Cost-effectiveness analysis of \textit{HLA-B*58:01} genetic testing before initiation of allopurinol therapy to prevent allopurinol-induced Stevens–Johnson syndrome/toxic epidermal necrolysis in a Malaysian population

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\textbf{Objective} Studies found a strong association between allopurinol-induced Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) and the \textit{HLA-B*58:01} allele. \textit{HLA-B*58:01} screening-guided therapy may mitigate the risk of allopurinol-induced SJS/TEN. This study aimed to evaluate the cost-effectiveness of \textit{HLA-B*58:01} screening before allopurinol therapy initiation compared with the current practice of no screening for Malaysian patients with chronic gout in whom a hypouricemic agent is indicated.

\textbf{Methods} This cost-effectiveness analysis adopted a societal perspective with a lifetime horizon. A decision tree model coupled with Markov models were developed to estimate the costs and outcomes, represented by quality-adjusted life years (QALYs) gained, of three treatment strategies: (a) current practice (allopurinol initiation without \textit{HLA-B*58:01} screening); (b) \textit{HLA-B*58:01} screening before allopurinol initiation; and (c) alternative treatment (probenecid) without \textit{HLA-B*58:01} screening. The model was populated with data from literature review, meta-analysis, and published government documents. Cost values were adjusted for the year 2016, with costs and health outcomes discounted at 3\% per annum. A series of sensitivity analysis including probabilistic sensitivity analysis were carried out to determine the robustness of the findings.

\textbf{Results} Both \textit{HLA-B*58:01} screening and probenecid prescribing were dominated by current practice. Compared with current practice, \textit{HLA-B*58:01} screening resulted in 0.252 QALYs loss per patient at an additional cost of USD 322, whereas probenecid prescribing resulted in 1.928 QALYs loss per patient at an additional cost of USD 2203. One SJS/TEN case would be avoided for every 556 patients screened. At the cost-effectiveness threshold of USD 8695 per QALY, the probability of current practice being the best choice is 99.9\%, in contrast with 0.1 and 0\% in \textit{HLA-B*58:01} screening and probenecid prescribing, respectively. This is because of the low incidence of allopurinol-induced SJS/TEN in Malaysia and the lower efficacy of probenecid compared with allopurinol in gout control.

\textbf{Conclusion} This analysis showed that \textit{HLA-B*58:01} genetic testing before allopurinol initiation is unlikely to be a cost-effective intervention in Malaysia. \textit{Pharmacogenetics and Genomics} 00:000–000 Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

\textbf{Keywords:} allopurinol, cost-effectiveness, genetic testing, \textit{HLA-B*58:01}, Stevens–Johnson syndrome, toxic epidermal necrolysis

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\section*{Introduction}

Gout is the most common inflammatory condition encountered in general practice, with a reported prevalence of gout worldwide ranging from 0.1 to 10\% [1], mostly affecting elderly patients aged 65–80 years [2,3]. Allopurinol, a xanthine oxidase inhibitor, is the most frequently used hypouricemic drug among practitioners [4], however, it is associated with cutaneous adverse reactions, ranging from mild rash and itching to severe cutaneous adverse reactions (SCARs) encompassing Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reactions with eosinophilia and systemic syndrome (DRESS), also known as allopurinol hypersensitivity syndrome (AHS) [5–7]. Although allopurinol-induced SCARs has a low annual incidence such as 5.76 per million person-years between 1995 and 2013 in the UK [8], the average mortality rates...
of SJS and TEN are as high as 1–5 and 25–35%, respectively [9]. More than 50% of patients surviving TEN suffer from long-term sequelae of the disease, such as severe dry eye syndrome (DES) [9,10].

Recent reports of strong association between HLA-B*58:01 and allopurinol-induced SJS/TEN [overall odds ratio = 79.28, 95% confidence interval (CI): 41.51–151.35] imply that HLA-B*58:01 genetic testing might be warranted to mitigate the risk of allopurinol-induced SJS/TEN [11–19]. It has been shown that the frequency of HLA-B*58:01 is higher in Thai, Han Chinese, Korean, and Southeast Asian populations than in the European population [20]. On the basis of a study in the Han Chinese population in Taiwan, with a predicted annual incidence of allopurinol-induced SCARs of 0.3%, the HLA-B*58:01 genetic test had a negative predictive value of 100%, but a positive predictive value of only 1.52% [11]. With this low positive predictive value, which indicates that out of 100000 HLA-B*58:01 positive patients treated with allopurinol, only 152 would develop SCARs, the role of HLA-B*58:01 screening in routine clinical practice remains doubtful.

In Malaysia, allopurinol was the causative drug most frequently reported to be associated with SJS/TEN from 2009 to 2014 [21]. Given the severity of SJS/TEN and its long-term sequelae, performing HLA-B*58:01 screening before the initiation of allopurinol therapy may reduce the number of allopurinol-induced SJS/TEN cases; thus, subsequently, the associated death can be prevented. This study aimed to evaluate the cost-effectiveness of HLA-B*58:01 screening before allopurinol initiation in a genetically diverse Malaysian population.

Methods
Overall description of the model
A hybrid model consisting of a decision tree model and a Markov model was developed to determine the clinical and economic outcomes of different treatment strategies in preventing allopurinol-induced SJS/TEN. The model began with a decision tree emulating different treatment strategies (Fig. 1). All patients subsequently encountered two possible outcomes at the end of the decision tree – (i) the development of SJS/TEN and (ii) no development of SJS/TEN. A Markov model with a 1-year cycle length was developed to estimate the lifetime effects of each outcome. In those who developed SJS/TEN, they may have either recovered with/without sequelae and be treated with an alternative drug (probenecid), or may have died. For those who did not develop SJS/TEN, they may have been continued to be treated with allopurinol and may either be controlled [target serum uric acid (SUA) level < 0.36 mmol/l], or remain uncontrolled, or may have died.

This study was carried out on a hypothetical cohort of 100 000 patients with chronic gout aged 50 years requiring hypouricemic therapy [22]. It was assumed that all patients have normal renal function (creatinine clearance > 50 ml/min), and lifestyle and dietary interventions are maintained as adjunct therapy to medication in all patients.

This cost-effectiveness analysis was calculated from a societal perspective. Lifetime horizon was used, as gout is a chronic disorder and hypouricemic therapy was maintained lifelong [22]. An annual discount rate of 3% was applied for both costs and outcomes in accordance with the Malaysian pharmacoeconomic guideline [23]. The outcome of the study was presented as incremental cost-effectiveness ratio, denoted by incremental cost per quality of life years (QALYs) gained. The analyses were carried out using Microsoft Excel (Microsoft Corp., Redwood, Washington, USA).

Treatment strategies
Three treatment strategies were modeled. To reflect current practice, allopurinol 300 mg/day was administered to all patients without HLA-B*58:01 screening. In the second strategy, HLA-B*58:01 screening was conducted before allopurinol initiation. In the third strategy, probenecid was prescribed as the first-line agent, thus eliminating the need for HLA-B*58:01 screening. Patients who are tested positive for HLA-B*58:01 allele received alternative drug – probenecid 2 g/day, whereas HLA-B*58:01-negative patients received allopurinol 300 mg/day. In patients who did not achieve the target SUA level with allopurinol 300 mg/day, the dose was increased to 600 mg/day. Patients who developed allopurinol-induced SJS/TEN and those who did not respond to allopurinol 600 mg/day were switched to probenecid. Patients who did not respond to probenecid 2 g/day continued probenecid treatment for lifetime, and acute gout flares were treated.

Allopurinol and febuxostat are recommended as first-line agents for the management of gout [24,25]. However, febuxostat is not commonly used in the usual clinical practice in Malaysia, where it is reserved for patients who cannot tolerate or are not responding to allopurinol treatment. Hence, febuxostat was not considered in this analysis. In patients who are unable to achieve the target SUA level with allopurinol, uricosuric agents such as probenecid and benzbromarone are recommended alone or in combination with allopurinol [22]. Evidence suggests that benzbromarone is a more potent uricosuric compared with probenecid; however, reports of hepatotoxicity limited its use and monitoring of liver function tests at follow-up is required [26]. Given that allopurinol and probenecid were the only two hypouricemic agent listed in the Malaysia Ministry of Health Medicines Formulary [27], probenecid was selected as the alternative to allopurinol in this analysis. Although febuxostat was not listed in the Formulary, febuxostat 80 mg/day was found to be more efficacious than allopurinol 300 mg/
Fig. 1

(a) Decision tree model. Patients with gout who require a hypouricemic agent received one of three different treatment strategies (current practice of no screening and prescribe allopurinol, HLA-B*58:01 screening-guided therapy, and probenecid prescribing). Decisions are indicated by squares and event outcome by circles. (b) Markov model I. Patients who developed Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (SJS/TEN) after receiving allopurinol entered this Markov model from the decision tree model. (c) Markov model II. Patients who did not develop SJS/TEN after receiving allopurinol and patients who were tested HLA-B*58:01 positive and received probenecid entered this Markov model from the decision tree model. DES, dry eye syndrome; HLA, human leukocyte antigen.
day. Hence, a sensitivity analysis was carried out to determine the cost-effectiveness of \textit{HLA-B*58:01} screening when febuxostat was used as the alternative hypouricemic drug.

The efficacy of allopurinol 300 mg/day was estimated from a meta-analysis of two phase III randomized clinical trials [28,29] cited by a cost-effectiveness study in Singapore [30] (see Supplementary Appendix 1, Supplementary digital content 1, http://links.lww.com/FPC/B294). The probability of achieving target SUA with allopurinol 300 mg/day was 38% (95% CI: 33–42%). The probability of achieving target SUA with allopurinol 600 mg/day and probenecid 2 g/day were 78% (95% CI: 59–89%) and 65% (95% CI: 45–81%), respectively [31,32]. Compared with allopurinol 300 mg/day, there was an increase of 82% in patients achieving target SUA associated with the use of febuxostat 80 mg/day [risk ratio = 1.82 (95% CI: 1.58–2.08)] [33].

**Predictive value of \textit{HLA-B*58:01} genetic testing**

Because of the ethnic diversity of the Malaysian population, the ethnicity-weighted prevalence of \textit{HLA-B*58:01} allele carriers was estimated to be 12.4%. This prevalence was pooled from reported \textit{HLA-B*58:01} allele frequencies of the Malaysian and Singaporean population from the allele frequency database (http://www.allelefrequencies.net) and published literature by meta-analysis [34,35] (see Supplementary Appendix 2, Supplementary digital content 2, http://links.lww.com/FPC/B295).

The incidence of allopurinol-induced SJS/TEN in Malaysia was assumed to be 0.2% [11], which was similar to that of Singapore. Using the prevalence data and association between \textit{HLA-B*58:01} and allopurinol-induced SJS/TEN (overall odds ratio = 74.18, 95% CI: 26.95–204.14), incidences of allopurinol-induced SJS/TEN in patients with and without \textit{HLA-B*58:01} risk allele were calculated to be 1.5% and 0%, respectively (see Supplementary Appendix 3, Supplementary digital content 3, http://links.lww.com/FPC/B296).

The probability of death caused by allopurinol-induced SJS/TEN was calculated to be 4.17% [36]. This mortality rate was comparable to the mortality rate reported in other literatures [37].

As severe DES was the most common late ocular complication of SJS/TEN [10,38], DES was modeled as the long-term sequelae of SJS/TEN. The probability of developing long-term ocular sequelae of SJS/TEN was 40.6% as calculated from the published literature [10,38].

**Costs**

The costs included (i) direct medical costs – costs of gout management, costs of \textit{HLA-B*58:01} testing, costs of SJS/TEN event, costs of long-term sequelae treatment, costs of allopurinol, and costs of probenecid, (ii) direct non-medical costs – costs of transportation and additional food, and (iii) indirect costs – productivity loss because of illness. All costs were converted into 2016 values using the Malaysia consumer price index [39]. The exchange rate of USD 1 per MYR 4.49 was used [40].

The costs of allopurinol and probenecid were MYR 0.14 per unit and MYR 0.33 per unit, respectively. The cost of SJS/TEN treatment was estimated on the basis of the resource utilization data collected [41] and cost data from the Ministry of Health Malaysia fee schedule for foreigners [42]. The average cost of an SJS/TEN event was MYR 6462.12 using a nonparametric bootstrap method with 10,000 resampling. The annual cost of DES treatment was MYR 561.69. The annual cost of gout management was MYR 638.70 for the first year, whereas MYR 319.35 was the cost for the subsequent years on the basis of an assumption of 4 and 2 outpatient visits for the first and subsequent year, respectively (see Supplementary Appendix 4, Supplementary digital content 4, http://links.lww.com/FPC/B297).

We assumed that chronic gout patients with uncontrolled gout experienced four gouty attacks per year, with 13% of the patients who experienced gouty attacks requiring emergency department visits and inpatient care [43]. On the basis of the resource utilization pattern for acute gout flare [44], the annual cost of acute gout flare management was MYR 914.28.

Direct nonmedical costs consisted of costs of transportation and additional food for patient with a caregiver, who visited hospitals for SJS/TEN, and clinic visits for DES and gout. These costs were calculated from government-approved rate and national survey [45,46].

Indirect costs reflected by productivity loss because of illness were estimated using age-specific mean monthly wage and the average length of hospital stay for SJS/TEN or acute gout flare, and regular follow-ups at clinics. The minimum retirement age of an employee in Malaysia was 60 years [47]. Assuming that all employees retire at the age of 65, productivity loss because of illness was considered only up to age 64 [48].

**Health state utilities**

The utility of each health state (i.e. SJS/TEN, DES, controlled gout, and uncontrolled gout) was derived for the QALY estimation on the basis of published [30,41,49,50].

**Literature**

As there were no data for utilities of overlapped health states, we estimated these utilities using the multiplicative approach by Ara and Brazier [51]. For example, the utility of gout patients with SUA level within target and long-term sequelae was estimated by multiplying the utility value of controlled gout with the utility value of DES.
Base case analyses
The expected costs and outcomes of three proposed treatment strategies for patients with chronic gout requiring hypouricemic drug were calculated using the societal perspective. The primary outcomes were presented as an incremental cost-effectiveness ratio for (a) current practice versus HLA-B*58:01 screening before allopurinol initiation (b) current practice versus probenecid prescribing without HLA-B*58:01 screening. The secondary outcome was the number of patients needed to screen to avoid a one SJS/TEN event.

As recommended by the Technical Advisory Committee for Health Technology Economic Evaluation of Malaysia [52], a cost-effectiveness threshold of MYR 39,000 (USD 8695) per QALY (equivalent to one gross domestic product per capita) was used to determine the best strategy in base-case and sensitivity analyses.

Sensitivity analyses
Sensitivity analyses (one-way sensitivity analyses and probabilistic sensitivity analyses) were carried out to assess the combination of uncertainty in all model inputs on robustness of model outcomes. In the one-way sensitivity analyses, parameters were varied one at a time, and the effect of each variation on the model outcomes result was examined. The results of a series of one-way sensitivity analyses were presented in a Tornado diagram. A probabilistic sensitivity analysis was carried out to assess all parameter uncertainty simultaneously. A Monte Carlo simulation with 10,000 iterations using values drawn randomly from predefined distributions was performed. All input parameters were assigned a probability distribution to reflect the feasible range of values that each parameter could attain (Table 1). The β distribution was assumed for probability variables, utilities, and hypouricemic agent efficacy parameters, which were bounded by 0–1; γ distribution and log-normal were used for all cost parameters [54]. A cost-effectiveness plane (cost-effectiveness scatterplot) was generated, with each dot representing a simulated outcome from Monte Carlo simulation. A cost-effectiveness acceptability curve was generated to illustrate the probability of being cost-effective for each strategy within the willingness-to-pay threshold.

Results
Base case analyses
Both HLA-B*58:01 screening and probenecid prescribing were dominated by current practice (Table 2). Compared with current practice, HLA-B*58:01 allele screening before allopurinol initiation resulted in 0.252 QALYs loss per patient at an additional cost of MYR 39,411 (USD 8797). However, probenecid prescribing resulted in 1.928 QALY loss per patient at an additional cost of MYR 30,716 (USD 6848). This finding was related to the low incidence of allopurinol-induced SJS/TEN in Malaysia and the estimated efficacy difference among hypouricemic agents modeled.

In both HLA-B*58:01 screening and probenecid prescribing, the incidence of allopurinol-induced SJS/TEN was two SJS/TEN cases per 10,000 patients compared with 20 cases per 10,000 patients in current practice. The number needed to screen to avoid one case of SJS/TEN is 556, indicating that 18 SJS/TEN cases could be avoided per 10,000 patients.

Sensitivity analyses
When febuxostat was used as the alternative hypouricemic drug, both HLA-B*58:01 screening and febuxostat prescribing were dominated by current practice (Table 3). HLA-B*58:01 allele screening before allopurinol initiation resulted in 0.045 QALYs loss per patient at an additional cost of MYR 9783 (USD 2181). Furthermore, febuxostat prescribing resulted in 0.375 QALY loss per patient at an additional cost of MYR 66,574 (USD 14,843).

The results of one-way sensitivity analyses were presented in Tornado diagrams as shown in Figs 2 and 3. The Tornado diagrams showed the incremental cost per QALY gained of 10 most influential parameters in the HLA-B*58:01 screening and probenecid prescribing compared with current practice. In both HLA-B*58:01 screening and probenecid prescribing, the efficacy of probenecid 2 g/day in achieving target SUA level had the highest potential influence on both incremental costs and incremental QALYs. The other key drivers on the incremental cost were the length of inpatient stay because of uncontrolled gout and the number of outpatient visits because of acute gout flare, whereas the discounting rate for outcomes and the probability of achieving target SUA level with allopurinol 600 mg/day had the greatest potential effect on the incremental QALYs.

Probabilistic sensitivity analyses showed that current practice was cost-effective in approximately 99.9% of simulations at the willingness-to-pay threshold of MYR 39,000 (Figs 4 and 5).

Discussion
Our study shows that either HLA-B*58:01 screening or probenecid prescribing is unlikely to be cost-effective compared with current practice in Malaysia. Although both strategies reduced the incidence of allopurinol-induced SJS/TEN, both strategies were more costly and less effective than current practice.

The cost-effectiveness findings were attributed to the reduced clinical efficacy of alternative hypouricemic agents, leading to poorer gout control, thus resulting in overall QALY loss. Although only 1.5% of HLA-B*58:01-positive patients will develop allopurinol-induced SJS/TEN, all patients who were tested HLA-B*58:01 positive
would be treated with probenecid. Because of the lower efficacy in gout control associated with probenecid [31, 32], greater QALYs loss resulted from the suboptimal gout management with a higher frequency of acute gout flares. Given the low incidence of allopurinol-induced SJS/TEN (0.2%), the switching from allopurinol to probenecid is likely to increase the lifetime cost of uncontrolled gout management and reduce patients’ QALYs.

Several country-specific economic evaluations have addressed the cost-effectiveness of \( HLA-B^*58:01 \)
screening before allopurinol initiation [30,44,55–57]. Controversial results were noted, ranging from being cost-effective for Koreans with chronic renal insufficiency, Thai and Taiwan Han Chinese populations to being dominated in the Singapore setting. The main reason for the discrepancies between our findings and those of Park and colleagues and Saokaew and colleagues was that our model had incorporated the efficacy of the alternative drug; therefore, a better representation of real-world clinical outcomes on the basis of the current evidence was attained. Furthermore, all possible health states of a gout patient were captured in our model so that the results generated in our study would be a more accurate estimate of the cost-effectiveness in the real-world setting.

Several guidelines have addressed the applicability of HLA-B*58:01 screening in routine clinical practice. Despite a number of guidelines recognizing the potential of HLA-B*58:01 testing in reducing the incidence and risk of allopurinol-induced SJS/TEN, routine HLA-B*58:01 screening is yet to be recommended [22, 58–60]. However, the American College of Rheumatology recommends HLA-B*58:01 testing for selected at-risk populations, such as Korean with stage 3 or worse CKD, and Han Chinese or Thai population irrespective of renal function [25]. Notably, the Singapore Health Science Authority decided that HLA-B*58:01 screening before the initiation of allopurinol therapy was not required, although the majority of Singapore population are of Han Chinese-ancestry [61]. Our analysis was consistent with the guideline recommendations; hence, implementation of HLA-B*58:01 screening-guided therapy in routine clinical practice may not be necessary in the current healthcare setting.

The sensitivity analyses showed that our findings are robust. The cost of HLA-B*58:01 genetic test played a minor part in the total cost of pharmacogenomic-guided treatment; eliminating the cost of HLA-B*58:01 had little impact on the cost-effectiveness findings. Although the efficacy of an alternative hypouricemic agent was the key driver influencing the overall cost-effectiveness findings, it remained unchanged when a more efficacious febuxostat 80 mg/day was used as the alternative treatment than probenecid 2 g/day. Compared with the results of base-case analysis, febuxostat use resulted in a higher cost incurred and lesser QALY loss as febuxostat was 60 times higher than allopurinol, but not as efficacious as high-dose allopurinol. Moreover, recent reports of febuxostat-related DRESS [62–64], which was another variety of SCARs, also precluded the use of febuxostat as the alternative agent in HLA-B*58:01-positive gout patients.

A strong association was found between the HLA-B*58:01 allele and allopurinol-induced SJS/TEN, with a reported overall odds ratio of 74.18 (95% CI 26.96–204.14) among the Asian population [20]. Alleles HLA-A*33:03, HLA-Cw*03:02 and HLA-DRB1*03:01 were also associated strongly with allopurinol-induced SCAR based on a pharmacogenetic study among the Han Chinese population [11]. Although 100% of allopurinol-induced SCAR patients presented with the HLA-B*58:01 allele, the extended haplotype formed by HLA-A*33:03-Cw*03:02-B*58:01–DRB*03:01 was presented only in 41% of patients, indicating that the HLA-B*58:01 allele was likely the most predictive genetic marker of this condition. Because of the paucity of evidence for the role of other associated alleles in allopurinol-induced SCAR, our analysis focused only on the cost-effectiveness of HLA-B*58:01 screening-guided therapy. Further investigation of other associated risk alleles

### Table 2 Results following base-case analyses

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cost (MYR/USD)</th>
<th>Effectiveness (QALYs)</th>
<th>Incremental cost (ΔMYR/USD)</th>
<th>Incremental effectiveness (ΔQALYs)</th>
<th>ICER (ΔMYR/ΔQALYs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current practice</td>
<td>13 023/2903</td>
<td>17.49</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>HLA-B*58:01 screening</td>
<td>14 665/3225</td>
<td>17.48</td>
<td>1443/322</td>
<td>–0.252</td>
<td>Dominated</td>
</tr>
<tr>
<td>Alternative drug (probenecid)</td>
<td>22 504/5105</td>
<td>17.43</td>
<td>9881/2203</td>
<td>–1.928</td>
<td>Dominated</td>
</tr>
</tbody>
</table>

All costs and outcomes are discounted at 3% per year. Costs are converted at the rate of USD 1 = MYR 4.485 [40]. HLA, human leukocyte antigen; ICER, incremental cost-effectiveness ratio; MYR, Malaysia Ringgit; QALY, quality-adjusted life years; USD, United States Dollar.

### Table 3 Results following sensitivity analyses (febuxostat as an alternative drug)

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cost (MYR/USD)</th>
<th>Effectiveness (QALYs)</th>
<th>Incremental cost (ΔMYR/USD)</th>
<th>Incremental effectiveness (ΔQALYs)</th>
<th>ICER (ΔMYR/ΔQALYs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current practice</td>
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<td>19.26</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>HLA-B*58:01 screening</td>
<td>49 614/11 061</td>
<td>19.22</td>
<td>9783/2181</td>
<td>–0.045</td>
<td>Dominated</td>
</tr>
<tr>
<td>Alternative drug (febuxostat)</td>
<td>106 405/23 723</td>
<td>18.84</td>
<td>66 574/14 843</td>
<td>–0.375</td>
<td>Dominated</td>
</tr>
<tr>
<td>HLA-B*58:01 screening</td>
<td>23 723</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

All costs and outcomes are discounted at 3% per year. Costs are converted at the rate of USD 1 = MYR 4.485 [40]. HLA, human leukocyte antigen; ICER, incremental cost-effectiveness ratio; MYR, Malaysia Ringgit; QALY, quality-adjusted life years; USD, United States Dollar.
is needed to improve the predictive value of the genetic test. Then, genetic testing before allopurinol initiation may be a potentially feasible intervention.

Our study was subjected to several limitations. First, the incidence of allopurinol-induced SJS/TEN and the association of the HLA-B*58:01 allele and allopurinol-induced SJS/TEN was derived using Asian population data, which may not accurately represent the genetically diverse Malaysian population. Second, the absence of other drug-related adverse effects may lead to an underestimation of cost related to gout management. Besides renal impairment, which was addressed by Park et al. [56], there are several other risk factors that would place patients at a higher risk for allopurinol-induced SJS/TEN, such as old age and concomitant thiazide diuretic therapy [65]. Given the limited evidence on the effect of multiple risk factors on the incidence of allopurinol-induced SJS/TEN, this impact was not assessed in this study. Third, the full spectrum of long-term SJS/TEN sequelae was not captured. Despite several severe complications of SJS/TEN having been documented [66], the evidence remains scanty. Thus, an accurate estimate could not be derived with the current evidence, potentially leading to an underestimation of the SJS/TEN sequelae cost. Fifth, although poor persistence with hypouricemic therapy has been reported [67,68], and this could lead to suboptimal treatment outcome, the local data on persistence remain limited. Thus, this has deterred such aspects from being taken into consideration in our analysis. In addition, because of the limited
data on the relative treatment effects of dose-specific allopurinol versus other hypouricemic agents, the approach used in estimating the efficacy of hypouricemic agents used was subjected to potential bias. Finally, a number of studies have reported the potential association between the \( HLA-B^*58:01 \) allele and allopurinol-induced DRESS syndrome [11,12,69]. Our analysis was only limited to SJS/TEN and not other SCARs; thus, the value of \( HLA-B^*58:01 \) screening in preventing allopurinol-induced SCARs might be underestimated.

It is important to note that \( HLA-B^*58:01 \) screening can potentially avoid life-threatening SCARs and their associated long-term complications. Although our findings showed that \( HLA-B^*58:01 \) screening was unlikely to be a cost-effective strategy compared with current practice based on the best available evidence, policy makers should take other factors, for example, ethical, social issues into considerations when making an informed decision.
Fig. 4

Cost-effectiveness plane. Each point represents the incremental costs (year 2016 values, societal perspective) and quality-adjusted life years (QALYs) gained between current practice versus HLA- B*58:01 screening before allopurinol initiation (blue dot) and current practice versus probenecid prescribing without HLA-B*58:01 screening (orange dot) from the Monte Carlo simulation. HLA, human leukocyte antigen; MYR, Malaysia Ringgit; WTP, willingness-to-pay.

Fig. 5

Cost-effectiveness acceptability curve. Each curve illustrates the probability being the most cost-effective option for a given willingness-to-pay value. HLA, human leukocyte antigen; MYR, Malaysian Ringgit; QALY, quality-adjusted life years.
Conclusion
Our cost-effectiveness analysis suggests that HLA-B*58:01 screening before initiation of allopurinol therapy in Malaysia is unlikely to be cost-effective in the current setting. Our sensitivity analyses showed that the result is robust.

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H.Y.C. and Y.H.L. supplied the acquisition of data, analysis, and interpretation of data, drafting of the manuscript, and take responsibility for the integrity of the data and the accuracy of the data analysis; H.Y.C. and J.P. conceived and designed the study; W.T. and Z.M. were responsible for critical revision of the manuscript for important intellectual content; N.C. revised manuscript critically for important intellectual content and provided final approval of the version to be submitted. All authors read and approved the manuscript.

Conflicts of interest
None declared.

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## Queries and/or Remarks

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