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Research Article

Economic evaluation of *HLA-B*13:01* screening for the prevention of phenobarbital-induced drug reaction with eosinophilia and systemic symptoms (DRESS) in Thai pediatric patients

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ABSTRACT

Pharmacogenetic testing plays a critical role in identifying individuals at risk for adverse drug reactions (ADRs). A case-control study demonstrated significant association between *HLA-B*13:01* gene and phenobarbital-induced Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) in Thai pediatric epilepsy patients, with an odds ratio of 4.3 (95% CI: 1.28–14.26, $p = 0.022$). Notably, *HLA-B*13:01* is the third most prevalent genetic marker associated with cutaneous ADRs in Thailand. However, there is currently no economic evaluation to guide decision-making for preventing severe ADRs. This study aims to perform a cost-utility analysis of *HLA-B*13:01* screening prior to initiating phenobarbital treatment to prevent DRESS and alternative drug with sodium valproate, a lower DRESS risk but higher cost, compared to phenobarbital treatment without screening in pediatric epilepsy patients.

Decision tree and Markov models were developed to evaluate lifetime costs and quality-adjusted life years (QALYs) from both payer and societal perspectives. Input data, including costs, utilities, and transition probabilities, were derived from relevant literature focused on Thai pediatric epilepsy patients. Sensitivity analyses were conducted.

Implementing *HLA-B*13:01* screening before initiating phenobarbital therapy and alternative treatment strategy was cost-saving compared to no-screening strategy, yielding higher QALYs and lower costs. Furthermore, the number needed to screen of 14 to prevent one DRESS case. One-way sensitivity analysis highlighted that the probability of death from DRESS was the most impacted on the ICER. At the Thai cost-effectiveness threshold of 160,000 THB/QALY, the alternative drug, sodium valproate demonstrated 94% probability of being cost-effective, indicating that it is the most cost-effective option.

Keywords:
Cost-utility analysis; Economic evaluation; *HLA-B*13:01*; Drug reaction with eosinophilia and systemic symptoms (DRESS); Phenobarbital-induced DRESS; Adverse drug reactions

1. INTRODUCTION

Adverse drug reactions (ADRs) are recognized as the fourth to sixth leading cause of death globally1. A retrospective study reported that 694,811 adverse events worldwide were associated with the use of antiepileptic drugs. Among these, antiepileptic drugs induce SCARs in approximately 64% of cases, leading to mortality (3.5%), life-threatening conditions (11.5%), and hospitalization or prolonged hospital stays (43.5%)[2]. The occurrence of SCARs encompasses Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis,

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Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), and SJS/TEN overlap, which represented 11,181 (9.1%), 3,645 (3.0%), 5,106 (4.1%), and 6 (0.004%) cases, respectively[2]. A similar trend is observed in Thailand; data from the Health Product Vigilance Center of the Thai Food and Drug Administration, Ministry of Public Health indicates that the most commonly reported ADRs are cutaneous adverse drug reactions (CADRs). Among these, antiepileptic drugs have been identified as the sixth leading cause of severe cutaneous adverse reactions (SCARs). Certain drugs associated with the development of SCARs include allopurinol, carbamazepine, phenobarbital, and phenytoin[3].

According to the clinical practice guidelines for epilepsy treatment for physicians in 2021, phenobarbital is considered a first-line treatment for neonatal seizures[4]. However, sodium valproate will be prescribed when the patient cannot tolerate phenobarbital. Compared to phenobarbital, sodium valproate exhibits a reduced risk of SCARs, especially DRESS, but it entails higher costs. Nowadays, phenobarbital is included in the National List of Essential Medicines (NLEM) for controlling seizures. However, the use of phenobarbital raises significant safety concerns, particularly regarding the risk of DRESS[4].

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is a severe, delayed hypersensitivity reaction marked by skin rash, fever, lymphadenopathy, hematological abnormalities (e.g., eosinophilia), and multi-organ involvement, including the liver, kidneys, and heart. Clinically, DRESS can result in significant morbidity, prolonged hospital stays, and mortality in severe cases. Economically, it increases healthcare costs due to extended treatment, intensive care, and potential long-term complications[5]. DRESS particularly affects the acute and long-term management of pediatric patients. Common drugs associated with DRESS in pediatric patients included carbamazepine, dapsone, lamotrigine, phenobarbital, and phenytoin[6].

Genetic factors can contribute to ADRs. Pharmacogenomics or pharmacogenetics plays a significant role in identifying individuals who respond effectively to medications and those who are at risk of experiencing ADRs[7]. Furthermore, there is a growing number of genetic associations evidence to the development of clinically relevant tests facilitated by international guidelines such as the Clinical Pharmacogenetics Implementation Consortium (CPIC)[8]. A case-control study revealed a significant association between the presence of the *HLA-B*13:01* allele and phenobarbital-induced DRESS in Thai pediatric epilepsy patients with an odds ratio of 4.3 (95%CI 1.28-14.26, *p = 0.022*)[9]. Moreover, a retrospective observational cohort study conducted in Thailand, which involved 13,985 participants receiving various antiepileptic drugs, suggested that the *HLA-B*13:01* gene was identified ranks third (12.91%) among genetic markers associated with cutaneous ADRs[10].

Screening for the *HLA-B*13:01* gene is crucial in guiding physicians to optimize treatment strategies and aiding policymakers in preventing severe ADRs. However, there is a lack of evidence on the cost-utility of *HLA-B*13:01* screening before initiating phenobarbital treatment to prevent DRESS. This gap challenges informed policy decisions for effective resource allocation in Thailand and globally.

To address this, the study conducted a cost-utility analysis of *HLA-B*13:01* screening prior to initiating phenobarbital treatment to prevent DRESS and alternative drug with sodium valproate, lower DRESS risk but higher cost, compared to phenobarbital treatment without screening in pediatric epilepsy patients. The findings aim to provide critical evidence for optimizing treatment protocols and guiding policy decisions. In particular, the results may support the inclusion of *HLA-B*13:01* screening in the Universal Coverage Scheme (UCS) benefit package to prevent severe ADRs, thereby improving patient outcomes.

2. MATERIALS AND METHODS

2.1 Study design

A hybrid decision tree and Markov model were constructed to evaluate the lifetime costs and health outcomes of Thai children with epilepsy. The analysis compared three strategies: (1) Current practice, phenobarbital treatment without *HLA-B*13:01* screening (no *HLA-B*13:01* screening), (2) *HLA-B*13:01* screening before phenobarbital treatment, and (3) prescribing alternative drug with sodium valproate without *HLA-B*13:01* screening. The analysis was conducted from governmental and societal perspectives.

2.2 Target population

The model simulated cohorts of patients aged 3 years and older with newly diagnosed epilepsy. These patients included those experiencing focal seizure or generalized absence seizure who were being treated with phenobarbital.

2.3 Interventions and comparator

The analysis evaluated three strategies for treating pediatric epilepsy as follows;

*1) Current practice: phenobarbital treatment without HLA-B*13:01 screening (No HLA-B*13:01 screening)*

In Thailand, pediatric patients with newly diagnosed epilepsy are typically initiated on phenobarbital as a first-line treatment due to its proven effectiveness, affordability, and availability across all types of hospitals. According to the clinical practice guidelines for treating epilepsy, phenobarbital was administered without prior *HLA-B*13:01* screening. The recommended dosage regimen included an initial dose of 1–3 mg/kg/day, followed by a maintenance dose of 3–5 mg/kg/day[4]. The unit dosages were adjusted based on the weight of specific age groups (1-3 years, 4-5 years, 6-8 years, 9-12 years, 13-18 years, and over 19 years)[11]. In cases where patients develop phenobarbital-induced DRESS, sodium valproate is recommended as an alternative, given its lower risk of inducing DRESS[4]; however, it is associated with higher costs[12].

*2) HLA-B*13:01 screening before phenobarbital treatment*

A case-control study conducted in Thai pediatric epilepsy patients has demonstrated an increased risk of phenobarbital-induced DRESS among individuals carrying the *HLA-B*13:01* allele[9]. Therefore, implementing *HLA-B*13:01* screening prior to initiating phenobarbital therapy could serve as an effective pharmacogenetic strategy. In this strategy, pediatric patients with newly diagnosed epilepsy underwent *HLA-B*13:01* genetic screening before initiating phenobarbital therapy. Patients with a positive test result were prescribed sodium valproate as an alternative, while those with a negative result proceeded with phenobarbital treatment.

Currently, *HLA-B*13:01* screening is available to individuals who can afford it, costing 1,000 THB, as reported in the reimbursement data provided by the National Health Security Office[12].

*3) Prescribing alternative drug with sodium valproate without HLA-B*13:01 screening*

According to the clinical practice guidelines for treating epilepsy, sodium valproate is considered an alternative treatment option[4] that does not require prior screening for *HLA-B*13:01*. The initial dosage was 15 mg./kg./day, subsequently adjusted to a maintenance dose of 30-40 mg./kg./day[4]. Dosage adjustments were made following the weight of specific age groups[11], consistent with those utilized for phenobarbital therapy.

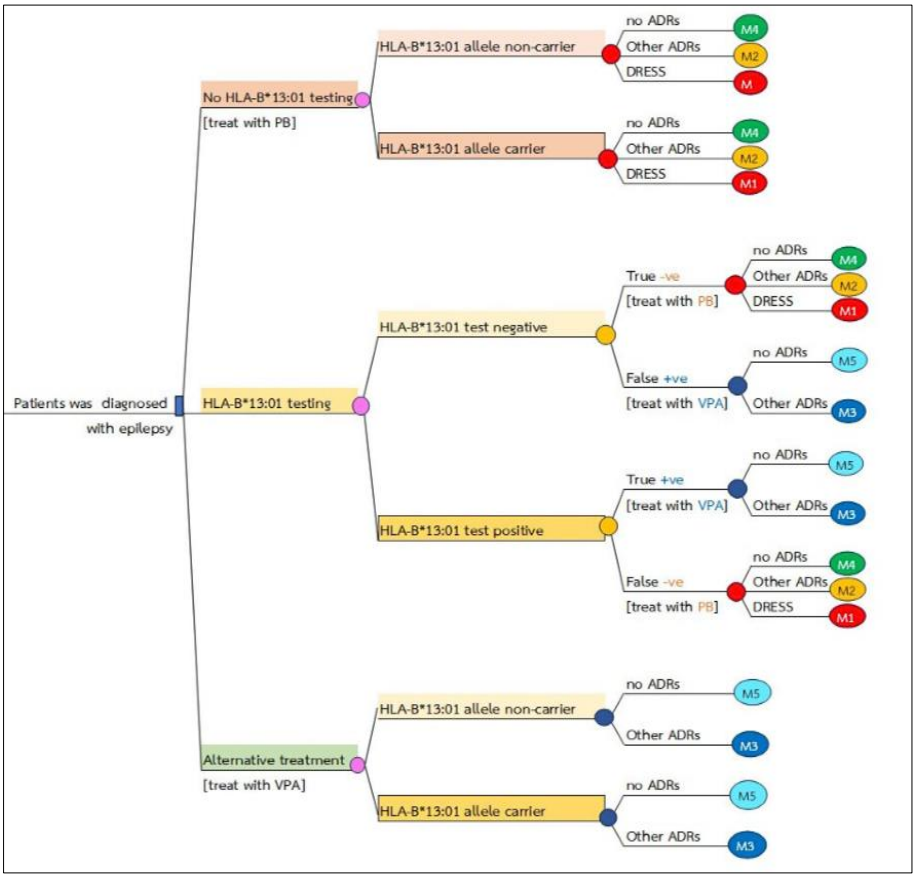

Figure 1 Decision tree models
ADRs: adverse drug reactions, **PB:** phenobarbital, **VPA:** sodium valproate, **DRESS:** Drug reaction with eosinophilia and systemic symptoms

All pediatric epilepsy patients require lifelong treatment. For those undergoing *HLA-B*13:01* screening, the risk of phenobarbital-induced DRESS was avoided by switching to sodium valproate in cases of positive screening results. Meanwhile, patients treated with sodium valproate experienced no occurrences of DRESS. Thus, implementing *HLA-B*13:01* screening prior to phenobarbital treatment or utilizing sodium valproate contributes to enhanced patient quality of life and decreased costs related to DRESS.

2.4 Model structure

A hybrid approach using decision trees and Markov models was developed to assess the lifetime costs and outcomes of various strategies for managing pediatric epilepsy. The model followed a cohort of pediatric epilepsy patients aged three years and older across different strategies, utilizing a lifetime horizon with a one-year cycle length.

In the first year, a decision tree model simulated three potential epilepsy management strategies, as outlined in "Section 2.3, Interventions and Comparator" (see Figure 1).

In the first strategy, all patients started phenobarbital treatment without *HLA-B*13:01* screening, which reflects current practice in Thailand. However, individuals carrying the *HLA-B*13:01* allele are at risk of developing phenobarbital-induced DRESS. For such cases, sodium valproate is prescribed as an alternative, while patients who do not develop DRESS continue with phenobarbital therapy. In the second strategy, all patients are screened for the *HLA-B*13:01* allele. Those who test positive are prescribed sodium valproate as an alternative medication, while those with negative test results receive phenobarbital therapy. In the third strategy, all patients were treated with sodium valproate and did not undergo *HLA-B*13:01* screening.

During the first year, regardless of whether patients receive phenobarbital or alternative medications, three possible outcomes are considered: 1) no occurrence of ADRs, 2) development of other ADRs without DRESS, and 3) development of DRESS.

After this initial analysis, patients transitioned to a long-term Markov model to predict lifetime costs and outcomes (see Figure 2). Figure 2 (M1) depicts patients who develop DRESS due to phenobarbital, with four possible health states: 1) experiencing DRESS, 2) recovering with sequelae, 3) recovering without complications, and 4) death. In this context, "death" encompasses mortality caused by both DRESS and other causes. Figure 2 (M2, M3) represents patients who develop other ADRs without DRESS, with the possibility of recovering or dying from other causes in subsequent cycles. Figure 2 (M4, M5) illustrates patients who do not experience ADRs, showing potential transitions to either remain in this health state or die from other causes.

2.5 Model assumptions

1) It is assumed that DRESS and other ADRs occur only once in a patient's lifetime and do not recur.

2) The probability of epilepsy remission is assumed to be the same for patients with or without a history of DRESS.

3) Patients are assumed to comply with their prescribed medication regimens fully.

2.6 Model parameters

Table 1 demonstrates the input parameters utilized in the model, categorized into four main categories: epidemiological data and transition probabilities, effectiveness of screening, cost, and utility data.

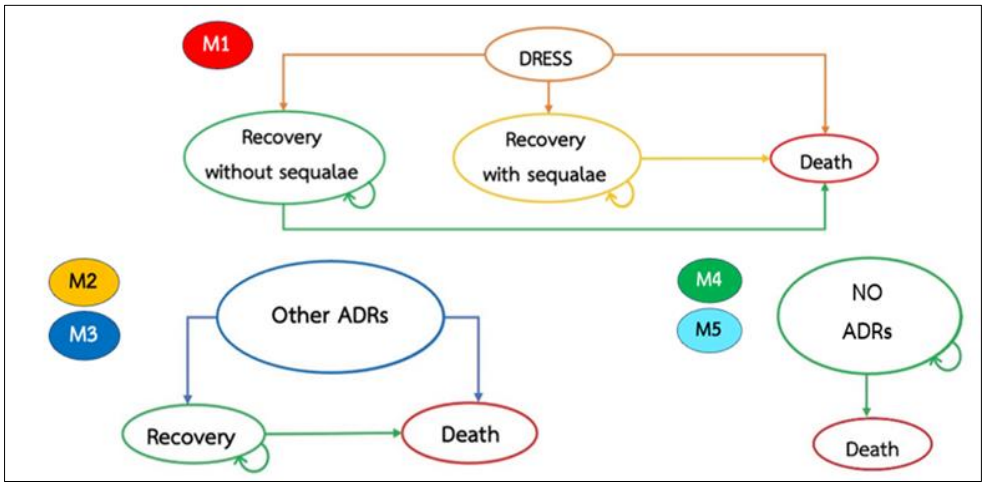

Figure 2 Markov model. **M1:** Patients who develop DRESS. **M2, M3**: Patients who develop other ADRs without DRESS from phenobarbital or alternative drugs, **M4, M5**: Patients who do not develop any ADRs from phenobarbital or alternative drugs. **ADRs:** adverse drug reaction, **DRESS:** Drug Reaction with Eosinophilia and Systemic Symptoms

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*13:01* allele in the Thai population	Beta	0.13	0.003	[10]
Probability of phenobarbital-induced DRESS in patients screening positive for *HLA-B*13:01* allele (PPV)	Beta	0.57	0.128	[9]
Probability of phenobarbital-induced DRESS in patients screening negative for *HLA-B*13:01* allele (1-NPV)	Beta	0.45	0.085	[9]
Probability of sequelae in DRESS patients	Beta	0.06	0.019	[13]
Probability of phenobarbital-induced other ADRs	Beta	0.16	0.065	[15]
Probability of death due to phenobarbital-induced DRESS	Beta	0.05	0.026	[22]
Probability of sodium valproate-induced other ADRs	Beta	0.14	0.022	[14]
Probability of DRESS to recovery with sequelae	Beta	0.06	0.019	[13]
Probability of DRESS to death	Beta	0.16	0.065	[22]
Probability of recovery to death	Beta	0.01	0.008	[23]
Probability of recovery with sequelae to death	Beta	0.01	0.006	[24, 25]
Probability of no ADRs to death or general population death rate	Beta	0.01	0.008	[23]
Sensitivity of *HLA-B*13:01* screening test		0.985		[26]
Specificity of *HLA-B*13:01* screening test		1.00		[26]
Costing parameters (Thai baht per year)				
Direct medical cost				
1. cost of screening				
Cost of *HLA-B*13:01* screening test	Fixed	1000		The reimbursement data [12]
Cost of out-patient unit	Fixed	95		[18]
2. Cost of treating epilepsy				
Annual drug costs of phenobarbital therapy in patients aged 1-3 years	Gamma	4,816.28	481.63	Calculating, [12]
Annual drug costs of phenobarbital therapy in patients aged 4-5 years	Gamma	6,848.15	684.82	Calculating, [12]
Annual drug costs of phenobarbital therapy in patients aged 6-8 years	Gamma	8,560.19	856.02	Calculating, [12]
Annual drug costs of phenobarbital therapy in patients aged 9-12 years	Gamma	13,564.61	1356.46	Calculating, [12]
Annual drug costs of phenobarbital therapy in patients aged 13-18 years	Gamma	306.04	30.60	Calculating, [12]
Annual drug costs of phenobarbital therapy in patients aged>19 years	Gamma	177.93	17.79	Calculating, [12]
Annual drug costs of sodium valproate therapy in patients aged 1-3 years	Gamma	1,746.60	174.66	Calculating, [12]
Annual drug costs of sodium valproate therapy in patients aged 4-5 years	Gamma	2,483.44	248.34	Calculating, [12]
Annual drug costs of sodium valproate therapy in patients aged 6-8 years	Gamma	3,104.30	310.43	Calculating, [12]
Annual drug costs of sodium valproate therapy in patients aged 9-12 years	Gamma	4,919.12	491.91	Calculating, [12]
Annual drug costs of sodium valproate therapy in patients aged 13-18 years	Gamma	6,034.24	603.42	Calculating, [12]
Annual drug costs of sodium valproate therapy in patients aged>19 years	Gamma	6,675.49	667.55	Calculating, [12]
3. cost of ADR treatment				
Treatment of no ADRs	Gamma	0.00	0.00	
Treatment of other ADRs	Gamma	82	8.20	[19]
phenobarbital-induced DRESS per event	Gamma	86,861	32,783	[19]
Treatment of recovery	Gamma	0.00	0.00	
Treatment of recovery with sequelae in patients age 1-5 years	Gamma	8,306.73	830.67	calculating
Treatment of recovery with sequelae in patients aged 6-12 years	Gamma	8,415.59	841.56	calculating
Treatment of recovery with sequelae in patients aged>13 years	Gamma	8,324.86	832.49	calculating
Direct non-medical cost				
Treatment with phenobarbital	Gamma	6,431	643.10	[18]
Treatment with sodium valproate	Gamma	6,431	643.10	[18]
Treatment of no ADRs	Gamma	0.00	0.00	
Treatment of other ADRs	Gamma	370.86	37.09	[19]
phenobarbital-induced DRESS per event	Gamma	780.00	356.00	[19]
Treatment of recovery	Gamma	0.00	0.00	
Treatment of recovery with sequelae	Gamma	12,178.72	1217.87	calculating
Utility				
no ADRs	Beta	0.68	0.003	[18]
Develop other ADRs	Beta	0.56	0.028	[21]
Develop DRESS	Beta	0.54	0.003	[22]
recover from DRESS without sequelae	Beta	0.68	0.003	[18]
recover from DRESS with sequelae	Beta	0.68	0.003	[18]
Discounting				
Yearly discount rate for costs		0.03		[20]
Yearly discount rate for outcome		0.03		[20]

Abbreviation: ADRs: adverse drug reactions, **NPV:** negative predictive value, **PPV:** positive predictive value, **THB**: Thai baht, **DRESS:** Drug Reaction with Eosinophilia and Systemic Symptoms

2.6.1. Epidemiological data and transition probabilities

All parameters were obtained from relevant literature, primarily in Thai pediatric epilepsy patients. The prevalence of *HLA-B*13:01* allele carriers was obtained from the published study, which investigated the Thai population[8]. The probability of phenobarbital-induced DRESS in patients screening positive and negative for *HLA-B*13:01* allele was obtained from studies on Thai pediatric epilepsy patients[9]. The likelihood of developing DRESS and subsequent sequelae was derived from a retrospective study on the Asian population[13]. Data on other ADRs from either phenobarbital or alternative drugs were retrieved from pediatric epilepsy patients[14,15]. Additionally, transitional probabilities between health states were obtained from both Thai and international published studies see Table 1.

2.6.2 Effectiveness of screening

The sensitivity and specificity of the *HLA-B*13:01* allele were specified by the manufacturer, with a sensitivity of 98.5% and a specificity of 100%[16].

2.6.3 Cost

All cost data were adjusted to 2024 values using the Consumer Price Index provided by the Ministry of Commerce[17]. The analysis was conducted from both a governmental perspective, which included direct medical costs, and a societal perspective, encompassing both direct medical and non-medical costs. The following details were provided.

1) Direct medical costs include:

- The costs associated with treating epilepsy, including phenobarbital and sodium valproate treatments, were derived from the Drug and Medical Supply Information Center (DMSIC) of the Ministry of Public Health[12]. These costs were calculated by multiplying the daily unit dose by the drug cost. The analysis calculated the unit dosage for pediatric epilepsy patients based on the weight of individuals within particular age groups, including 1-3 years, 4-5 years, 6-8 years, 9-12 years, 13-18 years, and over 19 years old.

- The costs associated with treating ADRs were derived from published studies involving Thai epilepsy patients[19].

- The costs associated with screening were obtained from reimbursement data supplied by the National Health Security Office.

2) Direct non-medical costs encompass expenses such as transportation for treatment, meals, and caregiver wages or the opportunity costs resulting from caregivers' absence. These costs were obtained from a literature review conducted among Thai epilepsy patients[18,19]. However, indirect costs, such as productivity loss due to sick leave and the opportunity costs associated with patient illness and mortality, were excluded from this study to prevent duplication, following health technology assessment guidelines in Thailand[20].

2.6.4 Utility

Utility values for each health state were sourced from a literature review conducted among Thai epilepsy patients who had not experienced any ADRs, those who had experienced other ADRs, and those who had developed DRESS[18, 21, 22]. The utility values range from 0 (indicating death) to 1 (representing optimal health).

2.7 Result presentation

The findings indicated the number needed to screen (NNS) for *HLA-B*13:01* screening required to prevent one occurrence of DRESS. The analysis also estimated the total cost, life years, and quality-adjusted life years (QALYs) associated with three potential strategies. The incremental cost-effectiveness ratio (ICER) was determined by incremental cost divided by incremental QALY of *HLA-B*13:01* screening or alternative drugs compared to no screening. Following Thailand's health technology assessment guidelines, the willingness-to-pay threshold (WTP) of 160,000 THB per QALY was utilized to assess the value for money of the intervention[20].

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

Interventions	Societal Perspective			Government Perspective		
	No screening	***HLA-B*13: 01* screening**	**Alternative drugs**	**No screening**	***HLA-B*13: 01* screening**	**Alternative drugs**
Cost of treating epilepsy (THB)	261,392	264,862	292,025	104,935	108,151	134,489
Cost of ADR treatment (THB)	72,340	60,939	121	52,579	44,220	22
Cost of screening (THB)	-	1,000	-	-	1,000	-
Total cost)THB(	**333,732**	**326,801**	**292,146**	**157,514**	**153,371**	**134,511**
Total life years)year(	24.45	24.49	24.60	24.43	24.46	24.58
Total QALYs	16.47	16.50	16.64	16.45	16.48	16.62
Incremental cost		**-6,931**	**-41,586**		**-4,143**	**-23,003**
Incremental LYs		**0.03**	**0.15**		**0.03**	**0.15**
Incremental QALYs		**0.03**	**0.17**		**0.03**	**0.17**
ICER)THB/QALY(		**Dominant**	**Dominant**		**Dominant**	**Dominant**

Abbreviation: ADRs: adverse drug reactions, **ICER**: incremental cost-effectiveness ratio**, LYs:** Life Years, **QALY:** quality-adjusted life year, **THB**: Thai baht

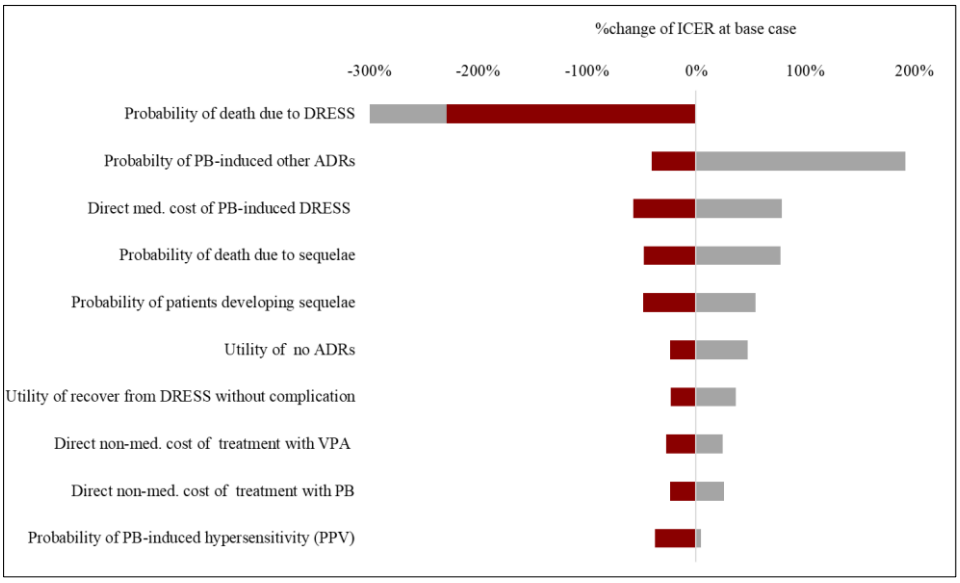

Figure 3 A one-way sensitivity analysis: Tornado diagram
Abbreviation: ADRs: adverse drug reactions, **DRESS:** Drug Reaction with Eosinophilia and Systemic Symptoms, **ICER**: incremental cost-effectiveness ratio, **NPV:** negative predictive value, **PB:** phenobarbital**, PPV:** positive predictive value, **THB**: Thai baht, **VPA:** sodium valproate

2.8 Uncertainty analysis

A one-way deterministic sensitivity analysis (DSA) and a multivariate probabilistic sensitivity analysis (PSA) were performed to address uncertainty in input parameters. In the DSA, each input parameter was varied within its 95% confidence interval, and the results were presented using tornado diagrams to show the range of ICER values. The PSA involved a Monte Carlo simulation with 1000 iterations to simultaneously assess uncertainty across all parameters, using appropriate statistical distributions—beta distribution for risks and utility values and gamma distribution for cost parameters. The Cost-Effectiveness Acceptability Curve (CEAC) displayed the probability of each alternative being cost-effective relative to a WTP threshold of 160,000 THB/QALY.

3. RESULTS

3.1 Base-case analysis

3.1.1 Costs

Table 2 demonstrates the results of cost-utility analysis, including total lifetime costs, life years, QALYs, and ICERs of each strategy.

Total lifetime costs consisted of three main components: 1) costs of treating epilepsy, 2) costs of managing ADR, and 3) costs of *HLA-B*13:01* screening. From a societal perspective, the total lifetime costs of the no-screening, *HLA-B*13:01* screening, and alternative drugs strategy were 261,392, 264,862, and 292,025 Thai baht (THB), respectively. The findings suggest that the alternative drug strategy with sodium valproate tends to have the highest costs compared to the other two strategies. As a result, when sodium valproate is prescribed instead of phenobarbital, the cost of treating epilepsy represents a significant portion of the total costs. Furthermore, it is worth highlighting that the cost of managing ADR can be reduced by implementing *HLA-B*13:01* screening prior to initiating phenobarbital therapy.

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

3.1.2 Health outcomes

The analysis of the number needed to screen (NNS) revealed that 14 pediatric epilepsy patients need to be screened for the *HLA-B*13:01* allele to prevent one case of DRESS.

Moreover, when compared to the no-screening strategy, the implementation of *HLA-B*13:01* screening before initiating phenobarbital treatment led to a minor increase in the number of life years saved and QALYs gained, with increments of 0.03 years and 0.03 QALYs, respectively. In contrast, the alternative drugs strategy demonstrated a more significant increase, with gains of approximately 0.15 years and 0.17 QALYs see Table 2.

3.1.3 Cost-utility analysis

From both societal and governmental perspectives, *HLA-B*13:01* screening before initiating phenobarbital therapy and alternative drugs strategy were cost-saving compared to the no-screening strategy, yielding higher QALYs and lower costs, as shown in Table 2.

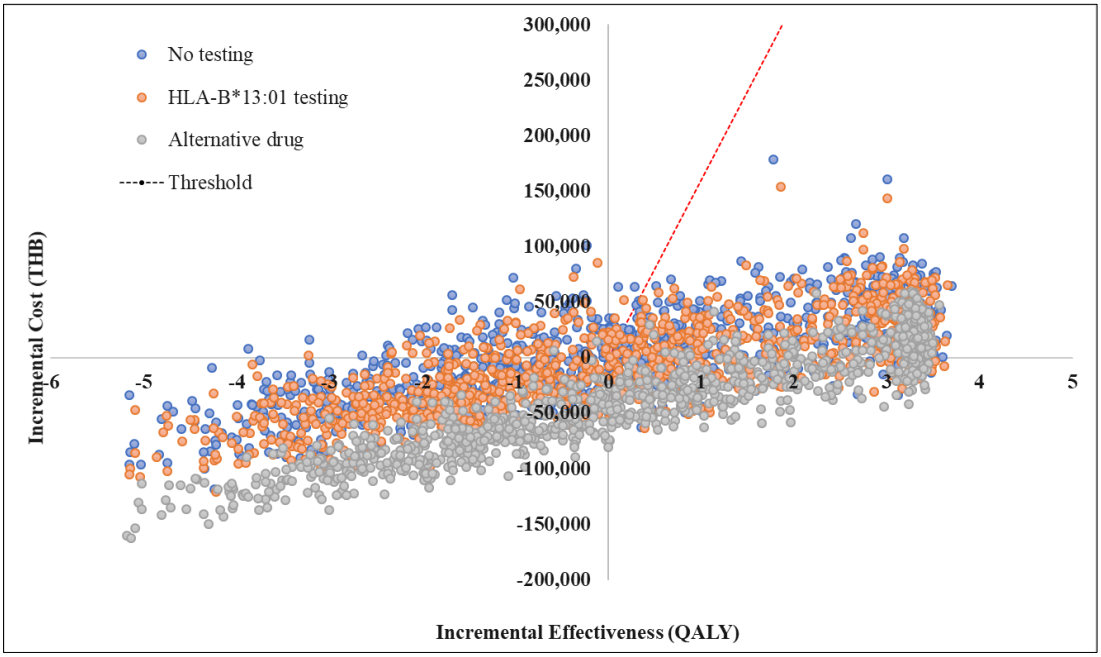

Figure 4 Cost-effectiveness plane
Abbreviation: QALY: quality-adjusted life year, **THB**: Thai baht

3.2 Uncertainty analysis result

A one-way sensitivity analysis was conducted, with the results depicted in a Tornado diagram, as shown in Figure 3. The analysis revealed that the variable contributing the most impact on the ICER value is the probability of death due to DRESS, followed by the probability of phenobarbital-induced other ADRs and direct medication cost of phenobarbital-induced DRESS

The cost-effectiveness plane (Figure 4) illustrated that implementing *HLA-B*13:01* screening and the alternative drugs strategy resulted in slightly reduced costs and increased QALYs gained compared to no screening strategy. Furthermore, the findings indicated some uncertainties surrounding the mean of the ICER. Figure 5 illustrates the cost-effectiveness acceptability curve. At the cost-effectiveness threshold of 160,000 THB/QALY in Thailand, the alternative drug strategy using sodium valproate is the most likely to be cost-effective (94%), followed by the *HLA-B*13:01* screening strategy (4%) and the no-screening strategy (2%). These findings suggest that the alternative drug strategy with sodium valproate is the most cost-effective option.

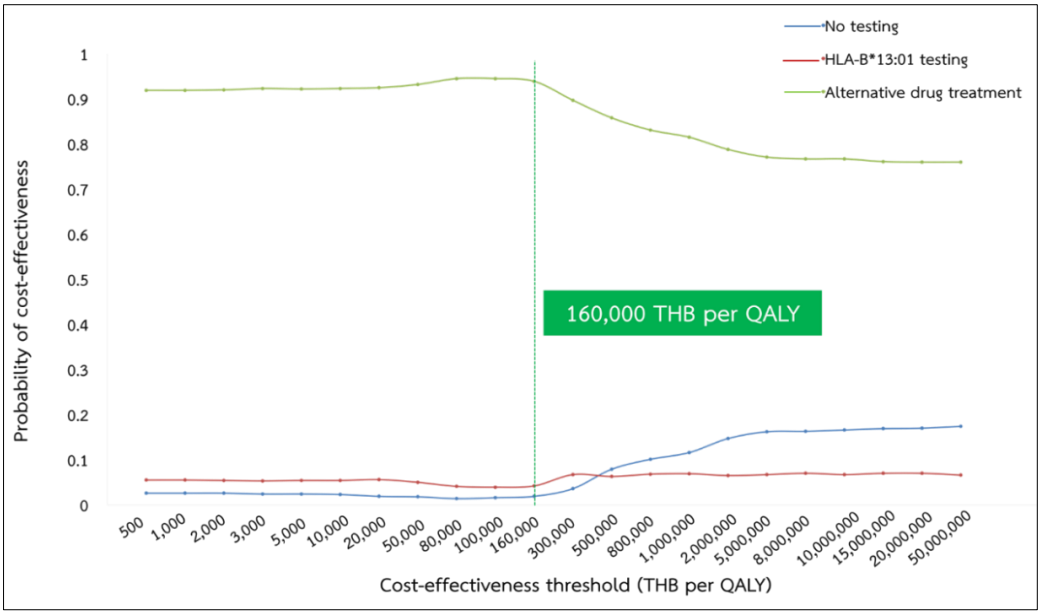

Figure 5 Cost-effectiveness acceptability curve
Abbreviation: QALY: quality-adjusted life year, **THB**: Thai baht

4. DISCUSSION

The results of this study indicate that implementing either *HLA-B*13:01* screening prior to initiating phenobarbital therapy or adopting an alternative drug strategy leads to cost savings in preventing phenobarbital-induced DRESS in pediatric epilepsy patients. Accordingly, the alternative drug strategy is the most cost-effective option when considering a willingness-to-pay threshold of 160,000 THB/QALY. These cost-saving advantages are observed from both societal and governmental perspectives. Moreover, the analysis of the number needed to screen found that 14 pediatric epilepsy patients need to be tested for the *HLA-B*13:01* allele to avoid one case of DRESS.

Given the safety concerns of phenobarbital, a common drug associated with DRESS in pediatric patients[6], sodium valproate, listed in the National List of Essential Medicines, should be the first-line treatment for at-risk populations. Additionally, *HLA-B*13:01* screening before phenobarbital therapy should be included in the UCS benefit package, as both strategies are cost-saving in the Thai context. Establishing genetic testing facilities and integrating screening into standard pediatric epilepsy care is essential for implementation.

To the best of our knowledge, this is the first study to conduct a cost-utility analysis of *HLA-B*13:01* screening before initiating phenobarbital treatment to prevent DRESS in pediatric patients with epilepsy. These findings could offer valuable insights to physicians for optimizing treatment and policymakers for making decisions to prevent serious ADRs, where data was previously lacking.

Our study has several inherent limitations. Firstly, owing to a lack of information on pediatric epilepsy patients, including the prevalence of *HLA-B*13:01* allele, the probability of developing DRESS and its subsequent sequelae, the costs of treating ADRs, and utility values, we relied on data extrapolated from adult epilepsy patients. Consequently, further research is required to obtain these data on pediatric epilepsy
Patients should ensure that the findings reflect the circumstances in those patients. Secondly, the prevalence of phenobarbital-induced DRESS in patients screening positive for *HLA-B*13:01* allele (positive predictive value; PPV) in the Thai pediatric epilepsy patients, the analysis relied on data from a single study. Therefore, a larger sample of individuals with DRESS is required for further research. In order to account for this constraint, we performed an uncertainty analysis to assess its effects on the ICER. Lastly, the analysis of serious ADRs and other ADRs related to drug therapy was assessed 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 screening.

Moreover, recent technological advancements, particularly in sequencing methods, have enabled the rapid screening of multiple genes. As well as substantial associations between genetic variations and serious ADRs, particularly among antiepileptic drugs. This highlights the potential for future research to explore the cost-effectiveness or cost-utility of multi-pharmacogenetic screening of antiepileptic drugs to assess their value for money.

5. CONCLUSION

The results of this study suggest that implementing *HLA-B*13:01* screening prior to initiating phenobarbital therapy or adopting an alternative drug with sodium valproate strategy could reduce the incidence of phenobarbital-induced DRESS and result in cost savings by preventing its occurrence in pediatric epilepsy patients. Accordingly, the alternative drug strategy is the most cost-effective option, considering a willingness-to-pay threshold of 160,000 THB/QALY.

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Author contribution
TS and NP performed an analysis and interpretation of data and drafted the paper. ST and JM are involved in the data's conception, design, analysis, and interpretation. ST was involved in drafting the paper and revising it critically for intellectual content. All authors granted the final approval of the version to be published and agreed to be accountable for all aspects of the work.

Conflict of interest
The authors declare that they have no conflict of interest.

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