investigations in 2019 (PHO data request, Table A16), and estimated the size of 2 subpopulations:
  - 11,915 people screened via contact investigations
  - 19,774 people screened via immigration screening

Next, we adjusted these 2 populations for the WHO-reported BCG-vaccination rate of 87%[106] and arrived at a total of 27,569 people to be screened in Year 1: 17,203 immigrants and 10,366 contacts (Table A17).

Lastly, we accounted for a growth rate of 3.4%[105] and estimated a total population of about 147,600 (immigrants and contacts) to be tested over the next 5 years (Table A17).

Limitations of iPHIS Data

Based on expert consultation (oral and email communications, L. Macdonald, MD, A. Saunders, MSc, M. Whelan, MSc and E. Rea, MD, June 10–14, 2024), the iPHIS data that we used for this calculation likely represent underestimates of the true numbers of LTBI episodes in the eligible population for the following reasons:

- We assume that, although notifiable to local public health units in Ontario, not all positive TB infection test results are reported to public health units
- Provider reporting practices may vary considerably
- Missing place of birth information reduced the number of LTBI episodes included in this calculation. Close to 30% of LTBI cases were missing information on place of birth; overall 5% of cases were reported to have been born in Canada, and over 65% of cases were born outside of Canada. Therefore, it could be possible that many of the missing cases were born outside of Canada

In addition, our estimate of the population size for Scenario 1 needs to be interpreted with caution because of additional caveats in iPHIS data reporting and extraction[112]:

- iPHIS is a dynamic disease reporting system that allows ongoing updates to data previously entered. As a result, data extracted represent a snapshot at the time of extraction and may differ from previous or subsequent reports.
- The data only represent cases reported to public health and recorded in iPHIS. As a result, all counts will be subject to varying degrees of underreporting due to a variety of factors, such as disease awareness and medical care–seeking behaviours, which may depend on the severity of illness; access to medical care; clinical practice; or changes in laboratory testing and reporting.
- Overall, LTBI episodes reported in iPHIS may be under-reported by clinicians administering and reading positive TSTs, or be under-recorded in iPHIS, and so may underestimate the number of true positive TSTs performed in Ontario in a given year, even when accounting for the potential

for a small number of these LTBI episodes to have been identified via IGRA rather than TST results.

- LTBI episodes generally do not have a diagnosis status reported in iPHIS; however, those with a diagnosis status entered as ”Does Not Meet Definition” are excluded from the counts.
- Only provincial case classifications listed in the Ontario Ministry of Health surveillance case definitions are included in the report counts. Cases are excluded if they do not meet the provincial case classifications that were in effect at the time that they were reported.
- Cases are reported based on “episode date.” The episode date is an estimate of the onset date of disease for a case. To determine this date, the following hierarchy is in place in iPHIS: Onset Date > Specimen Collection Date > Lab Test Date > Reported Date. If an onset date exists, it will be used as the episode date. If not (or it’s not available), then the next available date in the hierarchy will be used.
- Cases in which the Disposition Status was reported as entered in error, does not meet definition, is a duplicate, or any variation on these values have been excluded.
- Duplicate case records may be included if they were not identified and resolved at either the local or provincial level prior to data extraction from iPHIS.
- The assessment of LTBI varies by health care provider and public health unit. Comparisons of LTBI incidence reported between public health units and the province should be made with caution.

Table A15. Number and Percentage of LTBI Episodes by Origin of Birth and Episode Year: Ontario, 2015–2023

	2015	2016	2017	2018	2019	2020	2021	2022	2023
Origin of birth	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Born outside Canada	**4,375 (54.7)**	**4,641 (58.8)**	**4,799 (60.1)**	**4,826 (61.5)**	**4,884 (65.6)**	**2,736 (63.5)**	**2,521 (58.2)**	**3,313 (59.9)**	**4,075 (58.2)**
Born in Canada	384 (4.8)	432 (5.5)	389 (4.9)	386 (4.9)	372 (5.0)	186 (4.3)	150 (3.5)	187 (3.4)	170 (2.4)
Unknown/missing	3,236 (40.5)	2,825 (35.8)	2,794 (35.0)	2,641 (33.6)	2,191 (29.4)	1,385 (32.2)	1,657 (38.3)	2,029 (36.7)	2,761 (39.4)
Total	**7,995 (100.0)**	**7,898 (100.0)**	**7,892 (100.0)**	**7,853 (100.0)**	**7,447 (100.0)**	**4,307 (100.0)**	**4,328 (100.0)**	**5,529 (100.0)**	**7,006 (100.0)**

Abbreviation: LTBI, latent tuberculosis infection.

Data source: Ontario Ministry of Health. iPHIS (Database; extracted March 4, 2024).[112]

Table A16. Number and Percentage of TSTs Administered, by Reason for Testing and Year Given: Ontario, 2015–2023

	2015	2016	2017	2018	2019	2020	2021	2022	2023
Reason for testing	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Routine screening	5,850 (49.9)	6,015 (48.1)	5,548 (46.0)	5,174 (42.0)	5,175 (43.5)	2,709 (45.1)	3,285 (51.6)	4,230 (51.9)	5,218 (54.7)
Contact tracing	**3,788 (32.3)**	**4,274 (34.1)**	**4,284 (35.5)**	**4,805 (39.0)**	**4,467 (37.6)**	**2,133 (35.5)**	**2,054 (32.3)**	**2,034 (25.0)**	**2,397 (25.1)**
Immigration screening	788 (6.7)	1,051 (8.4)	1,164 (9.7)	1,087 (8.8)	1,192 (10.0)	590 (9.8)	514 (8.1)	1,069 (13.1)	921 (9.7)
Targeted screening	906 (7.7)	751 (6.0)	639 (5.3)	763 (6.2)	613 (5.2)	282 (4.7)	192 (3.0)	400 (4.9)	507 (5.3)
Symptoms	88 (0.8)	77 (0.6)	74 (0.6)	75 (0.6)	67 (0.6)	36 (0.6)	43 (0.7)	31 (0.4)	40 (0.4)
Unknown/missing	295 (2.5)	349 (2.8)	351 (2.9)	427 (3.5)	379 (3.2)	262 (4.4)	273 (4.3)	387 (4.7)	461 (4.8)
Total	**11,715 (100.0)**	**12,517 (100.0)**	**12,060 (100.0)**	**12,331 (100.0)**	**11,893 (100.0)**	**6,012 (100.0)**	**6,361 (100.0)**	**8,151 (100.0)**	**9,544 (100.0)**

Abbreviation: LTBI, latent tuberculosis infection.

Data source: Ontario Ministry of Health. iPHIS (Database; extracted March 4, 2024).[112]

Table A17: Estimation of Immigrant and Contact Subpopulations for Budget Impact, Based on the Reported LTBI Episodes for Ontario and Additional Assumptions

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Forecasted BCG-vaccinated immigrant population for IGRA testing Growth per year: 3.4%, n	17,203	17,788	18,393	19,018	19,665	92,068
Forecasted BCG-vaccinated contact population for IGRA testing Growth per year: 3.4%, n	10,366	10,718	11,083	11,460	11,849	55,477
Total (both populations)	**27,569**	**28,507**	**29,476**	**30,478**	**31,514**	**147,545**

Abbreviations: BCG, Bacillus Calmette-Guerin; IGRA, interferon-gamma release assay; LTBI, latent tuberculosis infection.

Appendix 14: Sensitivity Analysis: Immigrant Subpopulation

Table A18: Budget Impact Results—Sensitivity Analysis: Immigrant Subpopulation

Scenario	Total 5-year budget impact (IGRA strategies vs. TST alone)[a]	
	IGRA alone vs. TST	SEQ: TST/IGRA vs. TST alone
Reference case, total BI, all populations	$2.99	$14.07
Reference case, BI—test cost, all populations	$6.01	$8.28
Reference case, total BI, Immigrant	**−$1.63**	**−$3.45**
Reference case, BI—test cost, Immigrant	$1.09	$0.88
Change in population size		
Scenario 1: Number of people for testing in Ontario based on iPHIS LTBI data obtained from PHO and published LTBI prevalence estimates**,** immigrants, total BI	−$0.73	−$1.54
Scenario 1: BI—test cost	$0.48	$0.39
Scenario 2: all cancer types, Immigrants, total BI[b]	NA	NA
Scenario 2: BI—test cost[b]	—	—
Change in the uptake of IGRA		
Scenario 3: large uptake for all, immigrants (75%, year 1), total BI	−$15.86	−$33.56
Scenario 3: BI—test cost	$10.56	$8.51
Scenario 4: low uptake for all, immigrants (5% per year),total BI	−$2.72	−$5.76
Scenario 4: BI—test cost	$1.81	$1.46
Scenario 5: smaller uptake for immunocompromised (20% per year), immigrants, total BI[b]	NA	NA
Scenario 5: BI—test cost[b]	—	—
Scenario 6: smaller uptake for immunocompromised (10% per year), immigrants, total BI[b]	NA	NA
Scenario 6: BI—test cost[b]	—	—
Change in the testing pathway		
Scenario 7: no cost of referral, immigrants, total BI	−$1.63	−$3.54
Scenario 7: BI—test cost	$1.09	$0.79

Scenario	Total 5-year budget impact (IGRA strategies vs. TST alone)[a]	
	IGRA alone vs. TST	SEQ: TST/IGRA vs. TST alone
Scenario 8: all tests done by PHUs, immigrants, total BI	−$1.77	−$3.52
Scenario 8: BI—test cost	$0.95	$0.81
Scenario 9: tests done by MDs in immigrant/immunocompromised populations (with PPD waste), immigrants, total BI	−$1.50	−$3.39
Scenario 9: BI—test cost	$1.22	$0.94
Scenario 10a: no waste of PPD (no TST vial wastage at MD's office), immigrants, total BI	−$1.48	−$3.45
Scenario 10a: BI—test cost	$1.24	$0.88
Scenario 10b: large wastage of PPD (80% of the TST vial) MD's office, immigrants, total BI	−$2.26	−$3.45
Scenario 10b: BI—test cost	$0.46	$0.88
Change in cost of IGRA		
Scenario 11: IGRA cost 25% lower, immigrants, total BI	−$2.12	−$3.63
Scenario 11: BI—test cost	$0.60	$0.70
Scenario 12a: IGRA at hospital lab, no shipping cost, immigrants, total BI	−$1.53	−$3.42
Scenario 12a: BI—test cost	$1.19	$0.91
Scenario 12b: IGRA at hospital lab, with shipping cost in immigrant and contact testing, immigrants, total BI	−$1.47	−$3.39
Scenario 12b: BI—test cost	$1.25	$0.93
Scenario 13: change in probability of reactivation of LTBI into active TB for immunocompromised (hypothetical threshold value), immigrants, total BI[b]	NA	NA
Scenario 13: BI—test cost[b]	—	—

Abbreviations: BI, budget impact; IGRA, interferon-gamma release assay; iPHIS, Public Health Information System; LTBI, latent tuberculosis infection; MD, medical doctor (physician); NA, not applicable; PHO, Public Health Ontario; PPD, purified protein derivative; SEQ, sequential pathway; TST, tuberculin skin test.

[a]All costs are in millions CAD (2024).

[b]NA: remains the same as in the reference case for this subpopulation.

Appendix 15: Sensitivity Analysis: Contact Subpopulation

Table A19: Budget Impact Results—Sensitivity Analysis: Contact Subpopulation

Scenario	Total 5-year budget impact (IGRA strategies vs. TST alone)[a]	
	IGRA alone vs. TST	SEQ: TST/IGRA vs. TST alone
Reference case, total BI, all populations	$2.99	$14.07
Reference case, BI—test cost, all populations	$6.01	$8.28
Reference case, total BI, contacts	**−$1.63**	**−$1.76**
Reference case, BI—test cost, contacts	**$0.22**	**$0.62**
Change in population size		
Scenario 1: Number of people for testing in Ontario based on iPHIS LTBI data obtained from PHO and published LTBI prevalence estimates, contacts, total BI	−$9.38	−$10.12
Scenario 1: BI—test cost	$1.25	$3.58
Scenario 2: all cancer types, contacts, total BI[b]	NA	NA
Scenario 2: BI—test cost*	—	—
Change in the uptake of IGRA		
Scenario 3: large uptake for all, contacts, total BI[b]	NA	NA
Scenario 3: BI—test cost[b]	—	—
Scenario 4: low uptake for all, contacts (5% per year), total BI	−$0.28	−$0.30
Scenario 4: BI—test cost	$0.04	$0.11
Scenario 5: smaller uptake for immunocompromised (20% per year), contacts, total BI[b]	NA	NA
Scenario 5: BI—test cost	—	—
Scenario 6: smaller uptake for immunocompromised (10% per year), contacts, total BI[b]	NA	NA
Scenario 6: BI—test cost	—	—
Change in the testing pathway		
Scenario 7: no cost of referral, contacts, total BI	−$1.63	−$1.80
Scenario 7: BI—test cost	$0.22	$0.58
Scenario 8: all tests done by PHUs, contacts, total BI	−$1.96	−$1.66

Scenario	Total 5-year budget impact (IGRA strategies vs. TST alone)[a]	
	IGRA alone vs. TST	SEQ: TST/IGRA vs. TST alone
Scenario 8: BI—test cost	−$0.11	$0.72
Scenario 9: tests done by MDs in immigrants/immunocompromised populations, contacts, total BI[b]	NA	NA
Scenario 9: BI—test cost	—	—
Scenarios 10a: no waste of PPD (no TST vial wastage at MD's office), contacts, total BI	−$1.56	−$1.76
Scenario 10a: BI—test cost	$0.29	$0.62
Scenario 10b: large wastage of PPD (80% of the TST vial) at MD's office, contacts, total BI	−$1.76	−$1.91
Scenario 10b: BI—test cost	$0.62	−$0.07
Change in cost of IGRA		
Scenario 11: IGRA cost 25% lower, contacts, total BI	−$1.85	−$1.86
Scenario 11: BI—test cost	$0.00	$0.53
Scenario 12a: IGRA at hospital lab, no shipping cost, contacts, total BI	−$1.58	−$1.74
Scenario 12a: BI –test cost	$0.26	$0.64
Scenario 12b: IGRA at hospital lab, with shipping cost only in immigrant and contact testing, contacts, total BI	−$1.56	−$1.73
Scenario 12b: BI—test cost	$0.29	$0.66
Scenario 13: change in probability of reactivation of LTBI into active TB in immunocompromised (hypothetical threshold value)**,** contacts, total BI[b]	NA	NA
Scenario 13: BI—test cost	—	—

Abbreviations: BI, budget impact; IGRA, interferon-gamma release assay; iPHIS, Public Health Information System; LTBI, latent tuberculosis infection; MD, medical doctor (physician); NA, not applicable; PHO, Public Health Ontario; PPD, purified protein derivative; SEQ, sequential pathway; TST, tuberculin skin test.

[a]All costs are in millions CAD (2024).

[b]NA: remains the same as in the reference case for this subpopulation.

Appendix 16: Sensitivity Analysis: Immunocompromised Subpopulation

Table A20: Budget Impact Results—Sensitivity Analysis: Immunocompromised Subpopulations

Scenario	Total 5-year budget impact (IGRA strategies vs. TST alone)[a]		
	IGRA alone	SEQ: TST/IGRA vs. TST alone	SEQ: TST/IGRA & IGRA/TST[b]
Reference case, total BI, all populations	$2.99	$14.07	$18.80
Reference case, BI—test cost, all populations	$6.01	$8.28	$10.12
Reference case, total BI, immunocompromised population	$6.26	$19.29	$24.01
Reference case, BI—test cost, immunocompromised population	$4.70	$6.79	$8.62
Change in population size			
Scenario 1: number of people for testing in Ontario based on iPHIS LTBI data obtained from PHO and published LTBI prevalence estimates, immunocompromised, total BI[c]	NA	NA	NA
Scenario 1: BI—test cost[c]	—	—	—
Scenario 2: all cancer types, immunocompromised, total BI	$44.23	$136.36	$169.79
Scenario 2: BI—test cost	$33.25	$47.98	$60.97
Change in the uptake of IGRA			
Scenario 3: large uptake for all, immunocompromised, total BI[c]	NA	NA	NA
Scenario 3: BI—test cost[c]	—	—	—
Scenario 4: low uptake for all, immunocompromised (5% per year), total BI	$1.07	$3.29	$4.09
Scenario 4: BI—test cost	$0.80	$1.16	$1.47
Scenario 5: smaller uptake for immunocompromised (20% per year), immunocompromised, total BI	$4.26	$13.15	$16.37
Scenario 5: BI—test cost	$3.21	$4.63	$5.88
Scenario 6: smaller uptake for immunocompromised (10% per year), immunocompromised, total BI	$2.13	$6.57	$8.19
Scenario 6: BI—test cost	$1.60	$2.31	$2.94
Change in the testing pathway			
Scenario 7: no cost of referral, immunocompromised, total BI	$4.60	$16.49	$21.10

Scenario	Total 5-year budget impact (IGRA strategies vs. TST alone)[a]		
	IGRA alone	SEQ: TST/IGRA vs. TST alone	SEQ: TST/IGRA & IGRA/TST[b]
Scenario 7: BI—test cost	$3.05	$3.99	$5.71
Scenario 8: all tests done by PHUs in contacts and immigrants, immunocompromised, total BI[c]	NA	NA	NA
Scenario 8: BI—test cost[c]	—	—	—
Scenario 9: tests done by MDs in immigrants/immunocompromised populations, immunocompromised, total BI[c]	NA	NA	NA
Scenario 9: BI—test cost[c]	—	—	—
Scenario 10a: no waste of PPD (no TST vial wastage at MD's office), immunocompromised, total BI	$7.40	$19.29	$24.29
Scenario 10: BI—test cost	$5.85	$6.79	$8.90
Scenario 10b: large wastage of PPD (80% of the TST vial) at MD's office, immunocompromised, total BI	$1.66	$19.29	$22.91
Scenario 10b: BI—test cost	$0.11	$6.79	$7.52
Change in cost of IGRA			
Scenario 11: IGRA cost 25% lower, immunocompromised, total BI	$4.41	$18.01	$22.17
Scenario 11: BI—test cost	$2.86	$5.51	$6.78
Scenario 12a: IGRA at hospital lab, no shipping cost, immunocompromised, total BI	$6.48	$19.44	$24.23
Scenario 12a: BI—test cost	$4.92	$6.94	$8.84
Scenario 12b: IGRA at hospital lab, with shipping cost only for immigrants and contacts, immunocompromised, total BI	$6.48	$19.44	$24.23
Scenario 12b: BI—test cost	$4.92	$6.94	$8.84
Scenario 13: probability of reactivation of LTBI (at threshold value of 30%, hypothetical), total BI	$0.00	$4.81	−$39.82
Scenario 13: BI—test cost	$4.70	$8.62	$8.62

Abbreviations: BI, budget impact; IGRA, interferon-gamma release assay; iPHIS, Public Health Information System; LTBI, latent tuberculosis infection; MD, medical doctor (physician); NA, not applicable; PHO, Public Health Ontario; PPD, purified protein derivative; SEQ, sequential pathway; TST, tuberculin skin test.

[a]All costs are in millions CAD (2024).

[b]IGRA/TST vs. TST alone, the strategy applicable only to immunocompromised population.

[c]NA, remains the same as in the reference case for this subpopulation.

Appendix 17: Letter of Information

Thank you for participating in Ontario Health's Health Technology Assessment (HTA) on "Interferon Gamma Release Assay for Latent Tuberculosis Infection (IGRA for LTBI)".

What is a Health Technology Assessment (HTA)?

An HTA is a review of scientific evidence about health care services and interventions. This includes speaking with care providers to find out about the perceived benefits and disadvantages of health interventions and technologies.

What is this survey about?

We would like to know your perspective and opinion about TB skin test and blood test (IGRA) for the diagnosis of LTBI (latent tuberculosis infection).

IGRA is a blood test used for the diagnosis of LTBI. In Ontario, there is currently no standardized funding or access to the use of IGRA. Our HTA will conclude in a recommendation about public funding for IGRA in Ontario.

The last day to participate in this assessment is April 30, 2024.

Important note

Your participation in this HTA is completely voluntary. You are under no obligation to participate, and you can withdraw from the HTA at any time and/or refuse to answer any questions without any negative consequences.

If you choose to participate, please note that all information collected from participants will be kept confidential and your privacy will be protected, except as required by law. The overall findings from this survey will be published, however, we will not use your name or any personally identifiable information (e.g., names of clinics or doctors) in any presentations or publications related to this HTA.

If you have any questions about the survey or would like to submit your feedback in another format, please contact:

Thank you for your time and input! Your experience is valued and appreciated.

Appendix 18: Interview Guide

1. What is your job title?
2. Where is the location of your clinic/hospital?
3. Does your clinic/hospital currently offer TB skin test? (bullet)
    - Yes, on site
    - Yes, by referral
    - No

    a. (If yes) On average, how many TB skin tests (on site/referral) do you offer to your patients per month?
4. Does your clinic refer patients for IGRA (blood test)? (bullet)
    - Yes
    - No

    a. (If yes) On average, how many IGRA (blood test) referrals do you do per month?

5. What population do you serve for LTBI (latent tuberculosis infection) testing? (checkbox)
    - Immunocompromised patients
    - Healthcare workers who recently immigrated to Canada and are BCG vaccinated.
    - People living in congregate settings such as long-term care homes, homeless shelters, and hospitals.
    - Other (please specify)

6. What are the pros and cons of each test (TST skin test and IGRA-blood test) in your opinion? (consider the following: patient preference, workflow, equity)

7. Is there anything else to add that you feel would be important to our health technology assessment regarding IGRA (blood test)?

What happens next?

The Ontario Health Technology Advisory Committee (OHTAC), a group of scientific experts and people with lived experience, reviews our findings and, after careful deliberation, makes their draft recommendation. At that time, the report will be published on our website and available for public comment.

Following public comment, the review will conclude with a formal recommendation to the Ministry of Health and Long-Term Care on whether this intervention should be publicly funded.

For more information about Ontario Health and our health technology assessments, please go to: http://www.hqontario.ca/Evidence-to-Improve-Care/Health-Technology-Assessment

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Equity, Inclusion, Diversity and Anti-Racism

Ontario Health is committed to advancing equity, inclusion and diversity and addressing racism in the health care system. As part of this work, Ontario Health has developed an Equity, Inclusion, Diversity and Anti-Racism Framework, which builds on existing legislated commitments and relationships and recognizes the need for an intersectional approach.

Unlike the notion of equality, equity is not about sameness of treatment. It denotes fairness and justice in process and in results. Equitable outcomes often require differential treatment and resource redistribution to achieve a level playing field among all individuals and communities. This requires recognizing and addressing barriers to opportunities for all to thrive in our society.

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