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Research Article

Cost-Utility Analysis of *HLA-B*15:02* Testing for Preventing Phenytoin-Induced Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN) in Thailand

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ABSTRACT

Genetic testing has potential to identify individuals at risk of adverse drug reactions. Meta-analysis data indicated significant association between *HLA-B*15:02* and phenytoin-induced Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) with odds ratio of 4.12 (95% CI 1.77-9.59, *p=0.001*). Additionally, the prevalence of the *HLA-B*15:02* gene ranks second in the Thai population. Despite this, there is a lack of evidence from economic evaluation to inform policy decisions for optimizing resource allocation. Therefore, this study aims to conduct cost-utility analysis of *HLA-B*15:02* testing before initiating phenytoin treatment to prevent SJS/TEN and alternative drugs with sodium valproate, known to have a lower risk of SJS/TEN but higher cost compared to phenytoin treatment without testing. A decision tree and Markov models were constructed to evaluate the lifetime costs and quality-adjusted life year (QALY) with one-year cycle length in patients newly diagnosed with epilepsy. The analysis was conducted from government and societal perspective within the Thai context. Input parameters, including cost, utility, and transitional probabilities, were obtained from relevant literature predominantly conducted in the Thai population. One-way and probabilistic sensitivity analyses were performed to assess the robustness of the findings. Compared to no-testing, the incremental cost-effectiveness ratios (ICERs) were 57,185 THB/QALY gained for *HLA-B*15:02* testing before initiation of phenytoin therapy and 54,842 THB/QALY gained for alternative drugs strategy from societal perspective. One-way sensitivity analysis indicated that the phenytoin-induced other ADRs had the most impact on the ICER. At the Thai cost-effectiveness threshold of 160,000 THB/QALY, the probability of the alternative drugs strategy being the most cost-effective was 79%. Furthermore, the number needed to screen to prevent one case of SJS/TEN was 1,470. Implementing *HLA-B*15:02* testing and alternative drugs strategy were determined to be cost-effective compared to the no-testing strategy. These findings provide valuable guidance to physicians in optimizing treatment and policymakers considering decisions to prevent serious ADRs.

Keywords:
cost-utility analysis, *HLA-B*15:02* testing, phenytoin-induced SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis, Adverse Drug Reactions

1. INTRODUCTION

Severe adverse drug reactions (ADRs) constitute a significant cause of morbidity and mortality among the Thai population. Although severe ADRs occur in only 2-3% of hospitalized patients, they are associated with mortality rates ranging from 10-40% and can result in long-term disability[1]. According to data from the Health Product Vigilance Center, Thai Food and Drug Administration, Ministry of Public Health (Thai Vigibase), cutaneous adverse drug reactions (CADRs)

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have ranked as the most common type of ADR in Thailand from 1984 to 2022 Among these, antiepileptic drugs have been identified as the sixth leading cause, with phenytoin ranking ninth among all implicated medications[2]. Between 1984 and 2011, there were 10,492 documented Stevens- Johnson Syndrome/ Toxic Epidermal Necrolysis (SJS/ TEN) cases. Among these cases, certain drugs, including allopurinol, carbamazepine, phenobarbital, and phenytoin, were associated with the development of SJS/ TEN[2]. SJS/TEN are severe cutaneous adverse reactions (SCARs) with reported long-term morbidity and mortality rates of approximately 1- 5% for SJS and as high as 25-30% for TEN[3,4].

Currently, it has been observed that CADRs are associated with the human leukocyte antigen (*HLA- B*) genetic predisposition. A retrospective observational cohort study conducted in Thailand over 10 years from 2011 to 2020, involving 13,985 participants receiving various antiepileptic drugs, identified the top three *HLA- B* alleles in the Thai population as *HLA- B*58: 01* (16.03%), *HLA-B*15:02* (14.96%), and *HLA-B*13:01* (12. 91%), respectively. *HLA- B*15: 02* was the second most prevalent gene associated with CADRs in the Thai population[5]. The genetic profile of *HLA- B*15: 02* in patients receiving phenytoin was found to be significantly associated with the development of SCARs, specifically SJS/TEN, based on a meta-analysis in populations from East Asia, including Malaysians, Han Chinese, and Thais. Individuals carrying the *HLA- B*15: 02* allele and receiving phenytoin presented a statistically significant increased risk of developing SCARs, specifically SJS/TEN (OR 4.12, 95% CI 1.77–9.59, $p = 0.001$)[6].

According to the clinical practice guidelines for epilepsy treatment for physicians in 2021, phenytoin is a commonly used antiepileptic drug. It is considered a first- line drug for treating epilepsy or focal seizures in adults[7]. Phenytoin was included in the National List of Essential Medicines (NLEM) for controlling seizures[8]. Additionally, phenytoin is used off- label in patients with traumatic brain injury to prevent early posttraumatic seizures. However, the use of phenytoin raises significant safety concerns, particularly regarding the risk of SCARs, such as SJS/ TEN[7]. Therefore, screening for the *HLA- B*15: 02* gene is beneficial in aiding the decision to use phenytoin to reduce the risk of SCARs.

Recent studies have demonstrated the cost-effectiveness of *HLA-B*15:02* screening to avoid severe adverse drug reactions (ADRs) from carbamazepine therapy in Thailand[9] and internationally[10-12]. Consequently, *HLA-B*15:02* screening before carbamazepine therapy has been incorporated into Thailand's Universal Coverage Scheme (UCS) benefit package since October 1, 2018[13]. However, there is a lack of evidence regarding the cost-effectiveness of *HLA- B*15: 02* testing before initiating phenytoin therapy to prevent severe ADRs. This gap in evidence limits the ability of policymakers to make informed decisions about resource allocation, both in Thailand and globally. Therefore, this study aims to conduct a cost-utility analysis of *HLA-B*15:02* testing before initiating phenytoin therapy and alternative drugs, which is sodium valproate to prevent SJS/ TEN compared to phenytoin treatment without testing in patients with epilepsy. The findings from this study are expected to provide essential evidence for physicians in optimizing treatment strategies and inform policy decision-making. Specifically, the results may support the inclusion of *HLA-B15:02* testing prior to initiating phenytoin therapy in the UCS benefit package, with the aim of preventing severe ADRs.

2. MATERIALS AND METHODS

2.1 Study Design

A hybrid decision tree and Markov model were developed to determine lifetime costs and health outcomes in patients with epilepsy receiving *HLA- B*15: 02* testing before initiating phenytoin treatment and alternative drugs which is sodium valproate to prevent SJS/ TEN compared to phenytoin treatment without testing. The analysis was made from a governmental and societal perspective.

2.2 Target population

The model simulated cohorts of individuals aged 18 years and older who were newly diagnosed with epilepsy and initiated on phenytoin therapy

2.3 Interventions and comparator

The analysis included three strategies: 1) *HLA- B* 15: 02* testing before initiating phenytoin treatment, 2) phenytoin treatment without testing (no testing), and 3) the alternative drugs, sodium valproate. The following details were provided.

*1) HLA-B*15:02* testing

Prior to initiating phenytoin treatment, newly diagnosed epilepsy patients were tested with *HLA- B* 15: 02*. Patients with a positive test result were prescribed the alternative drug, sodium valproate. In contrast, those with a negative test result continued the phenytoin treatment.

2) No-testing

Patients newly diagnosed with epilepsy were treated with phenytoin without prior genetic testing, which reflects the current standard practice in Thailand. Based on the clinical practice guidelines for managing antiepileptic drugs in patients with epilepsy in 2021[7],

the first-line drug is phenytoin, with an initial dose of 200-300 mg/day and a maintenance dose of 300-500mg/day. If patients develop serious ADRs due to phenytoin, sodium valproate would be recommended as an alternative drug.

3) The alternative drug, sodium valproate

Sodium valproate is recognized for its lower risk of SJS/TEN; however, it is generally more expensive compared to phenytoin. It is included in the clinical practice guidelines for the treatment of epilepsy for physicians[7] and is listed in the NLEM for the treatment of epilepsy or focal seizures in adults[8].

Patients newly diagnosed with epilepsy were treated with sodium valproate, with an initial dose of 500-1,000 mg/day and a maintenance dose of 1,000-3,000 mg/day[7].

Accordingly, all treatment was provided life-long treatment. Patients who undergo *HLA-B*15:02* testing prior to phenytoin treatment can prevent SJS/TEN by switching to sodium valproate if the screening results are positive. Conversely, patients who begin treatment with sodium valproate do not experience any occurrences of SJS/TEN. Therefore, *HLA-B*15:02* testing prior to phenytoin treatment and using sodium valproate result in improved quality of life for patients and reduced costs associated with SJS/TEN.

2.4 Model Structure

A hybrid of decision tree and Markov models was constructed to estimate the lifetime costs and consequences of each strategy by following the same adult cohort for all strategies. The lifetime time horizon was employed with a one-year cycle length

The decision tree model simulated the three potential strategies for treating patients with epilepsy **(Figure 1)** as described in section 2.3, Interventions and comparator.

Under the no-testing strategy, all patients would receive phenytoin. However, individuals carrying the *HLA-B*15:02* allele are at an increased risk of developing SJS/TEN as a result of phenytoin treatment. In cases where SJS/TEN develops, sodium valproate would be prescribed as an alternative, while patients who do not develop SJS/TEN would continue phenytoin therapy.

In the *HLA-B*15:02* testing strategy, patients with a positive test result would be prescribed an alternative medication, sodium valproate, while those with a negative result would continue phenytoin therapy.

In the alternative drug strategy, all patients would receive sodium valproate.

During the initial year, all patients, whether they received phenytoin or alternative drugs, there were three possible outcomes: 1) no development of any ADRs., 2) the development of other ADRs without SJS/TEN, and 3) the development of SJS/TEN. After the decision tree, patients entered the long-term Markov model to predict the lifetime costs and outcomes. **Figure 2 (M1, M4)** presents patients who do not develop ADRs, who could remain in this state or die from other causes. **Figure 2 (M2, M5)** demonstrates that patients who develop other ADRs could transition to a state of recovery or death from other causes in the next cycle. **Figure 2 (M3)** shows patients who develop SJS/TEN from phenytoin. This scenario includes four possible health states: 1) occurrence of SJS/TEN, 2) recovery with sequelae, 3) recovery without complications, and 4) death. In this context, "death" in the model refers to mortality resulting from SJS/TEN and other causes.

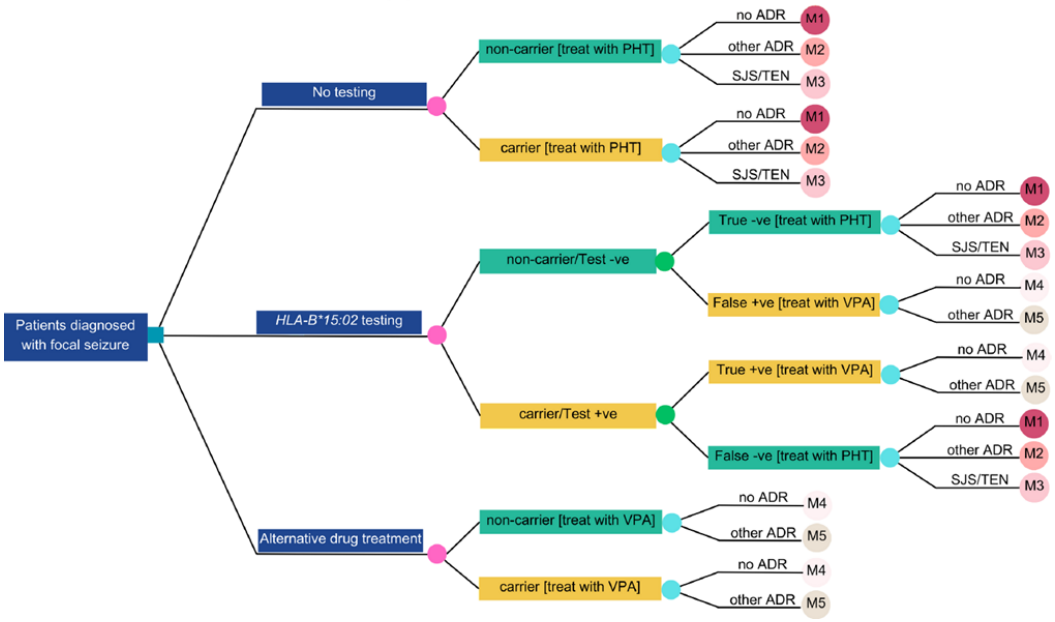

Figure 1 Decision tree models
ADRs: adverse drug reaction, **PHT**: phenytoin, **VPA**: sodium valproate, **SJS/TEN**: Stevens-Johnson syndrome/toxic epidermal necrolysis

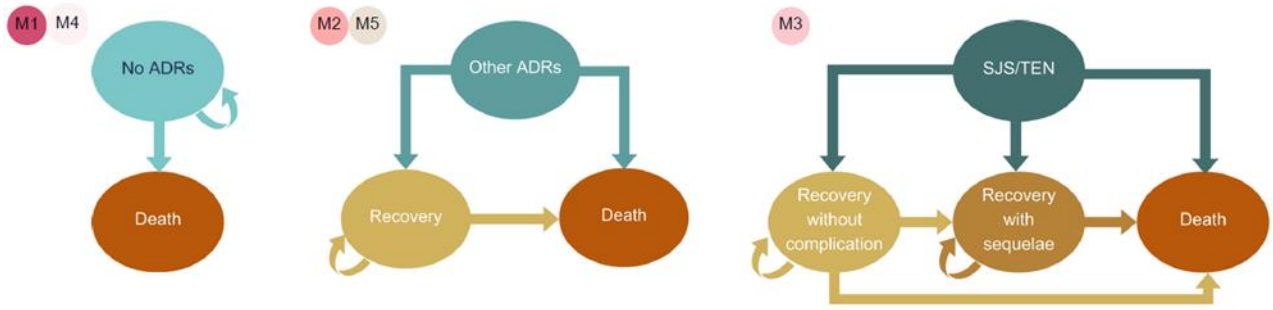

Figure 2 Markov model. **M1, M4**: Patients who do not develop any ADRs from phenytoin or alternative drugs. **M2, M5**: Patients who develop other ADRs without SJS/TEN from phenytoin or alternative drugs, **M3:** Patients who develop SJS/TEN.
ADRs: adverse drug reaction, **SJS/TEN:** Stevens-Johnson syndrome/toxic epidermal necrolysis

2.5 Model Assumptions

1) Patients experiencing SJS/TEN and other adverse reactions typically occur only once in a patient's lifetime and do not recur.

2) Patients have 100% medication adherence.

2.6 Model Parameters

Table 1 presents the variables used in the model, which are divided into four main categories: epidemiological data and transition probabilities, effectiveness of testing, cost data, and utility data.

2.6.1 Epidemiological data and transition probabilities

Transitional probabilities between health states were obtained from published domestic and international studies. The prevalence of *HLA-B*15:02* allele carriers was conducted in the Thai population[5]. The probability of phenytoin- induced SJS/ TEN in patients testing positive and negative for *HLA- B* 15: 02* allele was obtained from Thai patients[14]. Moreover, the probability of patients developing SJS/ TEN, sequelae, or other ADRs from either phenytoin or alternative drugs was retrieved from a retrospective study in the Taiwan population[15] see **Table 1.**

2.6.2 Effectiveness of testing

The PG 1502 test (PharmiGene, Inc., Taipei, Taiwan) was employed to detect the *HLA-B*15:02* allele. It exhibited a sensitivity of 100% and a specificity of 98.7% [9,16].

2.6.3 Cost

All cost data were adjusted to 2024 using the Consumer Price Index (CPI) provided by the Ministry of Commerce. The analysis was undertaken based on a governmental and societal perspective, and the cost data included direct medical and direct non-medical costs. The following details were provided.

1) Direct medical costs include:
The costs of treating epilepsy, phenytoin or sodium valproate treatment, were derived from the Drug and Medical Supply Information Center (DMSIC) of the Ministry of Public Health[17]. These costs were calculated based on the unit dose per day.

The costs of ADR treatment were obtained from published literature conducted in Thai patients with epilepsy[9,18-19].

Costs of testing were obtained from reimbursement data provided by the National Health Security Office.

2) Direct non- medical costs include transportation to receive treatment, food, and caregiver wages or opportunity costs due to caregivers' absenteeism. These costs are derived from a literature review conducted in Thai patients with epilepsy[9,19]. However, indirect costs, such as lost productivity due to sick leave and the opportunity cost of illness and death of patients, are not considered in this study to avoid double- counting, following the guidelines for health technology assessment in Thailand [20].

2.6.4 Utility

Utility values for each health state were obtained from a literature review conducted in Thai patients with epilepsy who had experienced no development of any ADRs., other ADRs, and the development of SJS/TEN[9,21] the utility value ranging from 0 (death) to 1 (optimal health).

2.7 Result Presentation

The results demonstrated the number needed to screen (NNS) for *HLA-B*15:02* testing required to prevent one occurrence of SJS/TEN. The total cost, life years, and QALYs of three potential strategies were estimated. The incremental cost- effectiveness ratio

(ICER) was calculated by incremental cost divided by incremental QALY of *HLA-B*15:02* testing or alternative drugs compared to no testing. The Thai societal willingness-to-pay threshold (WTP) of 160,000 THB per QALY was applied as recommended by Thailand's health technology assessment guidelines [20].

2.8 Uncertainty Analysis

One- way deterministic sensitivity analysis (DSA) and multivariate probabilistic sensitivity analysis (PSA) were conducted to address input parameter uncertainty. DSA involved varying each input parameter within its 95% confidence interval, with results displayed using tornado diagrams to illustrate the range of ICER values. Furthermore, PSA utilized a Monte Carlo simulation with 1000 iterations to simultaneously evaluate uncertainty across all parameters. Appropriate statistical distributions were employed, such as the beta distribution for risks and utility and the gamma distribution for cost parameters. The Cost-Effectiveness Acceptability Curve (CEAC) was employed to depict the probability of each alternative being cost- effective relative to a specified WTP threshold.

Table 1. Input parameters used in the model

Parameters	Distribution	Mean	Standard error	Source
Epidemiologic parameter and transitional probabilities (per year)				
Prevalence of *HLA-B*15:02* allele in the Thai population	Beta	0.1496	0.0032	5
Probability of phenytoin-induced SJS/TEN in patients testing positive for *HLA-B*15:02* allele (PPV)	Beta	0.0044	0.0313	14
Probability of phenytoin-induced SJS/TEN in patients testing negative for *HLA-B*15:02* allele (1-NPV)	Beta	0.0020	0.0313	14
Probability of sequelae	Beta	0.7238	0.0436	15
Probability of phenytoin-induced other ADRs	Beta	0.5600	0.0973	15
Probability of death due to phenytoin-induced SJS/TEN	Beta	0.2683	0.0317	15
Probability of sodium valproate-induced other ADRs	Beta	0.2500	0.1936	15
Probability of SJS/TEN to recovery without complication	Beta	0.236	0.038	15
Probability of SJS/TEN to recovery with sequelae	Beta	0.618	0.044	15
Probability of SJS/TEN to death	Beta	0.146	0.032	15
Probability of recovery to death	Beta	0.103	0.056	15
Probability of recovery with sequelae to death	Beta	0.026	0.018	15
Probability of other ADRs to recovery	Beta	0.992	0.992	
Probability of other ADRs to death	Beta	0.008297	0.008	22
Probability of no ADRs to death or general population death rate	Beta	0.008297	0.008	23
Probability of recovery from other ADR to death	Beta	0.008297	0.008	
Sensitivity of *HLA-B*15:02* screening test		1.000		9,16
Specificity of *HLA-B*15:02* screening test		0.987		9,16
Costing parameters (Thai baht per year)				
Direct medical cost				
1. cost of testing				
Cost of *HLA-B*15:02* screening test	Fixed	1,000	0	The reimbursement rate
2. Cost of treating epilepsy				
Annual drug costs of phenytoin therapy	Gamma	2,070	2,070	17
Annual drug costs of sodium valproate therapy	Gamma	6,956	6,956	17
3. cost of ADR treatment				
Treatment of no ADRs	Gamma	0.00	0	
Treatment of no other ADRs	Gamma	714	71	18
phenytoin-induced SJS/TEN per event	Gamma	25,868	192	9
Treatment of recovery	Gamma	0.00	0	
Treatment of recovery with sequelae	Gamma	37,082	3,708	19
Direct non-medical cost				
Treatment with phenytoin	Gamma	6,431	23	9
Treatment with sodium valproate	Gamma	6,431	23	9
Treatment of no ADRs	Gamma	0.00	0	
Treatment of no other ADRs	Gamma	1,870	187	9
phenytoin-induced SJS/TEN per event	Gamma	20,812	199	9
Treatment of recovery	Gamma	0.00	0	
Treatment of recovery with sequelae	Gamma	22,783.13	2,278	19

Parameters	Distribution	Mean	Standard error	Source
Utility				
no ADRs	Beta	0.68	0.003	9
Develop SJS/TEN	Beta	-0.08	0.002	9
Develop other ADRs	Beta	0.46	0.003	9
recover from SJS/TEN without complication	Beta	0.52	0.00	9
recover from SJS/TEN with sequelae	Beta	0.27	0.06	21
Discounting				
Yearly discount rate for costs		0.03		20
Yearly discount rate for outcome		0.03		20

ADRs: adverse drug reaction, **NPV:** negative predictive value, **PPV:** positive predictive value, **THB**: Thai baht, **SJS/TEN:** Stevens-Johnson syndrome/toxic epidermal necrolysis

3. RESULTS AND DISCUSSION

3.1 RESULTS

3.1.1 Base-Case Analysis Costs

Table 2 presents the results of cost-utility analysis, including total lifetime costs, life years, quality-adjusted life years (QALYs), and Incremental Cost-Effectiveness Ratios (ICERs) of each strategy.

Total lifetime costs consisted of three main components: 1) costs of treating epilepsy, 2) costs of ADR treatment, and 3) costs of *HLA-B*15:02* testing.

From a societal perspective, the total lifetime costs in the no-testing, *HLA-B*15:02* testing, and alternative drugs strategy were 294,561, 312,332, and 398,984 THB, respectively. They are suggesting that alternative drug strategies tend to incur higher costs compared to the other two strategies, consequently leading to epilepsy treatment expenses constituting a substantial proportion of total costs where sodium valproate is prescribed instead of phenytoin. Furthermore, it could be emphasized that the cost of ADR treatment can be mitigated by using alternative drug or adopting *HLA-B*15:02* testing before initiating phenytoin therapy.

From the government's perspective, the direction of total lifetime costs aligns with the societal perspective but yields lower total lifetime costs.

Health outcomes

An analysis was conducted on the number needed to screen (NNS), which showed that 1,470 patients need to be screened for *HLA-B*15:02* allele to prevent one case of SJS/TEN.

Furthermore, compared to the no-testing strategy, implementing of *HLA-B*15:02* testing before initiating phenytoin therapy resulted in a slight increase in the number of life years saved and QALYs gained, with gains of 0.21 years and 0.31 QALYs, respectively. Conversely, the alternative drugs strategy exhibited a more substantial increase, with gains of approximately 1.27 years and 1.90 QALYs (see **Table 2)**.

Cost-utility analysis

From a societal perspective, compared to the no-testing strategy, incorporating *HLA-B*15:02* testing before initiating phenytoin therapy incurred slightly higher costs, and QALYs gained. The ICER was approximately 57,185 THB/QALY. Conversely, the alternative drugs strategy resulted in greater gains in costs and QALYs, with an estimated ICER of 54,842 THB/QALY.

From the governmental perspective, the findings are consistent with the societal perspective but incur higher ICER. Compared to the no-testing strategy, the ICER of the *HLA-B*15:02* testing strategy was estimated at 71,497 THB/QALY, while the alternative drugs strategy was about 69,371 THB/QALY.

Based on the study findings, at the willingness-to-pay threshold of 160,000 THB/QALY in Thailand, *HLA-B* 15:02* testing before phenytoin therapy initiation and prescribed the alternative drugs strategy demonstrated cost-effectiveness strategy compared to no testing strategy in both the societal and government perspectives, as shown in **Table 2.**

3.1.2 Uncertainty Analysis Results

A one-way sensitivity analysis was undertaken, and the results are presented in a Tornado diagram in **Figure 3.** The variable contributing the most impact on the ICER value is the probability of phenytoin-induced other ADRs, followed by the probability of sodium valproate-induced other ADRs and the probability of phenytoin-induced SJS/TEN in patients testing positive for the *HLA-B*15:02* allele (PPV).

The cost-effectiveness plane **Figure 4** showed that the *HLA-B*15:02* testing strategy incurs slightly higher costs and increases the number of QALYs gained compared to no testing. It should be noticed that the use of an alternative drugs strategy significantly increases

both costs and the number of QALYs gained compared to no testing. Additionally, results suggested several uncertainties around the mean of the ICER.

Figure 5 depicts the cost- effectiveness acceptability curve. At the cost-effectiveness threshold of 160,000 THB/QALY in Thailand, the likelihood of the alternative drugs strategy being the most cost-effective was 79% , followed by no testing strategy (18%) and *HLA- B* 15: 02* testing strategy (3%) , respectively.

Table 2 Total lifetime costs and health outcomes of each strategy using societal and government perspectives

Interventions	Societal Perspective			Government Perspective		
	No testing	***HLA-B*15:02* testing**	**Alternative drugs**	**No testing**	***HLA-B*15:02* testing**	**Alternative drugs**
Cost of treating epilepsy (THB)	291,413	308,629	398,310	71,195	92,770	205,502
Cost of ADR treatment (THB)	3,148	2,703	674	1,576	1,318	186
Cost of testing (THB)	-	1,000	-	-	1,000	-
Total cost (THB)	**294,561**	**312,332**	**398,984**	**72,771**	**95,088**	**205,688**
Total life years (year)	22.45	22.66	23.72	22.39	22.60	23.67
Total QALYs	13.34	13.65	15.25	13.31	13.62	15.22
Incremental cost		17,770	104,423		22,317	132,917
Incremental LYs		0.21	1.27		0.21	1.28
Incremental QALYs		0.31	1.90		0.31	1.92
ICER (THB/QALY gain)		**57,185**	**54,842**		**71,497**	**69,371**

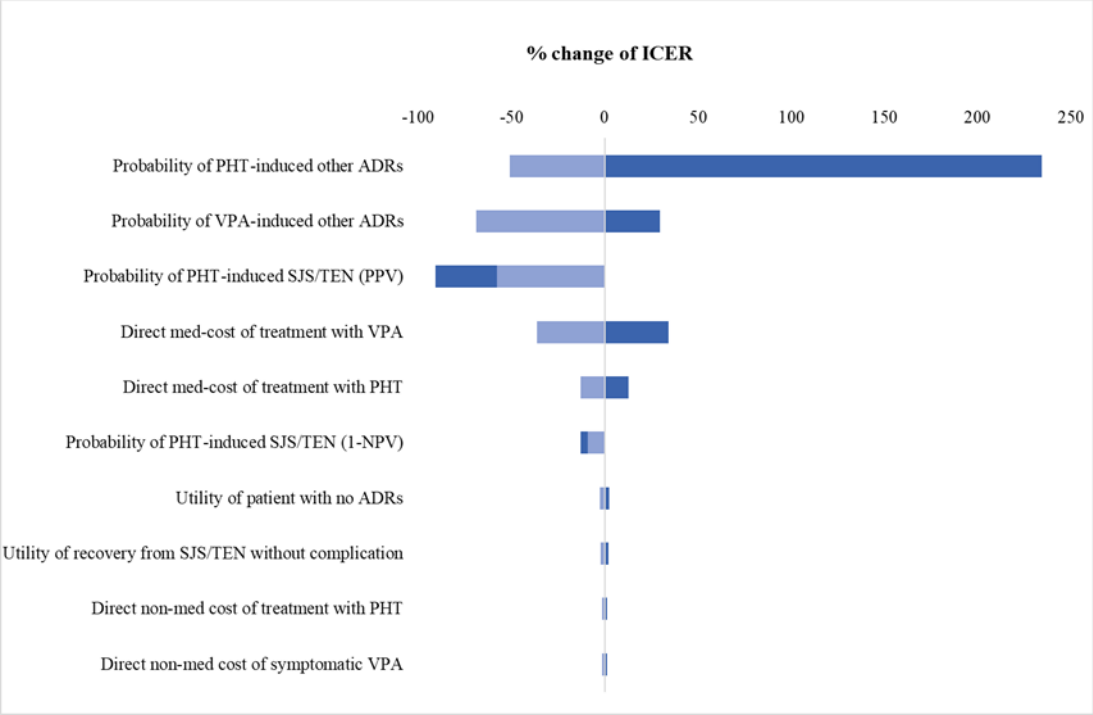

Figure 3 A one-way sensitivity analysis: Tornado diagram
ADRs: adverse drug reaction, **NPV:** negative predictive value, **PHT:** phenytoin**, PPV:** positive predictive value, **THB**: Thai baht, **SJS/TEN:** Stevens-Johnson syndrome/toxic epidermal necrolysis, **VPA:** sodium valproate

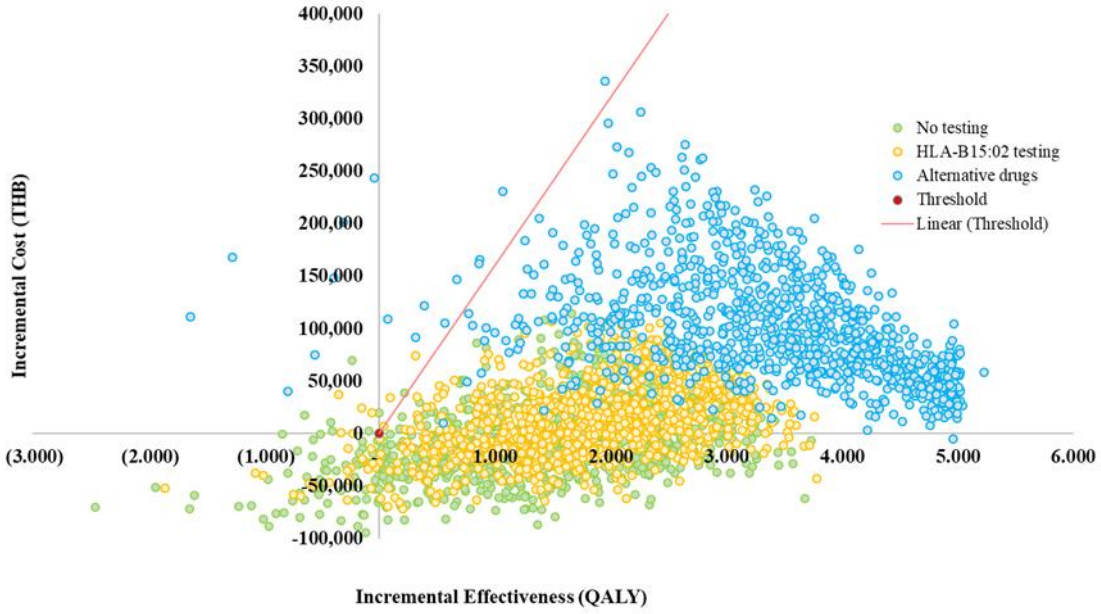

Figure 4 Cost-effectiveness plane,

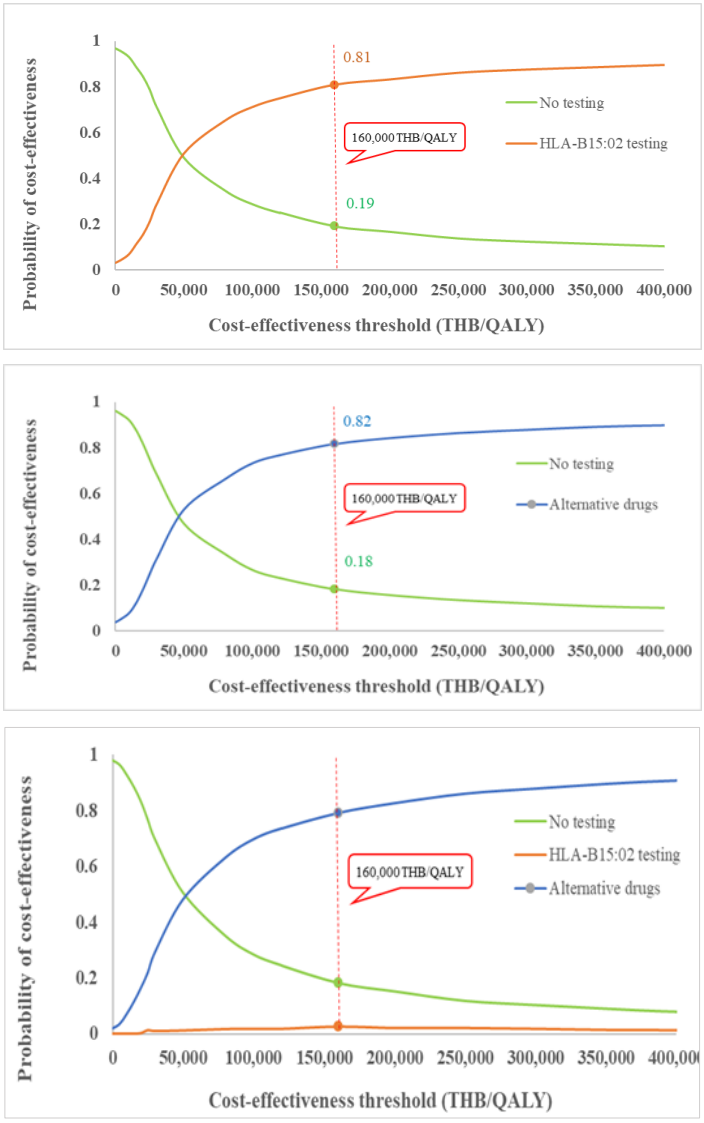

Figure 5 Cost-effectiveness acceptability curve

3.2 DISCUSSION

The findings of this study demonstrate that both the implementation of *HLA-B*15:02* testing prior to initiating phenytoin therapy and the alternative drug strategy provide good value for money in preventing phenytoin-induced SJS/TEN in patients with epilepsy, compared to the no-testing strategy, from both societal and governmental perspectives. Furthermore, at a willingness-to-pay threshold of 160,000 Baht per QALY gained, the alternative drug strategy is preferred over the *HLA-B*15:02* testing strategy due to its significant increase in life years saved and QALYs gained. Moreover, the analysis of the number needed to screen found that 1,470 patients need to be tested for the *HLA-B*15:02* allele to avoid one case of SJS/TEN. Cost-effectiveness results is sensitive to the probability of phenytoin and sodium valproate-induced other ADRs and the probability of phenytoin-induced SJS/TEN in patients testing positive for *HLA-B*15:02* allele (PPV).

To the best of our knowledge, no published data on the cost-utility analysis of *HLA-B*15:02* testing before initiating phenytoin treatment to prevent SJS/TEN in patients with epilepsy. Given the growing concerns regarding the safety of phenytoin therapy, it is recommended that sodium valproate, which is included in the NLEM, be considered the preferred strategy for preventing SJS/TEN in patients with epilepsy. This will be followed by the implementation of *HLA-B*15:02* testing prior to initiating treatment with phenytoin.

However, the successful implementation of pharmacogenomics-based medicine on a broader scale in clinical practice necessitates substantial resources beyond pharmacogenomics guidelines. This includes evidence of cost-effectiveness and clinical validity, as well as the establishment of laboratory facilities, laboratory standards, testing protocols, and quality assurance[24]. In Thailand, pharmacogenomic testing is effectively implemented in university-based medical centers and across 14 laboratories operated by the Department of Medical Sciences (DMS), Ministry of Public Health[24-25].

The findings could assist physicians in optimizing treatment strategies and inform policy decisions with the aim of preventing severe ADRs.

Nevertheless, the findings of this study should be interpreted with caution. First, the analysis of serious ADRs and other ADRs related to drug therapy was calculated only once during the first year of treatment, without accounting for lifelong ADRs or complications. This limitation could result in an underestimation of the value of one-time testing. Second, due to the limited data on the prevalence of phenytoin-induced SJS/TEN in the Thai population, the analysis relied on data from a single study. Therefore, a larger sample of individuals with SJS/TEN is required for further research to ensure that the results accurately reflect the current situation.

Moreover, recent technological advancements such as sequencing methods have facilitated the testing of numerous genes within a short timeframe. This approach may offer a higher predictive value compared to single-gene testing. Additionally, significant associations have been identified between genetic polymorphisms and drug-induced serious ADRs, particularly within the class of antiepileptic drugs. Consequently, there is potential interest for future research to investigate the cost-effectiveness of multi- pharmacogenetic testing of antiepileptic drugs to assess their value for money.

4. CONCLUSION

The implementation of *HLA-B*15:02* testing prior to initiating phenytoin therapy, and alternative drug strategy, resulted in a reduction in the incidence of phenytoin-induced SJS/TEN cases. The number needed to screen for the *HLA-B*15:02* allele to prevent one case of SJS/TEN was found to be 1,470. Additionally, both *HLA-B*15:02* testing and the alternative drug strategy were determined to be cost-effective compared to the no-testing strategy from societal and governmental perspectives. Furthermore, at a willingness-to-pay threshold of 160,000 Baht per QALY gained, the alternative drug strategy was preferred over the *HLA-B*15:02* testing strategy.

Conflict of interest

The authors declare that they have no conflict of interest

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Ethics approval

The Research Ethics Committee (MU-DT/PY-IRB) at Mahidol University has determined that this research does not involve human subject research, as it utilizes data derived from publicly available published research articles.

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