Cost-effectiveness of Interferon Gamma Release Assay (QFT-IT) as a Diagnostic Test for Intraocular Tuberculosis

by

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Thesis submitted in partial fulfillment of
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ABSTRACT

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Abstract:

Background:

Interferon Gamma Release Assays (IGRAs) have proven to be potential replacement of tuberculin skin test (TST) in screening and diagnosing tuberculosis as shown by previous health economic studies. Given that these studies all center on pulmonary tuberculosis, we sought to examine the cost-effectiveness of IGRAs, specifically QFT-IT, as a diagnostic test for intraocular tuberculosis among uveitis patients in Singapore.

Method:

A decision tree was constructed to evaluate the cost-effectiveness of the QFT-IT for diagnosing intraocular tuberculosis among uveitis patients over a 30-year horizon. The input data were based on a cohort of 102 patients who presented with symptoms of uveitis and underwent relevant treatment and follow-up visits from 2009 to 2010 at Singapore National Eye Center (SNEC). By calculating their incremental cost-effectiveness ratio, we compared the cost-effectiveness of three strategies: TST alone, QFT-IT alone and TST followed by QFT-IT as a confirmatory test.

Results:

Our results show that in cost terms alone, QFT-IT alone strategy is the most expensive one (889 SGD per person), followed by TST alone (850 SGD per person) and finally the dual strategy (789 SGD per person). While examining effectiveness alone, TST alone strategy is the most effective one that helps gain 17.4923 quality-adjusted life years (QALYs) followed by QFT-IT alone and the dual strategy. Using the conventional willingness to pay of 50,000 USD/QALY (63000 SGD/QALY), having an incremental cost-effectiveness ratio of 1644 SGD/QALY demonstrates that TST alone strategy is the best choice to screen ocular TB in Singapore.

Conclusion:

Given the local ocular tuberculosis prevalence and key assumptions made in the analysis model, the TST alone strategy is recommended to diagnose intraocular TB among uveitis patients in Singapore.

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1. Introduction:

1.1 Burden of Disease

Tuberculosis (TB) remains a major global health problem, which ranks as the second leading cause of death among infectious diseases after human immunodeficiency virus (HIV) (Global tuberculosis report, 2013). It was estimated that 8.6 million new TB cases and 1.3 million TB deaths occurred in 2012, which is unacceptably high given the preventability of the disease (Global tuberculosis report, 2013). TB is a gradually progressing granulomatous infectious disease caused by bacillus Mycobacterium tuberculosis, which usually affects the lungs (pulmonary TB). However, it can affect other sites (extrapulmonary TB) in the body as well, including the cardiovascular system, gastrointestinal system, musculoskeletal system, genitourinary tract, central nervous system, skin and eyes (M, El-Asrar, Abouammoh, & Al-Mezaine, 2009). The extrapulmonary involvement may occur either simultaneously or independently from clinically apparent pulmonary TB.

Intraocular TB mimics various uveitis infections, which is partially due to the similarity of infection site, the host response and the virulence of the organism (Gupta, Gupta, & Rao, 2007). Basically uveitis is inflammation inside the eye that affects uveal tract and adjacent structures and patients generally experience eye redness and irritation, blurred vision, ocular pain or even blindness, which severely affects their quality of life (Barisani-Asenbauer et al., 2012). Uveitis meets the criterion for classification as a rare disease with an estimated prevalence of around 38 cases per 100,000 people (Barisani-Asenbauer, et al., 2012). Although it is rare and more common in younger people, it

ranks as the fourth most common cause of blindness among the working-age population in the developed world (Barisani-Asenbauer, et al., 2012).Steroids given as eye drops are considered as the standard treatment for uveitis. Among all the intraocular changes caused by Mycobacterium tuberculosis, posterior uveitis appears to be the most common clinical presentation followed by anterior uveitis, panuveitis and intermediate uveitis (Gupta, et al., 2007). There exists no accurate estimate of the true prevalence of intraocular TB due to the lack of uniform diagnostic criteria and the difficulty of confirming the diagnosis by laboratory methods (M, et al., 2009). Generally, intraocular TB is much less common than pulmonary TB and the percentage of TB-associated uveitis among uveitis patients varies in regions and countries. For example, Wakabayashi et al found that in Japan among 189 referred uveitis patients, 6.9% were diagnosed with tuberculous uveitis (Wakabayashi, Morimura, Miyamoto, & Okada, 2003). The percentage was 4% in China according to a study by Abrahams and Jiang and 10.5% in Saudi Arabia (Abrahams & Jiang, 1986; Islam & Tabbara, 2002). A study in India found that tuberculosis only accounted for 0.39% of the 1,273 uveitis patients (Biswas, Narain, Das, & Ganesh, 1996).

1.2 Diagnosis of Intraocular TB

Due to the difficulty in obtaining microbiological evidence to confirm the presence of intraocular TB, diagnosis is presumptive and primarily based on clinical symptoms in almost all of the reported cases (Al-Mezaine, Al-Muammar, Kangave, & Abu El-Asrar, 2008; Cimino, Herbort, Aldigeri, Salvarani, & Boiardi, 2009; Morimura et al., 2002; Rosen, Spalton, & Graham, 1990; Sakai, Matsuzawa, Usui, & Yano, 2001; Sheu et al.,

2001; Wolfensberger, Piguet, & Herbort, 1999). In most studies, the diagnostic criteria for the presumptive ocular TB are: "1) ocular findings consistent with possible intraocular TB with no other cause of uveitis suggested by history of symptoms or ancillary testing; 2) strongly positive tuberculin skin test (TST) results (≥15 mm area of induration/necrosis); 3) response to antituberculous therapy with absence of recurrences" (M, et al., 2009). Of the three diagnostic criteria, the positive result of TST, already used for about a century to screen TB, is regarded as one critical sign in making the diagnosis. Despite its widespread usage, TST is limited in its non-specific reactivity in persons vaccinated with BCG and infected with non-tubercular mycobacteria. Advances in molecular biology have resulted in the development of the Interferon Gamma Release Assays (IGRAs) that measure IFN-γ responses to TB-specific antigens. This newly introduced diagnostic test has been suggested as a replacement for TST (Nienhaus, Schablon, Costa, & Diel, 2011; Pooran et al., 2010). Currently there are two different commercially available IGRAs: the ELISA-based QuantiFERON Gold (QFT-G) or QuantiFERON Gold In-Tube (QFT-IT) of Cellestis, Australia and the T-SPOT-based T-SPOT.TB of Oxford, UK.

Many studies have observed a higher specificity of IGRAs but evidences remain conflicting in terms of their sensitivity compared with TST (Nienhaus, et al., 2011). Apart from higher specificity, IGRAs offer the additional advantage of not requiring patients to come back after 48-72 hours as TST does. The direct testing cost of IGRAs, however, is higher than TST, which necessitates the use of economic evaluation studies that compare the cost-effectiveness of TST and IGRAs in screening and diagnosing TB.

1.3 Literature review:

1.3.1 Overall description of the analysis model

Recent studies all focused on pulmonary TB to evaluate the cost-effectiveness of IGRAs. Nienhaus et al (2011) conducted a systematic review of cost-effectiveness studies that compared different TB-screening strategies. They only included studies that used Markov modelling to take into account the health transition from latent TB infections (LTBI) to active TB and time-varying treatment outcomes. In the eight included studies, participants were followed from two years to life-long and costs and effectiveness were discounted at a rate of 3%. All studies relied on incremental cost effectiveness ratio (ICER) to select the best testing strategy but differentiated in terms of the measurement of effectiveness. Six of the reviewed studies measured effectiveness using quality-adjusted life years (QALYs) or life years gained (LYG) and the other two used active TB cases prevented due to lack of data.

1.3.2 Summary of available evidence

Evidences available shows inconsistency of the cost-effectiveness of different TB testing strategies: TST only, IGRA only, TST followed by an IGRA confirmatory test. Factors that contribute to the inconsistency include TB prevalence, the screening population, test and treatment costs, assumed sensitivity and specificity of the tests and the health financial constraint to gain a unit increase of effectiveness.

Seven out of the eight reviewed studies by Nienhaus et al (2011) compared the cost-effectiveness of three strategies: IGRA only, TST only and the dual strategy. Regardless of differences in assumptions and baseline input values of key variables, results of six of out of the seven studies unanimously showed that TST only was the most expensive strategy to achieve one-unit gain of effectiveness, thus suggesting it be replaced by either of the two other strategies. The only exceptional study found out that TST was cost saving in close contacts who did not receive BCG vaccination after infancy (Oxlade et al 2013), but for subjects from low-incidence countries the dual strategy was the optimal one. Four out of the seven studies found out that the dual strategy was the least expensive one to achiever per unit of effectiveness gain and others favored the IGRA only as the most cost-effective strategy.

1.3.3 Detailed review of four representative studies

In Canada, Marra et al analyzed the cost-effectiveness of three strategies: TST, QFT-G and TST+QFT-G for screening TB among contacts with active TB patients (Marra et al., 2008). Given that the performance of QFT-G varied among different population, they stratified their study participants by ethnicity (foreign-born, non-aboriginal Canadian-born and aboriginal) and BCG-vaccination status. They assumed that TST and QFT-G had the same sensitivity of 0.99; specificity of TST was higher than 0.99 in BCG-unvaccinated group and that of QFT-G was 0.96. Using a 20-year Markov model and QALYs as the measurement of effectiveness, they found out that QFT-G was most cost-effective among BCG-vaccinated contacts while least cost-effective if applied to all cases. TST alone-strategy, however, proved to be most cost-effective for all cases with an

incremental net monetary benefit of Canada $3.70 given the assumed high sensitivity and specificity. Therefore, they concluded that it might not be wise to completely replace TST with QFT-G before more evidences about the performance characteristics of QFT-G become available in Canada.

In contrast, Kowada et al demonstrated that QFT-IT alone was the most cost-effective strategy to screen pulmonary TB in Japan where almost everyone was BCG vaccinated from infancy(Kowada et al., 2008). They conducted a similar study among a cohort of 1000 immunocompetent 20-year-old close contacts of pulmonary tuberculosis patients. They assumed QFT sensitivity of 0.76 and specificity of 0.96 at baseline. As for TST, the sensitivity was assigned to be 0.71 while specificity was 0.15 for base case, 0.60 for BCG-vaccinated in older children and 0.98 for non-BCG-vaccinated population. Probability of having LTBI/TB infections was assumed to be 0.2 at baseline. Both direct costs including inpatient and outpatient costs and indirect costs arising from productivity loss were calculated. Set against such a background, they found out that QFT-IT alone was the dominant strategy: the least expensive (471.54 USD) and the most effective (28.1099 QALYs) option. TST alone strategy proved to be the dominated one with the highest cost and lowest effectiveness.

Pooran et al (2010) analyzed the cost-effectiveness of five different scenarios: TST, TSPOT-TB, QFT-IT, TST+TSPOT-TB and TST+QFT-IT in the UK. They built a two-year model to estimate costs and measured the effectiveness with active TB cases prevented. Both probabilities and costs data were obtained from published literature. They assumed a prevalence of LTBI at 30% and high sensitivity and specificity for both

IGRA and TST (IGRAs performed better than TST in both sensitivity and specificity). They also added branches of hepatitis incurred by anti-tuberculosis treatment in their decision tree. Results showed that QFT-IT was the most expensive strategy while the TST+QFT-IT was the least costly choice. In effectiveness terms alone, T-SPOT.TB alone strategy ranked first for preventing 3.70 cases for a cohort of 1,000 contacts over the 2 year examination period, followed by QFT-IT alone (3.47 cases), TST alone (2.98 cases), TST+T-SPOT.TB (2.83 cases), and TST+QFT-IT (2.65 cases). Compared with no screening, they concluded that TST+TSPOT-TB was most cost-effective with the lowest incremental cost at £37,206/TB case avoided while TST alone was the least preferred one.

A recent study conducted in Brazil showed that in the short run TST remained the most cost-effective strategy compared with QFT-G alone and the dual strategy(Steffen et al., 2013). Their study was conducted in a hypothetical cohort of 1,000 immunocompetent 35-year-old close contacts of TB cases who were followed for two years. Effectiveness was measured by new TB cases averted and cost data from the National Health System in Brazil. They assumed a baseline value of 0.35 for the prevalence of LTBI, 0.70 for QFT-IT sensitivity, 0.95 for QFT-IT specificity, 0.77 for TST sensitivity and 0.59 for TST specificity. Their results demonstrated that QFT-IT was the most effective one in averting 6.63 TB cases per 1,000 contacts, followed by TST alone (6.56 cases prevented) and the dual strategy (4.59 cases prevented). In the costs term alone, the dual strategy stood out as the most cost-saving one with 101,945 USD to screen and treat 1,000 contacts while the QFT-IT alone strategy was the most expensive one with 121,054 USD. However, final results show that the cost per averted TB case is lowest for TST alone strategy

(16,021 USD) and highest for the dual strategy (22,211 USD). As a result, they concluded that TST alone was the most cost-effective strategy that prevented 1,837 new TB cases per year with a total cost of around 30 million USD based on the local LTBI/TB incidence.

Based on conflicting evidences in different study settings (see Table 1 and 2 for the brief summary of the four representative studies), countries issue different guidelines in screening tests recommendations. The Center for Disease Control (CDC) in the US recommends TST alone as the first-line test and IGRA alone is preferred for patients who are BCG-vaccinated or who cannot return to the physician within 48-72 hours after being administered with TST(Mazurek et al., 2010). It is suggested that health care providers choose which test to administer based on individual circumstances but the dual test (IGRA as a confirmatory test following initial TST positive results) is not recommended. In contrast, the National Institute of Health and Clinical Excellence (NICE) in the UK recommends the dual test strategy to screen for TB ("Clinical diagnosis and management", 2006).

1.4 Hypothesis:

Despite the positive results that demonstrate the cost-effectiveness of IGRAs in screening pulmonary TB, no study has been conducted to evaluate IGRAs in screening and diagnosing intraocular TB. To fill the gap, the present study based on the data from a cohort of 102 uveitis patients in Singapore to analyze the cost-effectiveness of the three strategies: TST alone, QFT-IT alone and TST followed by QFT-IT as a confirmatory test.

Given that almost everybody is BCG-vaccinated in Singapore, we hypothesized that the dual test was the most cost-saving strategy and the QFT-IT alone strategy was the most effective one in screening TB among uveitis patients in Singapore.

Table 1A: Summary of the four representative studies

	Study period	Study setting	Study Population	TB prevalence	Strategies	Results
Marra et al	20 years	Canada	Close contacts of foreign0born, non-aboriginal, Canadian-born and aboriginal TB cases	0.10-0.11	TST-only; QFT-G only; TST+QFT-G	QFT-G most effective for BCG-vaccinated contacts; TST most effective for all cases
Kowada et al	Lifetime	Japan	Close contacts: immunocompetent and BCG-vaccinated	0.2	QFT-only; TST-only; TSTQFT	QFT only>TST+QFT>TST only
Pooran et al	2 years	UK	Close contacts	0.3	TST-only; T-SPOT.TB-only; TST+T.SPOT; QFT-only; TST+QFT	TST+T.SPOT TB>TST+QFT-IT>T.SPOT TB only>QFT-IT only>TST
Stefen et al	2 years	Brazil	Close contacts	0.35	QFT-IT-only; TST-only; TST+QFT-IT	TST>QFT-IT>TST+QFT-IT

Table 1B: Summary of the baseline data of the test-specific variables in the four representative studies

	TST Sensitivity	IGRA Sensitivity	TST Specificity	IGRA Specificity
Marra et al	0.99	0.99	>0.99 (BCG unvaccinated)	0.96
Kowada et al	0.71	0.76	0.15	0.96
Pooran et al	0.85	0.89 (QFT-IT); 0.95 (T SOPT.TB)	0.8	0.95 (QFT-IT); 1.00 (T SPOT.TB)
Stefen et al	0.77 (>5 mm)	0.7	0.59 (>5mm)	0.95

2. Methodology:

2.1 Patients and Procedures:

The input data were based on a two-year prospective cohort study among patients with new onset of uveitis at the Singapore National Eye Centre (SNEC) from January 1st, 2009 to December, 31st, 2010. Patients presented with active uveitis at SNEC were recruited consecutively and they all underwent a full systemic check-up, ocular examination and standard baseline investigation after they consented to participate in the study. All patients were followed up for a minimum of one year after completing anti-TB treatment, or one year from initial recruitment if no treatment was given. Patients who did not complete follow-up, or who did not have one of the above tests, or who did not consent to participate were excluded from the study. Altogether 120 patients were enrolled into the study and 106 patients completed the follow-up. Four out of the 106 patients did not have TST and therefore were excluded from this particular analysis. In the end a total number of 102 patients with a mean age of 48.2 were included into the final analysis. Ethical approval was obtained from the Singapore Health Services Centralized Institutional Review Board. The current study adhered to the tenets of the Declaration of Helsinki.

Participants received both QFT-IT and TST tests. Blood was taken before TST was administered. Patients were referred to the Department of Infectious Disease at Singapore General Hospital (SGH) if they tested positive for either QFT-IT or TST. Every patient was prescribed with steroids (eye treatment) for uveitis and those tested positive for TB were given the option of initiating the standard nine-month anti-tuberculosis therapy

(ATT), specifically the isonicotinylhydrazine (INH) chemoprophylaxis, or not. Given the hepatotoxicity incurred by the INH chemoprophylaxis, liver function tests were performed in patients who initiated ATT at baseline, once a month for the first three months after starting ATT and once every three months for the rest six months of treatment. Patients diagnosed with hepatitis terminated ATT at once but still received eye treatment. Patients were followed up once a month for the first three months and three/six monthly thereafter if the eye symptoms remained active/inactive.

2.2 Model Design:

We built a decision tree using TreeAge Pro 2013 (TreeAge Software, Williamstown, MA) to analyze the cost-effectiveness of TST and QFT-IT as a diagnostic test of intraocular TB among patients presented with uveitis in Singapore. Currently TST remains the first-line screening and diagnostic test for TB and is routinely administered among uveitis patients in clinical practice. In our model, three optional strategies were developed to compare the cost-effectiveness: 1) TST alone; 2) QFT-IT alone; 3) TST+QFT-IT. The decision trees of the three strategies are shown in Figure 1, Figure 2 and Figure 3 respectively.

We modeled four possible outcomes for the patients presenting with uveitis: asymptomatic, eye symptoms resolved, recurrent or persistent inflammation and death from hepatitis incurred by the ATT. As for patients whose uveitis is caused by tuberculosis, they were likely to end up in: 1) asymptomatic (if they consented to receive the ATT and got completely cured); 2) eye symptoms resolved (if they declined the ATT

but temporarily got cured by the eye treatment); 3) recurrent or persistent inflammation (if they received the ATT but it did not work or they declined the ATT and the eye treatment did not work either); 4) death from hepatotoxicity due to ATT. For patients whose uveitis is irrelevant to tuberculosis, they might become asymptomatic if the eye treatment worked or ended up with recurrent inflammation if the eye treatment failed. Patients with the same outcome were assumed to share the same utilities regardless of the causality of their uveitis.

The model is comprised of three stages: treatment period (four months of eye treatment or nine months of ATT), follow-up period and post-treatment period. It was extended to 30 years to represent the remaining life expectancy of the patients given their mean age (48.2 years old) and the life expectancy of Singaporeans (80 for males and 85 for females). A discount rate of 3% was used to calculate the health-related quality of life (QoL) assuming that the health of all patients deteriorates at the same rate constantly and no other major health risk would occur in the post-treatment period. Besides, we also assumed a 100% return rate for TST reading and perfect medication adherence. Patients who refused TB treatment would not initiate it in the modeling 30 years. The impact of these assumptions was evaluated via sensitivity analysis.

2.3 Model Inputs:

All the input variables and sensitivity ranges were displayed in Table 2.

2.3.1 Probabilities:

Probability inputs consist of test-specific and treatment-specific variables. The test-specific probabilities were obtained from a to-be-published paper that examined the sensitivity and specificity of TST and IGRAs based on the same study cohort. Other probabilities such as the positive/negative predictive value and probability of positive/negative result were calculated based on prevalence, sensitivity and specificity at baseline. The TB prevalence among uveitis patients was calculated from the current study given its enormous variability in different countries as mentioned earlier. Five of the six treatment-specific probabilities were calculated using the data of the present study; the only one from the published literature was the probability of death incurred by the side effects of ATT since no death occurred in the present study.

2.3.2 Cost:

The total cost can be divided into three parts: test, treatment and follow-up consultations. All the cost data were calculated based on the current study (the discharge data from SNEC and SGH) except for the cost to patients who died from side effects of ATT. As Table 1 shows, the cost of having QFT-IT test was 156 Singapore dollars (SGD) while of TST was 22 SGD. The nine-month ATT cost 194 SGD in total. As the eye treatment costs varied moderately among patients, we calculated the individual costs first and then averaged them within the same treatment and outcome groups. Considering the hepatotoxicity of ATT, patients who initiated ATT received six liver function tests during the nine-month treatment period, accounting for a total cost of 552 SGD.

The number of follow-up visits varied depending on the diagnosis and treatment that the patients received. Patients who tested positive were asked to visit both eye and infectious disease doctors while those who tested negative were only required to visit eye doctors. The frequency of infectious disease doctor visits was six times in nine months while that of eye doctor visits depended on the activity of the eye symptoms. Cost was not discounted for it was only a two-year study.

2.3.3 Utilities:

We used health-related QoL to measure the utilities of the patients. All the utility data were from published literature and all of them were measured by the EQ-5D instrument. The EQ-5D is a self-reported preference-based measure of general health status and covers questions on 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The scores range from -0.11 (worst possible health) to 1.0 (best possible health) (Fryback et al., 2007).

It was assumed that patients at baseline had the same QoL and patients with the same prognosis shared the same QoL. Specifically, the QoL of patients at baseline was 0.80, of patients with persistent inflammation was 0.82, of TB uveitis patients with only eye symptoms resolved was 0.84 and of completely cured patients was 0.89 regardless of the etiology of their uveitis. Utilities were discounted at a rate of 3% and extended to 30 years in the analysis model.

2.4 Sensitivity Analysis:

The robustness of the baseline results was tested through one-way sensitivity and probabilistic analyses. For the sensitivity analyses, each parameter was varied within a reasonable range (based on literature values) to estimate its impact on the final results. For the probabilistic sensitivity analyses, we performed 10,000 iterations of Monte Carlo simulation and in each iteration a value was drawn from the assigned distribution of each variable. Thus, the cost-effectiveness estimates were calculated accordingly based on the 10,000 repeated draws. In our model, the probabilities and utilities were assumed to follow beta distributions and costs were assumed to follow gamma distribution.

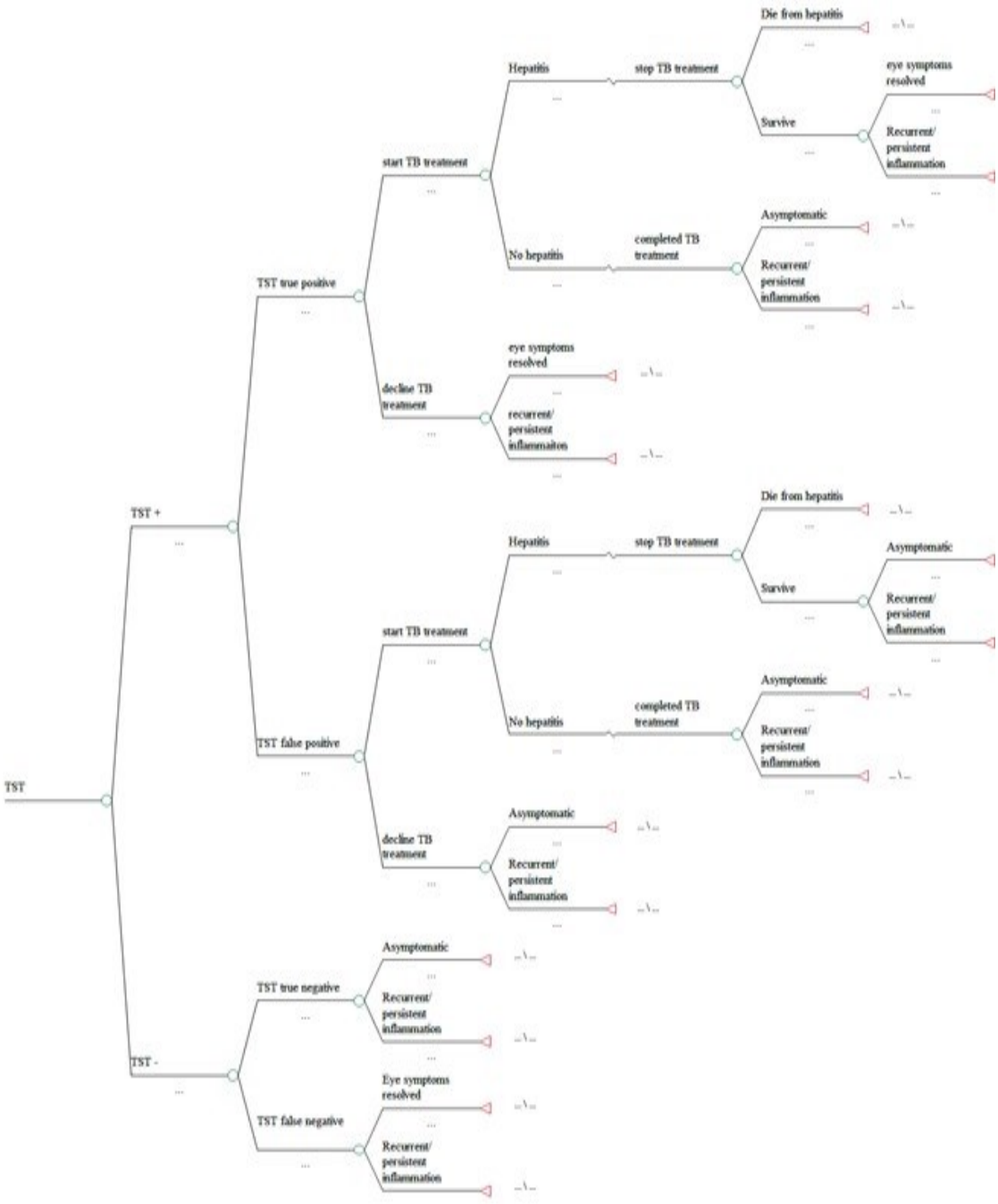

Figure 1 TST only strategy for diagnosis of presumed intraocular TB infection

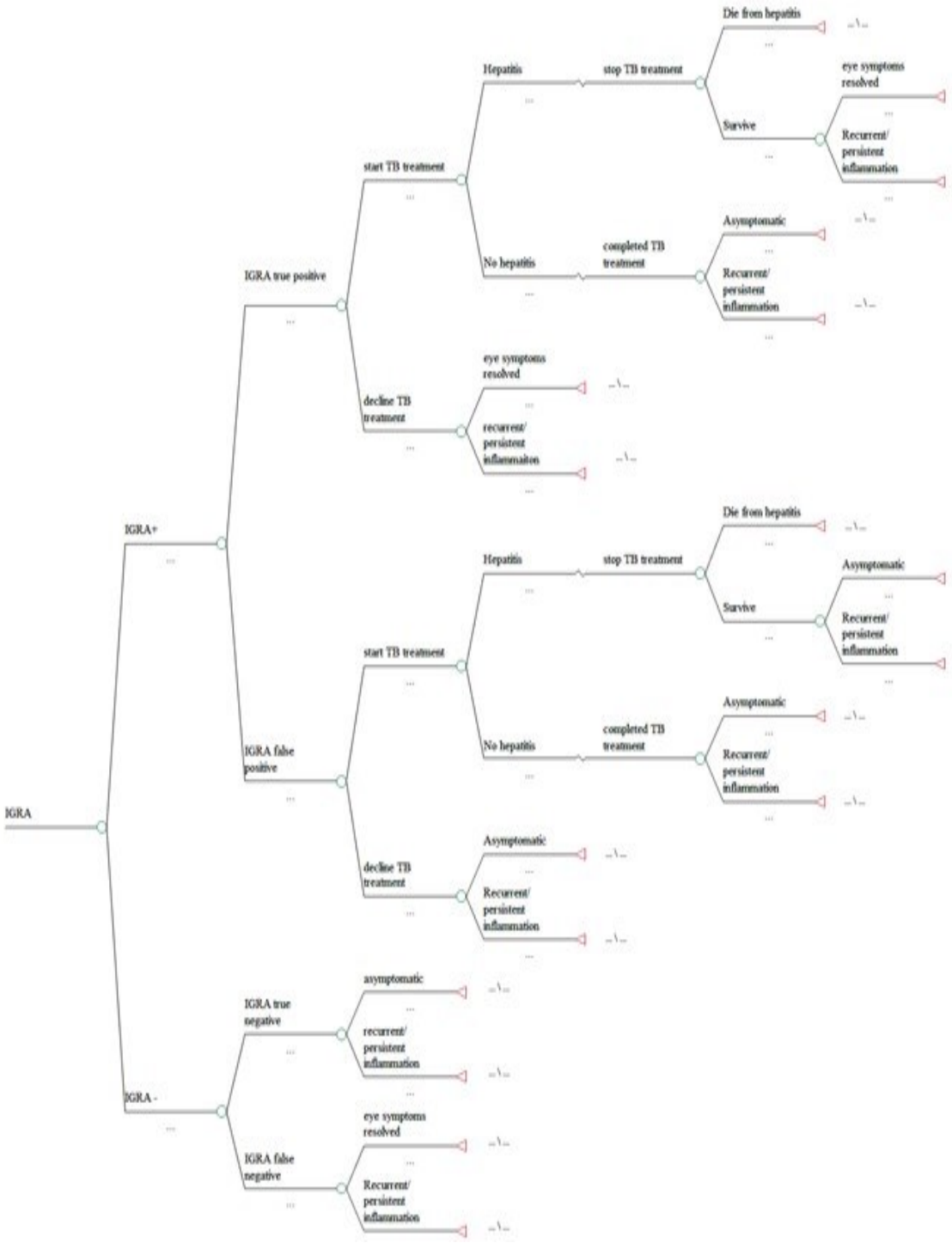

Figure 2 IGRA only strategy for diagnosis of presumed intraocular TB infection

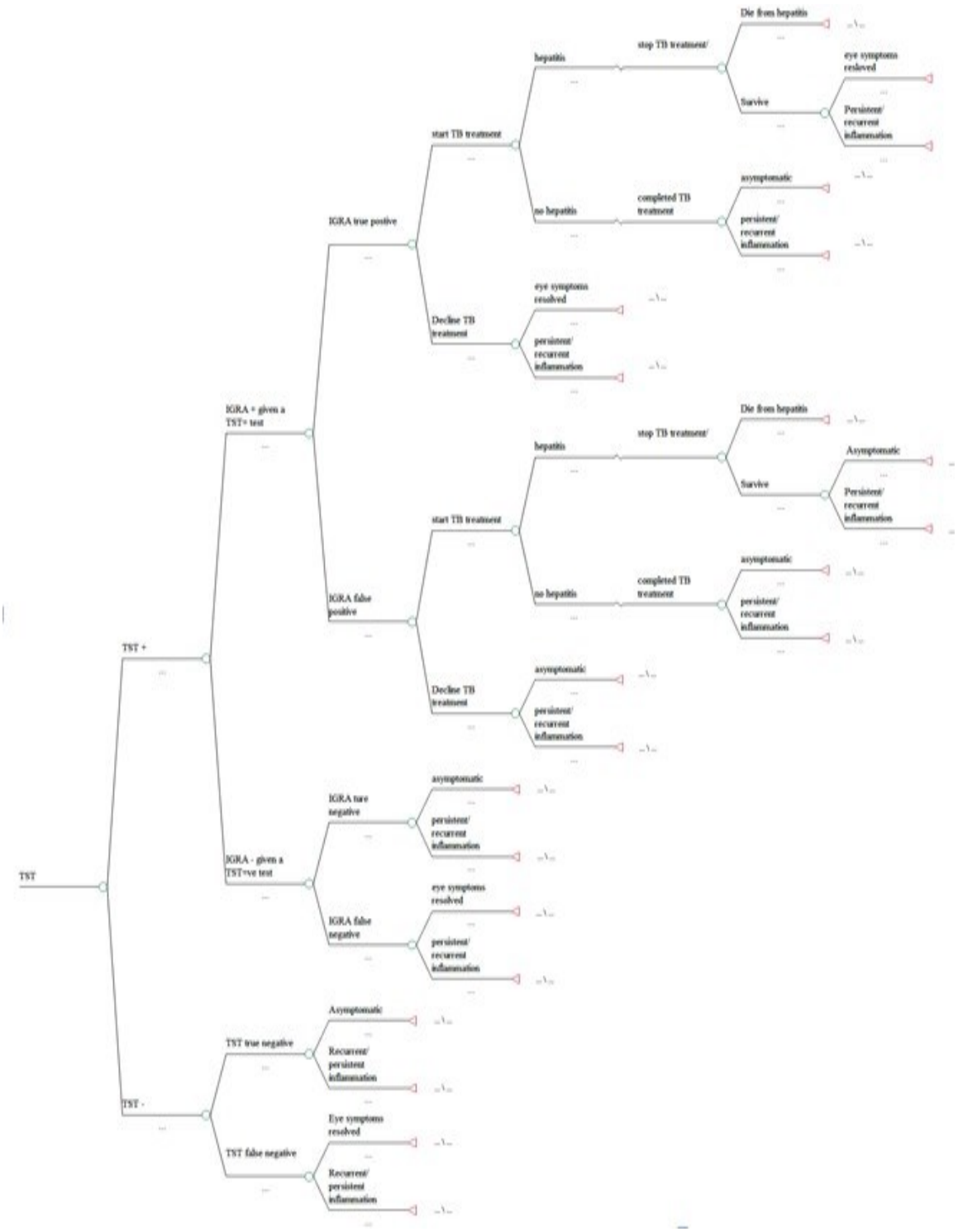

Figure 3 Dual strategy for diagnosis of presumed intraocular TB infection

Table 2 Probabilities and costs used in the base case and sensitivity analysis

Variables	Baseline Value	Range	Sources
TB prevalence among uveitis patients	0.225	0.2%-26.2%	Calculated & (M, et al., 2009)
TST sensitivity	0.69	0.64-0.95	SNEC & (Ferrara et al., 2006; Huebner, Schein, & Bass, 1993; Lalvani et al., 2001; Meier, Eulenbruch, Wrighton-Smith, Enders, & Regnath, 2005)
TST specificity	0.74	0.60-0.90	SNEC&(Lee et al., 2006; Schwartzman & Menzies, 2000)
TST positive result	0.36		
TST PPV	0.44		Calculated
TST NPV	0.89		Calculated
QFT-IT sensitivity	0.64	0.60-0.95	SNEC & (Goletti et al., 2005; Ravn et al., 2005)
QFT-IT specificity	0.995	0.900-0.999	SNEC & (Goletti, et al., 2005; Ravn, et al., 2005)
QFT-IT positive result	0.15		
QFT-IT PPV	0.97		Calculated
QFT-IT NPV	0.90		Calculated
QFT-IT PPV given a positive TST	0.99		Calculated
QFT-IT NPV given a positive TST	0.78		Calculated
Probability of becoming asymptomatic for TB patients	0.909	0.73-1.00	Calculated
Probability of becoming asymptomatic for non-TB patients	0.778	0.75-0.9	Calculated
Probability of getting eye symptoms resolved for TB patients	0.600	0.55-0.65	Calculated
Probability of starting INH treatment	0.437	0.423-0.514	Calculated
Probability of having hepatitis incurred by INH	0.109	0.015-0.241	(Bass et al., 1994; Salpeter, 1993; Smieja, Marchetti, Cook, & Smaill, 2000; Steele, Burk, & DesPrez, 1991; Taylor, 2000)
Probability of dying from hepatitis incurred by INH	0.00002	0.00001-0.0001	(Salpeter, 1993; Salpeter & Salpeter, 2004)
Cost of QFT-IT	156	20-200	SNEC & SGH(Nienhaus, et al., 2011)
Cost of TST	22	10-160	SNEC & SGH(Nienhaus, et al., 2011)
Cost for having TB treatment (having hepatitis) asymptomatic	1054	-	SNEC & SGH
Cost for having TB treatment (having hepatitis) persistent inflammation	1686	-	SNEC & SGH
Cost for having TB treatment (no hepatitis) asymptomatic	1752	1636.52-1814.31	SNEC & SGH
Cost for having TB treatment (no hepatitis) persistent inflammation	2069	-	SNEC & SGH
Cost for not having TB treatment (no hepatitis) asymptomatic	525	505.09-612.59	SNEC & SGH
Cost for not having TB treatment (no hepatitis) persistent inflammation	1071	625.64-1271.38	SNEC & SGH
Cost for having TB treatment but dying from hepatitis	1258	-	SNEC & SGH
Baseline utility	0.8	0.66-0.95	(Frick et al., 2012)
Patients end up in persistent inflammation	0.82	0.66-0.95	(Frick, et al., 2012; Naik, Gries, Rentz, Kowalski, & Revicki, 2013)
Patients end up in only eye symptoms resolved	0.84	0.7-0.98	(Frick, et al., 2012; Naik, et al., 2013)
Patients end up in asymptomatic	0.89	0.88-0.90	(Bernert et al., 2009)

3. Results:

3.1 Base case analysis:

Table 3 shows the base case results of the cost-effectiveness of the three strategies as diagnostic tests for intraocular tuberculosis in Singapore. The cost is measured in Singapore dollars and the effectiveness is presented as QALYs, meaning the remaining life years after adjusting for QoL. The results demonstrate that both the total cost and QALYs are lowest for the dual strategy, with an average cost-effectiveness ratio of 789/17.4552 SGD/QALYs. The TST alone strategy yields an incremental cost of 61 SGD as well as an incremental QALY gain of 0.0371 compared with the dual strategy. QFT-IT alone strategy proves to be the most expensive one and achieve intermediate QALY gains.

A strategy is dominated if it has higher cost and lower effectiveness gains. In our study, the QFT-IT alone strategy is dominated by TST alone with an incremental cost-effectiveness ratio (ICER) of -1980 SGD per QALY gained. Although the dual strategy has the lowest average cost-effectiveness ratio, it does not achieve as much QALYs gains as TST in this context. Given the conventional willingness to pay (WTP) of 63,000 SGD per QALY gained (50,000 USD/QALY: one US dollar equals to 1.26 Singapore dollars), our results (an ICER of 1644 SGD/QALY) recommend that conducting TST test alone is the optimal option to diagnose ocular TB in Singapore as it can help achieve most QALY gains within the assigned WTP threshold.

3.2 Sensitivity analysis:

The one-way sensitivity analysis results reveal that the ICER of TST does not exceed the threshold of 63,000 SGD/QALY by varying any parameter within the assigned range. As reflected in the Tornado diagram in Figure 4, the major drivers of the change in ICER are: the QALYs for patients who end up with persistent inflammation, the intraocular TB prevalence among uveitis patients, the QALYs for patients who result in only eye symptoms resolved, the cost of QFT-IT test, the TST specificity and the probability of initiating ATT.

See appendix for the detailed report of the one-way sensitivity analysis of the primary drivers. We observe an increasing trend of the ICER with the growth of QALYs for patients who end up with persistent inflammation and QALYs for patients who result in only eye symptoms resolved. The QFT-IT alone strategy remains to be the dominated one regardless of how the QALYs change. Tuberculosis prevalence among uveitis patients proves to be negatively associated with the ICER of TST alone strategy. The ICER decreases to 1467 SGD/QALY when the prevalence reaches to 26.2%. QFT-IT alone strategy still remains dominated when the prevalence is varied within the assigned range. The testing cost of QFT-IT turns out to be an important driver of the cost-effectiveness of QFT-IT alone strategy, which is not dominated until its cost surpasses 155 SGD. Nevertheless, having a lower QALYs gained renders QFT-IT alone a suboptimal strategy compared with TST alone. When varying the TST specificity from 0.60 to 0.90, the ICER of TST decreases from 4758 to 856 SGD/QALY. The QFT-IT alone strategy becomes more cost-saving than the TST alone when the TST specificity is as low as 0.60 but the

advantage vanishes after the TST specificity exceeds 0.675. A positive correlation is found between the probability of initiating TB treatment and the incremental cost of TST alone strategy, resulting in an increasing ICER of TST alone strategy as the probability climbs. The effectiveness gains for all the three strategy grow as more people are willing to initiate ATT.

Figure 5 displays the cost effectiveness acceptability curve generated by the Monte Carlo simulation. It shows that TST alone strategy is cost-effective among 50% of iterations when the WTP is 3,300 SGD/QALY. Once the WTP increases to 6,300 SGD/QALY, TST alone strategy becomes cost-effective among 100% of the iterations.

Table 3: Cost-effectiveness of the three strategies as diagnostic tests for intraocular tuberculosis in Singapore

Strategy	Cost (SGD)	Incremental cost (SGD)	QALYs	Incremental QALYs	ICER (SGD/QALY)	Dominance
Dual	789	-	17.4552	-	-	Not dominated
TST	850	61	17.4923	0.0371	1644	Not dominated
QFT-IT	889	39	17.4726	-0.0197	-1980	Dominated

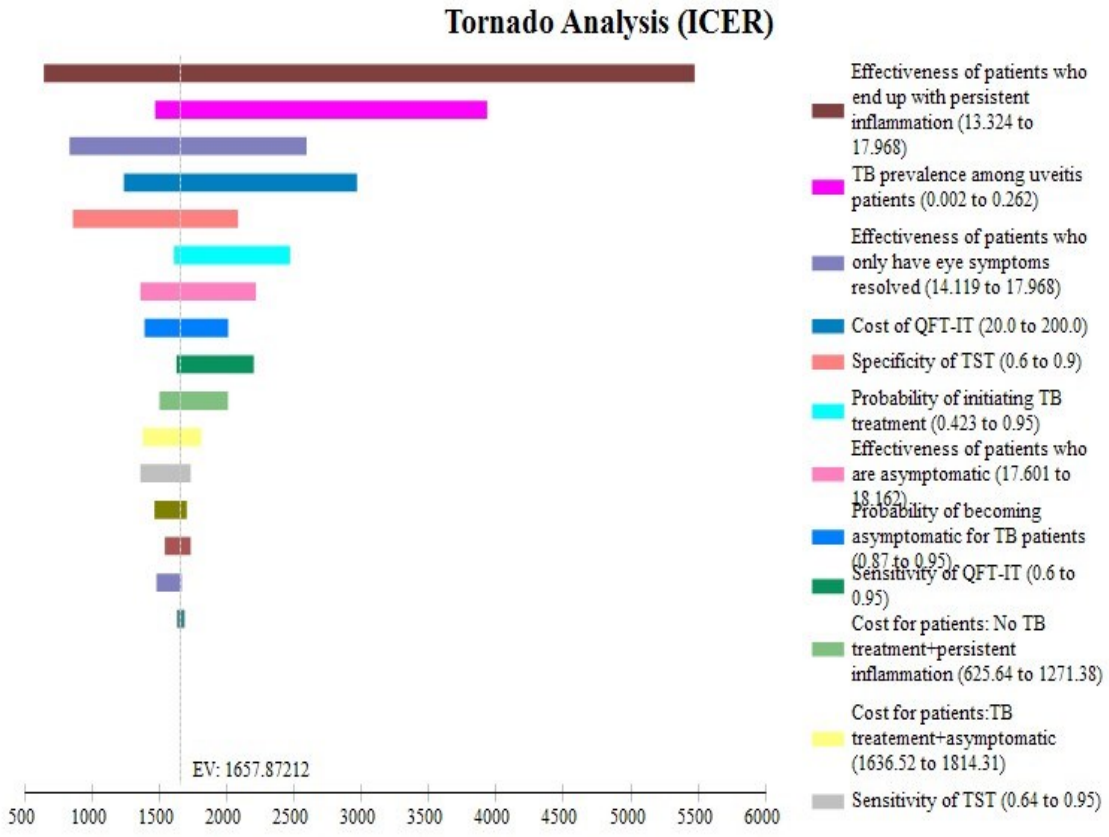

Figure 4 One-way sensitivity analysis: Tornado analysis output

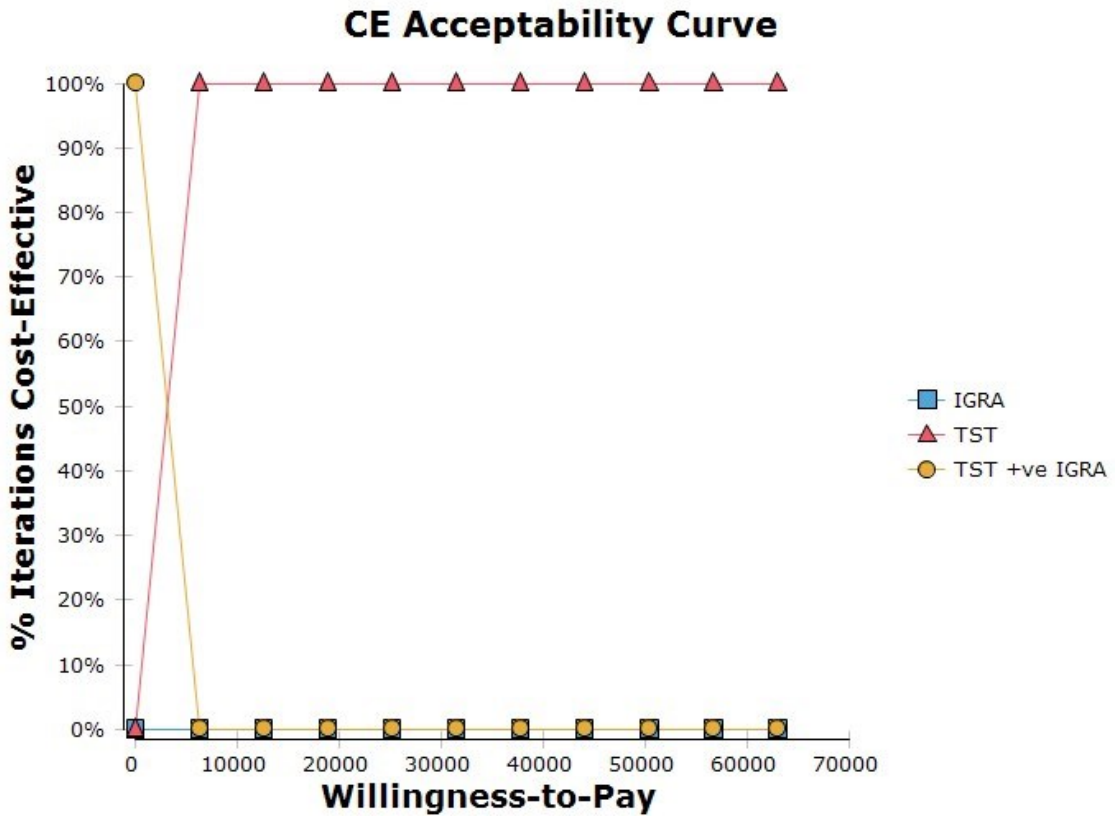

Figure 5 Probabilistic sensitivity analysis: cost-effectiveness acceptability curve

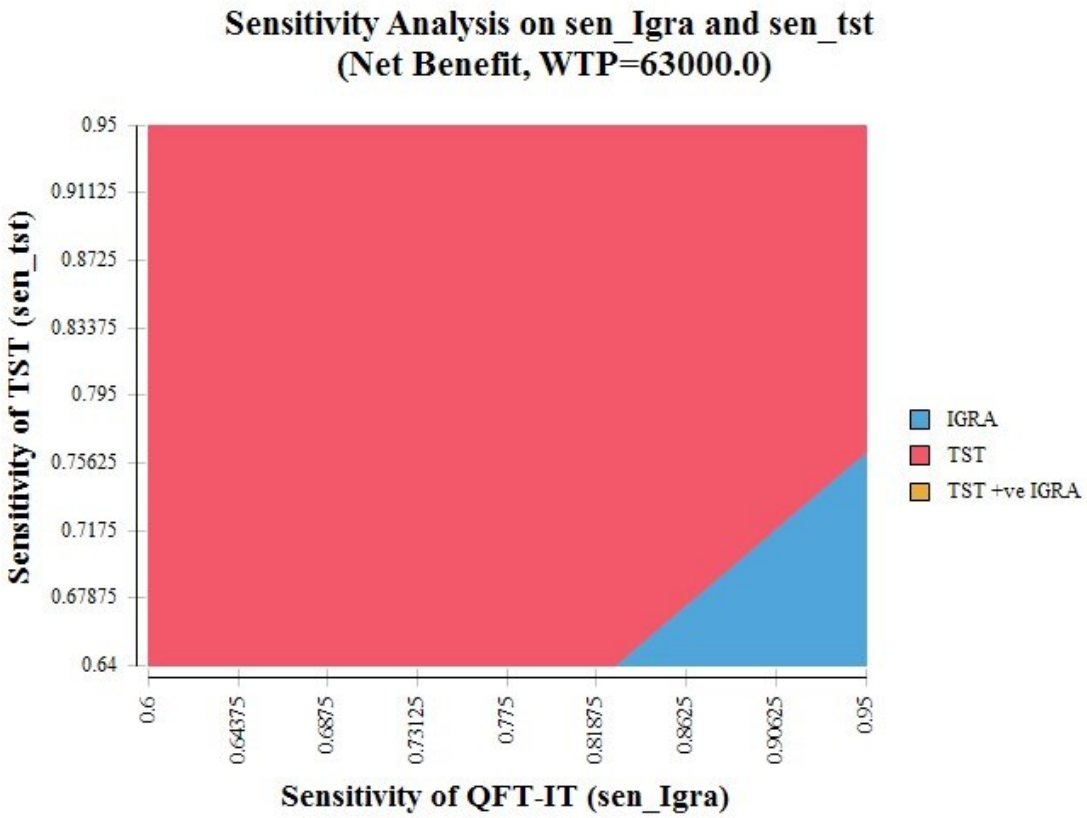

Figure 6 The impact of the sensitivities on the optimality of each strategy

4. Discussion:

The low specificity of TST in BCG-vaccinated and immunocompromised population necessitates the birth of IGRAs that can more specifically measure molecular responses to TB antigens. New technology often brings with new cost, making it necessary to evaluate whether the incurred cost is outweighed by increased effectiveness before widespread implementation. Results of previous studies recommended using either IGRA alone or dual strategy to replace the present TST alone strategy in screening and diagnosing pulmonary TB (Nienhaus, et al., 2011). Unlike the findings of most previous studies, the present incremental cost-effectiveness analysis demonstrates that performing single TST test to diagnose intraocular TB among uveitis patients is optimal in Singapore.

In our analysis, the dual strategy, performing QFT-IT as the confirmatory test following a positive TST result, is the least costly one as it avoids unnecessary INH chemoprophylaxis by decreasing the number of false positive cases. QFT-IT alone strategy turns out to be the most expensive one and suboptimal in cost terms alone, thus rendering it to be dominated by TST alone strategy that helps to gain more QALYs and costs less. The advantage of the dual strategy in saving costs is offset by its comparative ineffectiveness measured by QALYs gained. Therefore, using the conventional WTP of 63, 000 SGD per QALY gained, TST alone surpasses the dual strategy as the preferred choice for it gains more QALYs within the financial constraint.

Interpretation and generalizability of the study results relies on specific key assumptions, the study setting and population. One key assumption in the present study is the lower

sensitivity of QFT-IT compared with TST, unlike most of the previous studies that assume QFT-IT outperforms, if not as good as, TST in terms of sensitivity (Nienhaus, et al., 2011; Oxlade, Pinto, Trajman, & Menzies, 2013). The mechanism behind QFT-IT test determines its higher specificity than TST especially among BCG-vaccinated and immunocompromised people, whereas the evidence remains conflicting in terms of their performance in sensitivity. For example, Mazurek et al found in their cross-sectional study of navy recruits that IGRAs might be less sensitive than TST given the negative QFT-G results for recruits born in high-prevalence countries and whose TST induration was ≥ 15mm(Mazurek et al., 2007). Pollock et al also raised serious concerns about the sensitivity of IGRA due to the extreme inconsistency between the results of their clinical diagnostic algorithm and the test outcome (Pollock et al., 2008). However, in a study among 54 patients with pulmonary TB disease, the sensitivity of QFT was found to be 81% compared with 78% for TST (Kang et al., 2005). Another study among a population of 318 hospitalized patients found that the sensitivity of QFT was much greater than that of TST (67% vs. 33%)(Ferrara, et al., 2006). Given the inconsistent evidence and the different testing population in the present study, we obtained the test-related data from a local study, assuming TST had a sensitivity of 0.69, compared with 0.64 for QFT-IT. As a result, TST outperforms QFT-IT in screening out more true positives, resulting in more QALY gains to become the best option in diagnosing TB in uveitis patients.

The impact of the test-specific sensitivity assumption on the outcome is further explored through sensitivity analysis (See Figure 6 for how the optimality of each strategy changes with the variance of sensitivity of the two tests). By varying the QFT-IT sensitivity from

0.60 to 0.95, QFT-IT alone transforms from a dominated strategy to the optimal choice once its sensitivity surpasses 0.87, holding TST sensitivity at the baseline level of 0.69. The QALYs gained for QFT-IT alone strategy reaches to 17.4995 when its sensitivity increases to 0.95, with an incremental effectiveness of 0.0073 compared with TST alone. Such findings suggest that TST may lose its advantage when QFT-IT sensitivity gets higher. Therefore, careful examination of the test performance in local setting and particular population is highly recommended for evaluation accuracy improvement.

Another key assumption that favors the TST alone strategy is the 100% TST return rate, meaning nobody will miss the reading after 48-72 hours of the first skin test. It is true in Singapore where patient compliance and adherence is perfect but might not be the case in other study settings. For example, in the UK, up to 60% of patients fail to show up for TST readings (Bothamley et al., 2002; Dewan et al., 2006). In a study carried out in Brazil, 10% of the subjects failed to show up again for TST readings (Steffen, et al., 2013). Failure to return significantly lowers the effectiveness of both TST alone and the dual strategy; however, the magnitude of the impact needs to be assessed based on the specific return rate in the study setting before recommending IGRAs for widespread adoption.

Apart from the difference in key assumptions that gives rise to the inconsistency of results, it is noticeable that the present study population is uveitis patients rather than close contacts of pulmonary TB patients in most of the previous studies. In our study, all patients receive eye treatment regardless of the etiology of the uveitis. Unlike pulmonary TB patients whose symptoms are primarily relieved by ATT, intraocular TB patients

depend on both eye treatment (steroids) and ATT for full recovery. Thus, for false negatives who only receive eye treatment, there is a big chance that their eye symptoms will get resolved as well in the short run. The high efficacy of eye treatment minimizes the prognostic difference between true and false negatives, rendering the low specificity of TST less disadvantageous in this case.

The huge gap between the testing cost of QFT-IT (156 SGD) and TST (22 SGD) in the present study is another contributor to the winning of TST alone strategy. The cost ratio of the two strategies is 7.09, significantly higher than previous studies which have the highest ratio of 5.6 (Nienhaus, et al., 2011). By varying the QFT-IT cost from 20 to 200 SGD, we find out that QFT-IT alone outperforms TST as long as the QFT-IT testing cost remains lower than 155 SGD in cost terms alone. Although TST alone still stands out as the optimal choice with greatest QALYs gained based on the key assumptions mentioned above, QFT-IT alone is no longer dominated once the cost lowers down and might be recommended as the preferred strategy depending on how the assumptions change.

Interestingly, we find that TST alone strategy can gain more QALYs compared with QFT-IT alone in Singapore where BCG vaccination is given to all the newborns since 1957 ("Discontinuation of repeat," 2001). We assume a specificity of 0.995 for QFT-IT and 0.74 for TST at baseline. When varying the TST specificity from 0.60 to 0.90 in the one-way sensitivity analyses, TST outperforms QFT-IT with an incremental effectiveness of 0.028 QALYs even when its specificity decreases to 0.60. Such findings suggest that the higher specificity of IGRAs do not necessarily go with higher effectiveness gains even in BCG-vaccinated population.

We also observe the great impact of the probability of initiating ATT on the effectiveness gains of the three testing strategies. In our study, the probability of initiating ATT for uveitis patients who tested TB positive is 43.7%, compared with the widely used percentage of 80% among pulmonary TB positives (Taylor, 2000). The huge gap is largely attributed to the high expense of ATT in comparison to eye treatment alone which can also help relieve eye symptoms in the short run. The one-way sensitivity analysis observes a dramatic increase of effectiveness gains for all of the three strategies and the TST remains to be the optima strategy in saving 17.5809 QALYs with a cost of 1038 SGD when the probability increases to 95%. It may suggest the need to promote ATT among uveitis patients who are tested TB positive to maximize the effectiveness gained.

Our decision model assumes adherence of the nine-month INH treatment is perfect in Singapore, which might not be the case in other study settings. Adherence of the nine-month ATT has always been an important concern as shown in previous studies. In a recent study conducted by Goswami et al among 496 adults who met the CDC guidelines for latent TB infection (LTBI), it is found that the completion rate is only 53% (Goswami et al., 2012). Low adherence will undoubtedly drive down the overall effectiveness of the three strategies, which might be necessary to model into the decision trees for a more comprehensive evaluation in settings where adherence is a concern.

To our knowledge, the present study is the first one that compares the cost-effectiveness of the QFT-IT and TST in diagnosing TB among uveitis patients. Previous studies are all conducted among pulmonary TB patients for evaluation. Our findings recommend conducting TST single test in Singapore to diagnose ocular TB as it achieves the most

QALY gains given the financial threshold of 63,000 SGD/QALY. This is inconsistent with most of the findings of previous studies that recommend either QFT-IT alone or dual strategy to replace TST alone strategy (Nienhaus, et al., 2011). Causes for the inconsistency, as discussed previously, are different values assigned to test-specific parameters and assumptions made during modeling. For example, the NICE analysis, conducted in 2004, assumed that IGRAs had the same sensitivity with TST and only performed slightly better in terms of specificity ("Clinical diagnosis and management", 2006). Therefore, generalizability of the results of the present study substantially depends on the key assumptions made in the model. It is never too cautious to examine the assumptions when generalizing the results in another population.

There are several limitations of the present study. In our model, we only calculated the direct treatment cost instead of including other relevant costs to patients. One prominent issue is the opportunity cost associated with the 72-hour waiting time when screened with TST. However, it is justifiable in the current study as we are evaluating cost from the perspective of Singaporean healthcare system. Studies that aim to evaluate the test from the patients' perspective might need to include the cost in their modeling. Besides, we only calculated costs incurred during the two-year cohort study due to data availability, thus underestimating the future treatment costs especially for patients who end up with persistent inflammation. Although the two-year treatment cost has already demonstrated the tendency that patients with persistent inflammation spend more on treatment, it is still necessary to add estimated future cost into the model for optimized accuracy.

Our study used a static decision tree instead of a Markov model to estimate the cost effectiveness of the three testing strategies. The static framework assumes that the patients stick to the same eye status as that in or after the treatment for 30 years, underestimating the effectiveness gains of the nine-month INH chemoprophylaxis as the uveitis will come back to the TB patients who only receive eye treatment in a more frequent and severer manner in the long run.

Further, that we applied 3% discounting rate to all patients regardless of their prognosis neglects the existing differential mortality between diagnosed and undiagnosed ocular TB patients, which also underestimates the effectiveness gains of the INH chemoprophylaxis. One ideal way to fix it is to calculate their QoL year by year to capture the effectiveness differentials. However, limited data availability prevents the current study from making it happen. Therefore, it might be an important area for future studies to measure the post-treatment QoL changes among TB-associated and non-TB uveitis patients.

In addition, our analysis did not sub-divide study participants according to their age group, immune status and ethnic groups. It is a challenge in the present study due to small sample size but can be an important area of future research.

In conclusion, given the local prevalence and the key assumptions made in the analysis model, the TST alone strategy is recommended in diagnosing intraocular TB among, uveitis patients in Singapore.

Appendix

Detailed report of the one-way sensitivity analyses results: the top six drivers

1. QALYs of patients who end up with persistent inflammation

Sensitivity Cost Effectiveness Analysis

effectiveness_PI	Strategy	Cost	Incr cost	Eff	Incr Eff	C/E	Incr C/E (ICER)	Dominance
13.324								
	TST +ve IGRA	788.7348	0.0000	16.6491	0.0000	47.3741	0.0000	
	TST	850.1991	61.4643	16.7448	0.0958	50.7738	641.8750	
	IGRA	888.6967	38.4975	16.6844	-0.0605	53.2653	-636.6322	(Dominated)
14.485								
	TST +ve IGRA	788.7348	0.0000	16.9394	0.0000	46.5622	0.0000	
	TST	850.1991	61.4643	17.0140	0.0746	49.9706	823.6431	
	IGRA	888.6967	38.4975	16.9682	-0.0458	52.3742	-841.2148	(Dominated)
15.646								
	TST +ve IGRA	788.7348	0.0000	17.2297	0.0000	45.7778	0.0000	
	TST	850.1991	61.4643	17.2832	0.0535	49.1924	1149.0285	
	IGRA	888.6967	38.4975	17.2521	-0.0311	51.5124	-1239.5438	(Dominated)
16.807								
	TST +ve IGRA	788.7348	0.0000	17.5200	0.0000	45.0192	0.0000	
	TST	850.1991	61.4643	17.5523	0.0324	48.4380	1899.3974	
	IGRA	888.6967	38.4975	17.5360	-0.0164	50.6785	-2354.3826	(Dominated)
17.968								
	TST +ve IGRA	788.7348	0.0000	17.8102	0.0000	44.2855	0.0000	
	TST	850.1991	61.4643	17.8215	0.0112	47.7064	5474.5002	
	IGRA	888.6967	38.4975	17.8198	-0.0016	49.8712	-23402.0994	(Dominated)

2. Prevalence of intraocular TB among uveitis patients

Sensitivity Cost Effectiveness Analysis

TBprev_uveitispatients	Strategy	Cost	Incr cost	Eff	Incr Eff	C/E	Incr C/E (ICER)	Dominance
0.002								
	TST +ve IGRA	709.8164	0.0000	17.5987	0.0000	40.3335	0.0000	
	TST	789.1410	79.3246	17.6188	0.0202	44.7896	3932.7858	
	IGRA	805.0160	15.8750	17.5991	-0.0197	45.7419	-804.5628	(Dominated)
0.067								
	TST +ve IGRA	732.8195	0.0000	17.5568	0.0000	41.7398	0.0000	
	TST	806.9382	74.1187	17.5820	0.0251	45.8958	2953.2537	
	IGRA	829.4073	22.4690	17.5622	-0.0197	47.2267	-1140.4222	(Dominated)
0.132								
	TST +ve IGRA	755.8226	0.0000	17.5150	0.0000	43.1528	0.0000	
	TST	824.7354	68.9128	17.5450	0.0300	47.0067	2295.2169	
	IGRA	853.7985	29.0630	17.5254	-0.0197	48.7178	-1477.2678	(Dominated)
0.197								
	TST +ve IGRA	778.8258	0.0000	17.4732	0.0000	44.5726	0.0000	
	TST	842.5326	63.7069	17.5082	0.0350	48.1223	1822.7099	
	IGRA	878.1897	35.6570	17.4885	-0.0196	50.2152	-1815.1038	(Dominated)
0.262								
	TST +ve IGRA	801.8289	0.0000	17.4314	0.0000	45.9992	0.0000	
	TST	860.3299	58.5010	17.4713	0.0399	49.2426	1466.9636	
	IGRA	902.5809	42.2510	17.4516	-0.0196	51.7190	-2153.9347	(Dominated)

3. QALYs of patients who result in only eye symptoms resolved

Sensitivity Cost Effectiveness Analysis

effectiveness_eyesymptomsresolved	Strategy	Cost	Incr cost	Eff	Incr Eff	C/E	Incr C/E (ICER)	Dominance
◢ 14.119								
	TST +ve IGRA	788.7348	0.0000	17.1393	0.0000	46.0191	0.0000	
	TST	850.1991	61.4643	17.2132	0.0740	49.3921	830.8968	
	IGRA	888.6967	38.4975	17.1862	-0.0271	51.7099	-1422.6952	(Dominated)
◢ 15.08125								
	TST +ve IGRA	788.7348	0.0000	17.2468	0.0000	45.7321	0.0000	
	TST	850.1991	61.4643	17.3083	0.0614	49.1210	1000.8956	
	IGRA	888.6967	38.4975	17.2837	-0.0245	51.4181	-1569.3703	(Dominated)
◢ 16.0435								
	TST +ve IGRA	788.7348	0.0000	17.3544	0.0000	45.4487	0.0000	
	TST	850.1991	61.4643	17.4033	0.0488	48.8529	1258.3502	
	IGRA	888.6967	38.4975	17.3813	-0.0220	51.1296	-1749.7652	(Dominated)
◢ 17.00575								
	TST +ve IGRA	788.7348	0.0000	17.4620	0.0000	45.1687	0.0000	
	TST	850.1991	61.4643	17.4983	0.0363	48.5876	1694.1184	
	IGRA	888.6967	38.4975	17.4788	-0.0195	50.8443	-1977.0182	(Dominated)
◢ 17.968								
	TST +ve IGRA	788.7348	0.0000	17.5696	0.0000	44.8922	0.0000	
	TST	850.1991	61.4643	17.5933	0.0237	48.3253	2591.5887	
	IGRA	888.6967	38.4975	17.5763	-0.0169	50.5622	-2272.1116	(Dominated)

4. QFT-IT testing cost

Sensitivity Cost Effectiveness Analysis

cost_IGRA	Strategy	Cost	Incr cost	Eff	Incr Eff	C/E	Incr C/E (ICER)	Dominance
◢ 20.0								
	TST +ve IGRA	740.2168	0.0000	17.4552	0.0000	42.4067	0.0000	
	IGRA	752.6967	12.4799	17.4726	0.0174	43.0786	715.5040	
	TST	850.1991	97.5025	17.4923	0.0196	48.6043	4966.4620	
◢ 65.0								
	TST +ve IGRA	756.2706	0.0000	17.4552	0.0000	43.3264	0.0000	
	IGRA	797.6967	41.4261	17.4726	0.0174	45.6541	2375.0706	
	TST	850.1991	52.5025	17.4923	0.0196	48.6043	2674.3071	
◢ 110.0								
	TST +ve IGRA	772.3243	0.0000	17.4552	0.0000	44.2461	0.0000	
	IGRA	842.6967	70.3724	17.4726	0.0174	48.2295	4034.6371	
	TST	850.1991	7.5025	17.4923	0.0196	48.6043	382.1522	
◢ 155.0								
	TST +ve IGRA	788.3780	0.0000	17.4552	0.0000	45.1658	0.0000	
	TST	850.1991	61.8211	17.4923	0.0371	48.6043	1667.4947	
	IGRA	887.6967	37.4975	17.4726	-0.0196	50.8050	-1910.0027	(Dominated)
◢ 200.0								
	TST +ve IGRA	804.4318	0.0000	17.4552	0.0000	46.0855	0.0000	
	TST	850.1991	45.7673	17.4923	0.0371	48.6043	1234.4784	
	IGRA	932.6967	82.4975	17.4726	-0.0196	53.3804	-4202.1576	(Dominated)

5. TST specificity

Sensitivity Cost Effectiveness Analysis

Sp_tst	Strategy	Cost	Incr cost	Eff	Incr Eff	C/E	Incr C/E (ICER)	Dominance
0.6								
	TST +ve IGRA	805.9125	0.0000	17.4552	0.0000	46.1703	0.0000	
	IGRA	888.6967	82.7841	17.4726	0.0174	50.8622	4757.6877	
	TST	900.5465	11.8498	17.5007	0.0280	51.4579	422.7848	
0.675								
	TST +ve IGRA	796.7102	0.0000	17.4552	0.0000	45.6431	0.0000	
	TST	873.5747	76.8645	17.4962	0.0410	49.9295	1876.9044	
	IGRA	888.6967	15.1220	17.4726	-0.0235	50.8622	-642.6608	(Dominated)
0.75								
	TST +ve IGRA	787.5078	0.0000	17.4552	0.0000	45.1160	0.0000	
	TST	846.6029	59.0951	17.4917	0.0365	48.4004	1620.0407	
	IGRA	888.6967	42.0938	17.4726	-0.0190	50.8622	-2211.6803	(Dominated)
0.825								
	TST +ve IGRA	778.3055	0.0000	17.4552	0.0000	44.5888	0.0000	
	TST	819.6311	41.3256	17.4872	0.0320	46.8704	1291.3360	
	IGRA	888.6967	69.0656	17.4726	-0.0145	50.8622	-4751.7673	(Dominated)
0.9								
	TST +ve IGRA	769.1031	0.0000	17.4551	0.0000	44.0617	0.0000	
	TST	792.6593	23.5562	17.4827	0.0275	45.3397	855.7508	
	IGRA	888.6967	96.0373	17.4726	-0.0100	50.8622	-9568.3917	(Dominated)

6. Probability of initiating ATT

Sensitivity Cost Effectiveness Analysis

pofstart_TB	Strategy	Cost	Incr cost	Eff	Incr Eff	C/E	Incr C/E (ICER)	Dominance
0.423								
	TST +ve IGRA	787.3482	0.0000	17.4540	0.0000	45.1100	0.0000	
	TST	845.0605	57.7123	17.4898	0.0359	48.3172	1608.1896	
	IGRA	886.6176	41.5571	17.4708	-0.0190	50.7484	-2186.8435	(Dominated)
0.55475								
	TST +ve IGRA	800.3969	0.0000	17.4655	0.0000	45.8272	0.0000	
	TST	893.4186	93.0217	17.5126	0.0471	51.0158	1976.4972	
	IGRA	906.1829	12.7643	17.4877	-0.0249	51.8184	-512.1681	(Dominated)
0.6865								
	TST +ve IGRA	813.4456	0.0000	17.4771	0.0000	46.5435	0.0000	
	IGRA	925.7482	112.3026	17.5045	0.0274	52.8862	4098.5771	
	TST	941.7768	16.0285	17.5354	0.0308	53.7073	519.7149	
0.81825								
	TST +ve IGRA	826.4944	0.0000	17.4887	0.0000	47.2588	0.0000	
	IGRA	945.3136	118.8192	17.5214	0.0327	53.9521	3638.1824	
	TST	990.1349	44.8213	17.5581	0.0368	56.3919	1219.3019	
0.95								
	TST +ve IGRA	839.5431	0.0000	17.5003	0.0000	47.9731	0.0000	
	IGRA	964.8789	125.3358	17.5382	0.0379	55.0159	3305.4868	
	TST	1038.4930	73.6141	17.5809	0.0427	59.0695	1724.8456	

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