Published in final edited form as:

Public Health Genomics. 2018 ; 21(5-6): 217–227. doi:10.1159/000500725.

Generic Cost Effectiveness Models: A Proof of Concept of a Tool for Informed Decision-making for Public Health Precision Medicine

Susan R. Snyder¹, Jing Hao¹, Larisa H. Cavallari², Zhi Geng¹, Amanda Elsey², Julie A. Johnson², Zahurin Mohamed³, Nathorn Chaikunapruk^{4,5,6,7,14}, Huey Yi Chong⁴, Maznah Dahlui⁸, Fatiha H. Shabaruddin⁹, George P. Patrinos^{10,11}, Christina Mitropoulou¹², Marc S. Williams¹³

¹Department of Epidemiology and Health Services Research, Geisinger Health System, Danville, Pennsylvania, USA ²Department of Pharmacotherapy and Translational Research, University of Florida, Gainesville, FL, USA ³Department of Pharmacology, University of Malaya, Kuala Lumpur, Malaysia ⁴School of Pharmacy, Monash University Sunway Campus, Subang Jaya, Malaysia ⁵Center of Pharmaceutical Outcomes Research (CPOR), Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Naresuan University, Phitsanulok, Thailand ⁶School of Pharmacy, University of Wisconsin, Madison, USA ⁷Asian Centre for Evidence Synthesis in Population, Implementation and Clinical Outcomes (PICO), Global Asia in the 21st Century (GA21) Platform, Monash University Malaysia ⁸Department of Social and Preventive Medicine, Julius Centre, University of Malaya, Kuala Lumpur, Malaysia ⁹Department of Pharmacy, University of Malaya, Kuala Lumpur, Malaysia ¹⁰University of Patras School of Health Sciences Department of Pharmacy, Patras, Greece ¹¹United Arab Emirates University, College of Medicine, Department of Pathology, Al-Ain, United Arab Emirates ¹²The Golden Helix Foundation, London, UK ¹³Genomic Medicine Institute, Geisinger Health System, Danville, Pennsylvania, USA ¹⁴Department of Pharmacotherapy, College of Pharmacy, University of Utah, Salt Lake City, UT 84112, USA

Abstract

Background/Aims—Economic evaluation is integral to informed public health decision-making in the rapidly growing field of precision and personalized medicine (PM), however this research requires specialized expertise and significant resources. Generic models are a novel innovation to efficiently address a critical PM evidence shortage and implementation barrier by enabling use of

Correspondence: Susan R. Snyder, PhD, MBA, Geisinger Dept. of Epidemiology and Health Services Research, c/o Bethann M. Puderbaugh, Administrative Assistant, Henry Hood Center for Health Research, 100 North Academy Avenue MC 44-00, Danville, PA 17822, Susan Snyder: Mobile: 404-276-9368; srsnyder1@geisinger.edu, Bethann Puderbaugh Office Phone: 570-214-9825; bmpuderbaugh@geisinger.edu, Fax: 570-214-9451.

Disclosure

None of the authors have any disclosures of involvement or commercial associations that might pose or create a conflict of interest with the information presented in this manuscript.

Ethics Statement:

This paper is not directly related to human or animal research as all data relating to human subjects were obtained from previously conducted and published studies.

local input values. This is a generic PM economic evaluation model proof-of-concept study for a pharmacogenomic use case.

Methods—An eight-step generic economic model development process was applied to the use case of *HLA-B*15:02* genotyping for prediction of carbamazepine-induced cutaneous reactions, with a user-friendly decision-making tool relying on user-provided input values. This generic model was transparently documented and validated, including cross-validation comparing cost-effectiveness results with three country-specific models.

Results—A generic pharmacogenomic use case cost-effectiveness model with decision-making tool was successfully developed and cross-validated using input values for six populations which produced consistent results for *HLA-B*15:02* screening at country-specific cost-effectiveness threshold values. Differences between the generic and country-specific model results were largely due to differences in model structure and assumptions.

Conclusion—This proof on concept demonstrates the feasibility of generic models to provide useful PM economic evidence, supporting their use as a pragmatic and timely approach to address a growing need.

Keywords

Cost effectiveness; Modelling; Precision Medicine; Decision analysis; Pharmacogenomics

INTRODUCTION

Precision medicine (PM) promises to transform selection of health interventions from intuitive and empiric to individualized, targeted strategies that are predictably effective for disease diagnosis and treatment.[1] One of the most rapidly growing areas of PM is pharmacogenomics (PGx), where insight into genetic variation associated with likelihood for drug effectiveness and risk for drug toxicity can inform individualized treatment approaches. A recent review of the Genetic Testing Registry lists 45 PGx tests being available for 31 genes involving 168 drugs/conditions. [2]

For PM to reach targeted populations, high quality economic evaluations are needed to support value-based decision making by stakeholders involved in coverage decisions.[3,4] PM applications may involve trade-offs common to new technologies between higher healthcare costs, especially in the short term, for improved health outcomes while the evidence base is still emerging. Case-by-case assessment meaningful to decision makers is needed to determine if a PM application's likely value from potential improvement in health outcomes is considered acceptable relative to its cost.

Health economic evaluation using decision analytic modeling is a structured and systematic approach. They should meet rigorous methodological and transparency standards [5] that can be used to assess the potential value of PM applications. It can be especially useful for emerging technologies when there is a relative scarcity of health outcome and cost evidence since it enables combining data from multiple sources within a single framework. However developing traditional economic evaluation models is a time-consuming and resource-intensive process requiring expertise and experience. Health economic evaluations typically

focus on a single application in a specific context using data and assumptions which may not be generalizable to other settings and populations. Additionally, disparate modeling approaches for a single application are common from one economic evaluation to another. Designing relatively simple economic models to inform healthcare decision-making has been recommended to reduce the heterogeneity in approaches, with sensitivity analyses to address uncertainty associated with insufficient evidence, followed by refinement as evidence becomes available.[6,7]

Modifying conventional decision analytic cost-effectiveness models to make them broadly applicable is a potential solution to meet decision and policy maker needs for PM case-by-case assessment that addresses the persistent resource constraints of skilled labor and funding.[8] A proposed innovation is *generic economic evaluation models* that can be disseminated as tools requiring less user expertise to provide meaningful value-based information from locally relevant and population-based input values.[9,10]

This article presents a proof-of-concept study of a PM generic economic evaluation model and a user-friendly decision support tool for a PGx use case. Similar to other PGx implementation decisions, this example involves a choice between maintaining a uniform standard pharmaceutical treatment for all patients newly diagnosed with a condition versus introducing universal screening with a genetic test prior to selecting the treatment. The specific aims of this study are to: (1) create and implement a process to develop a PGx use case generic economic model with a decision-making tool, and (2) provide validation evidence from the PGx use case for the hypothesis that a generic model can produce relevant economic evaluation evidence of acceptable quality for value-based decision-making compared to conventional models.

Generic Cost Effectiveness Model: Pharmacogenomics Use Case

The PGx use case of human leukocyte antigen (*HLA*)-*B*15:02* allele genotyping to predict risk for the carbamazepine (CBZ) induced severe cutaneous adverse reactions (SCARs) Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) in the treatment of adult onset epilepsy was chosen for several reasons. First, there is significant variability in *HLA-B*15:02* frequency across populations, with the highest frequency observed in southeastern Asians. Thus, an economic model specific to one population is likely not applicable to another. Second, while the risk allele is generally uncommon, these CBZ use consequences in a patient with the *HLA-B*15:02* allele can be devastating, with the potential for lifelong sequelae for those who survive SJS/TEN. This has prompted a CBZ genotyping guideline from the Clinical Pharmacogenetics Implementation Consortium (CPIC) [11] and a boxed warning from the U.S. Food and Drug Administration (FDA) [12] on the labeling for CBZ. Third, alternative anti-epileptic agents (e.g., valproic acid (VPA)) are available for patients with the at-risk allele. Finally, we had access to a previous cost effectiveness model from Thailand and interest from other Asian countries to formally evaluate the cost effectiveness of universal adoption of *HLA-B*15:02* testing.

MATERIALS AND METHODS

Generic Model Development Process

A general eight-step approach to develop a generic economic evaluation model and decision-making tool as summarized in Figure 1 was applied to the PGx use case by an international multidisciplinary group of collaborators, the Global Genomics Team (Step 1: Team). The Global Genomics Team completed this work under Genomic Medicine Implementation: The Personalized Medicine Program led by the University of Florida College of Pharmacy and funded by the U.S. National Human Genome Research Institute as part of IGNITE (<https://ignite-genomics.org/>) to support the implementation of genomics in healthcare. A country-specific, Microsoft® (Redmond, Washington) Excel-based model was adapted to make it generalizable and relevant to decision makers for any country or local setting using a revised and copyrighted version of a published Thailand model [13] and a corresponding user manual.[14] In addition two countries represented on the team, Indonesia and Malaysia, adapted the model which along with an independently developed published model from Singapore [15] were used. These models were supplemented by relevant published and unpublished data sources, and consultation with other clinical and health economics subject matter experts to inform development of the PGx use case generic model (Step 2: Original Model(s)).

The Thai model variables and assumptions were reviewed to identify which ones were population-specific and/or unlikely to be generalizable to other locations. From those, the team identified which ones generic model users were unlikely to have the information needed to provide input values (i.e., would require initiating a new data collection process). Next, variables and assumptions identified as neither generalizable nor likely to have available data were further reviewed to decide whether they could be eliminated from the generic model. Finally, variables and assumptions considered potentially generalizable were reviewed for evidence supporting their relevance for inclusion and input values. Extensive focused searches, reviews and syntheses were completed to inform the team's generic model parameter inclusion and exclusion decisions (Step 3: Evidence). For example, variables associated with adverse drug reactions other than SJS/TEN were omitted due to insufficient publicly available evidence to support inclusion.

The PGx use case generic model variables and assumptions identified for inclusion underwent a final review to assign them to three categories related to requiring a user-specified input value (Step 4: Generic Model).

1. *Input value only.* Requires a user-specified value to reflect local/population context (e.g., population allele frequency; all medical cost variables)
2. *Default value only.* Considered universal and independent of local/population context (i.e., generalizable) based on one of the following criteria: a) supported by strong available evidence (e.g., test sensitivity and specificity); b) very limited evidence (e.g., health state utility of a very rare disease); or c) otherwise required by the model to meet certain logic requirements (e.g., health state utility value constrained by its relationship to other health states).

3. *Default value with an input option.* Allows users to select either an input or default value to address their needs and/or preferences, offering more sophisticated users the opportunity for additional customization.

Transparent support for all PGx use case generic model input default values was developed by synthesizing information from relevant sources to inform team reviews of proposed base case values and sensitivity analysis ranges applicable to most country and local circumstances. Team consensus decisions resulted in new default values replacing most of the original country-specific model values relying on internal data or a single reference source. As is generally the case, there was considerable variation in the quantity and quality of evidence available to support model values. The PGx use case generic model parameter and assumption values with evidence syntheses are provided in Appendix A.

Generic Model Validation

Validation tests whether the mathematical representations used in the model consistently generate realistic results of the impact of changes in policy or treatment that are meaningful for informing policy decisions. Consistent with International Society of Pharmacoeconomics and Outcomes Research-Society for Medical Decisionmaking (ISPOR-SMDM) recommendations for modeling transparency and validation practices,[16] detailed PGx use case generic model documentation was developed (Appendix A) to enable experts and others to evaluate and reproduce it. The PGx use case validation approach relied on face validity, internal validity and cross validation as described in the ISPOR-SMDM recommendations. External validation, which tests a model's ability to calculate actual outcomes and requires real healthcare and disease event data, was not feasible due to a lack of available data which is common for new PM applications and rare occurrences of serious drug reactions.

Several members of the team and their associates reviewed the completed PGx use case generic model for face and internal validity. Face validity was established by completing a thorough examination of the model's documentation which included reviewing its structure, data sources, assumptions and results, and assessing whether it corresponded to current science and evidence (Step 5: Face Validity). Internal validity assessment was completed by checking the accuracy of the model's coding, formulas and calculations to determine if it performed as intended and worked correctly (Step 6: Internal Validity).

Cross validation involves the comparison of a model's simulation results with those of other models analyzing the same problem to assess whether they produce similar results. Cross validation for the PGx use case generic model was performed using three country-specific models (Singapore,[15] Thailand [13] and Malaysia [17]), each with a different structure and assumptions. In addition, Singapore's model included input values and results for three ethnic subgroups (Chinese, Malays and Indians) which were also compared to the generic model (Step 7: Cross Validation). A total of six PGx use case generic model cross-validation comparisons were completed by generating results using each country-specific model's assumption and input values pertaining to the generic model (Appendix B).

Following validation of the PGx use case generic model, the finalized version was converted into an Excel-based decision-making tool by adding detailed descriptions and instructions in a user-friendly format (Step 8: Decision-Making Tool). After all required values are input in the PGx use case generic model decision-making tool (Appendix C), appendix c data miss]running the model evaluates lifetime costs and outcomes for the three treatment options and generates cost effectiveness analysis results as described in the Results section.

RESULTS

Generic Economic Evaluation Model and Decision-making Tool

The process implemented to develop and validate a PGx generic cost effectiveness model and decision support tool (the tool) from a country-specific model is summarized in Figure 1 and described in the Methods section. The generic model was developed from a country-specific cost-utility model for newly diagnosed adult epilepsy patients. A decision analysis and Markov model structure (Figure 2) from a healthcare payer/provider perspective using direct medical care costs was used to compare three different treatment strategies: 1) current practice - CBZ initiation without *HLA-B*15:02* screening; 2) universal *HLA-B*15:02* screening before CBZ initiation with patients testing positive classified as being at high risk for an adverse drug reaction and prescribed an alternative antiepileptic drug – valproic acid (VPA), and; 3) alternative drug VPA without *HLA-B*15:02* screening. PGx use case generic economic evaluation model documentation of parameter values and assumptions with supporting references is provided in Appendix A.

The primary objective of the tool was to allow users to generate pragmatic evidence from population-relevant assumption and input values comparing the three strategies for treatment of newly diagnosed adult epilepsy patients and prevention of CBZ-induced SJS/TEN. A secondary objective was to facilitate user-guided sensitivity analysis to produce additional results to further inform decision-making. The Microsoft® Excel tool is provided in Appendix C appendix c data miss]and contains the following four worksheets: Model Overview, Model Diagrams, Input Table and Results. The Input Table worksheet contains user instructions and descriptive information for required and optional input variables allowing users to either specify a value or select a generalizable default value. All input variables are listed and described in Supplemental Appendix A, Table 2. The PGx generic model analysis results are calculated after the user enters all the input values in the tool and then runs the simulation on the Results worksheet. An important feature of the decision-making tool is that the user can input different variable and assumption values and then re-run the model to obtain information on the impact of these changes on the results.

The results are displayed as shown in Table 1 using Singapore input values as an example. The first two sections show incremental cost effectiveness analysis results comparing the current practice of no screening and CBZ treatment to universal *HLA-B*15:02* screening (option 1) and no screening with alternative VPA treatment (option 2). The first results are for a deterministic case using base case values for the model parameters followed by probabilistic results using simulated values from parameter ranges and distributions for 1,000 iterations. The results displayed are values and incremental values for costs, life years (LYs) and quality-adjusted life years (QALYs) gained, with incremental cost effectiveness

ratios (ICERs) per LY and per QALY expressed in the user-selected currency and base year. The ICERs compare the difference in cost to the difference in LYs and QALYs gained for the current practice of no genetic screening and CBZ treatment to the two options of universal genetic screening prior to treatment and no screening and an alternative medication (VPA). The bottom section displays estimates for cases prevented per patient screened and the number of patients needed to be screened (NNS) to prevent one SJS/TEN case which are calculated by comparing the estimated SJS/TEN cases between the current no-screening practice versus universal *HLA-B*15:02* screening.

The PGx generic model cost effectiveness results are displayed graphically in the tool's Results worksheet as shown in Figure 3 using Singapore input values. The top graph is a base case QALY ICER plot of the two policy options versus the current practice (no screening and CBZ treatment). The middle graph is a cost effectiveness (CE) plane plotting the incremental cost and incremental QALYs of 1,000 probabilistic analysis simulations. The bottom graph is a cost effectiveness acceptability curve (CEAC) of the simulation-based probability that a decision-maker would favor each policy option at different ceiling ratio values of their willingness to pay per QALY gained.

PGx Generic Model Validation Evidence

Results for the PGx generic model cross-validation analysis from three country-specific model base case comparisons for genetic screening versus treatment without genetic screening options are summarized in Table 2, with complete results for all six comparisons provided in Appendix B. Costs are reported in country-specific currencies rather than a common currency as the generic model and tool's objective is to allow users to generate pragmatic evidence from population-relevant assumption, input and threshold values rather than comparing cost-effectiveness study results for each country using a common currency. As this is a proof-of-concept and not a conventional cost-effectiveness study, its primary objective is to develop and validate a generic precision medicine economic evaluation model for a pharmacogenomic use case, and demonstrate its utility for providing country-specific information for decision making. Consequently, comprehensive generic and country-specific model results are not reported as findings, however as they are relevant to the study, they are reported along with detailed analysis supporting the generic and country-specific model comparisons in Appendix B with explanations on the sources accounting for differences in the results (e.g., length of epilepsy treatment duration).

Due to multiple differences between the generic and country-specific models, comparing their incremental cost effectiveness ratio (ICER) results to each country's reported ICER threshold value to identify the most cost-effective strategy was more useful than comparing actual ICER result values. The primary sources accounting for the differences in results are identified in Appendix B.

The PGx generic model base case results were in agreement with all three country-specific models as to which of the three strategies was the most cost effective at their respective ICER currency threshold values. For Malaysia and Thailand the current practice of no genetic screening and CBZ treatment was the most cost effective at the Malaysia ringgit currency (MYR) ICER threshold value of 37,000 MYR/QALY and the Thai baht currency

(THB) ICER threshold value of 160,000 THB/QALY, respectively. For Singapore universal genetic screening prior to treatment was the most cost effective at the ICER threshold value of U.S. \$50,000/QALY. For the three Singaporean ethnic population subgroups, the generic and country-specific model results were also in agreement with the published results at the ICER threshold value with universal genetic screening as the most cost-effective for Chinese and Malays but not for Indians. In summary, these cross-validation results comparing the PGx generic model to three conventional economic evaluation models using common input values for six populations found consistent cost-effectiveness results of relevance to decision makers.

DISCUSSION

This study of a PGx use case is the first publicly available proof of concept successfully demonstrating a process to develop and validate a PM economic evaluation generic model generating population-based results as well as serving as the basis for a user-centric decision-making tool. The consistency of the PGx generic model use case cross-validation results for the most cost-effective strategy when compared to three conventional country-specific models using input values for six populations supports the hypothesis that generic economic evaluation models can produce evidence of acceptable quality for value-based decision making. Moreover, these results support the utility and strength of the generic economic evaluation model approach for PGx and potentially PM applications. Importantly, the addition of a decision-making tool enabling users to input different variable and assumption values facilitates strategic development of relevant information. The interactive nature of the tool makes it more useful as a decision aid by being responsive to a user's needs and sources of uncertainty for a given population and application, and allowing analyses to be updated as new evidence becomes available.

Successful translation of PM applications into clinical practice and public health policy may depend on demonstrating their cost-effectiveness relative to available standards of care.[18] Lack of reimbursement for tests has been identified as a major barrier to clinical implementation of PM applications, yet as testing and sequencing costs continue to fall, the likelihood that they can be cost-effective or even cost-saving increases.[19–21] As PM applications continue to grow, so will the need for timely, value-based PM application evidence. This need may be addressed to some extent, as demonstrated by this study, using generic, broadly applicable economic evaluation models that synthesize available and emerging evidence and facilitate pragmatic assessment under population-specific conditions.

Enabling earlier and more rapid evaluation of PM applications using generic models to support decision-making may also foster generation of relevant data and evidence needed to reduce uncertainty and increase the value of conducting an evaluation. To further support PM decision-making, additional criteria and strategies can be implemented. One such approach is using a risk-benefit policy matrix with varying levels of uncertainty to facilitate interpretation of evaluations and evidence development.[21] In the meantime, the paucity of relevant population-based economic evidence will likely contribute to delayed PM adoption and use disparities, particularly in low and middle income countries, resulting in lost population health benefits.

The lessons learned from this proof of concept study primarily relate to translating one or more specific PGx model to a generic one. Upon close inspection, the peer-reviewed published models had fundamental differences and unanticipated gaps in generalizable support for many key assumptions, impacting their applicability to a generic model. Areas requiring further work to support new approaches in cases of model conflicts and evidence deficiencies included finding replacements for population-specific data, practices, and expert opinion on conventional treatment and patient experience. To address these discrepancies the team employed a consistent strategy of completing a thorough and transparent review and synthesis of available evidence to support a proposed approach and facilitate a consensus decision. These decisions impacted model input base case and range values, excluding, including and changing the form of variables and assumptions, and offering decision-making tool users the option to choose between providing their own or using default input values for some variables.

This proof of concept for a PGx generic economic evaluation model has several limitations. Although this study demonstrated the potential generalizability of a generic PM model, it is unclear whether a similar process can be readily translated to other PGx or PM applications. The PGx use case relied on having a multi-disciplinary international team of researchers with access to at least one previous model and input value information for multiple populations. Comparable resources may not be available or applicable to other PM interventions, and even when available, translating them into a generic model is a resource-intensive process. Also, the real-world utility of the decision-making tool has not yet been demonstrated by testing beyond this research project. Despite our best intentions to make the tool accessible to inexperienced users, they may find it is not easy to use and/or encounter barriers to obtaining the required input values which would limit the tool's generalizability, or even provide erroneous results. Conversely, PGx is well suited to a generic modeling approach given the availability of evidence-based guidelines that can inform care pathways, dose adjustments and alternative therapies. In addition, the time horizon to therapeutic effect or adverse event is shorter, reducing the complexity of the modeling.

In conclusion, demand is increasing for cost-effectiveness evidence to support the use of rapidly growing PM technologies although generating economic evidence sufficient to inform healthcare decision-making is costly. This study demonstrates the promising approach of generic economic modeling to efficiently increase the capacity to supply economic evaluations. Developing generic models adaptable to decision-makers' population-specific circumstances may serve to provide timely information to guide adoption decisions for PM applications yielding substantial health improvements. This approach could be especially beneficial for low- and middle-income countries or health systems with severely constrained resources for performing PM economic evaluations.[8] While cost effectiveness evidence is one of many decision-making criteria, its absence is considered a common PM reimbursement barrier limiting its use. Generic models offer decision and policy makers a realistic and much needed means to strategically assess population-relevant PM value. Focused implementation of generic models to pragmatically generate value-based evidence for priority areas can contribute to the timely realization of the benefits offered by precision medicine and genomic advances.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding support

This study is funded by the US National Human Genome Research Institute as part of the IGNITE Network (research grant number U01 HG007269).

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Figure 1. Generic Economic Evaluation Model and Decision-Making Tool Development Process Steps

[No additional text beyond what is contained in the figure.]

A. Decision Tree Model

B. Markov Models

1) Patients who developed SJS/TEN after receiving CBZ

2) Patients who did not develop SJS/TEN after receiving CBZ or VPA

Figure 2. Pharmacogenomic Use Case Generic Model

A. Decision Analysis Model

Comparing three treatment strategies for adult patients with newly diagnosed epilepsy: two without genetic screening and one with universal genetic screening for HLA-B*15:02 to prevent a carbamazepine (CBZ) induced serious adverse reaction.

B. Markov Models

1) Patients who developed SJS/TEN after receiving CBZ

Patients either recover with or without SJS/TEN sequelae or die from SJS/TEN, and recovered patients will die from other causes.

2) Patients who did not develop SJS/TEN after receiving CBZ or VPA

Abbreviations: SJS: Stevens-Johnson Syndrome; TEN: toxic epidermal necrolysis; CBZ: carbamazepine; VPA: valproic acid

Incremental Cost-Effectiveness Ratio (ICER) – Base Case

Cost Effectiveness (CE) Plane of Probabilistic Sensitivity Analysis Simulations

Cost Effectiveness Acceptability Curve (CEAC)

Figure 3. Pharmacogenomic Use Case Generic Model Decisionmaking Tool Cost-Effectiveness Results

Singapore model input values (2010 U.S. dollars)

[No additional text beyond what is contained in the figure.]

Abbreviations:

PGx: pharmacogenomics; HLA: human leukocyte antigen; CBZ: carbamazepine; VPA: valproic acid; QALY: quality-adjusted life year

Table 1:
Pharmacogenomic Use Case Generic Model Decisionmaking Tool Cost-Effectiveness Results

Singapore model input values (2010 U.S. dollars)

<u>Deterministic/Base-case</u>	<u>Baseline</u>	<u>Option 1</u>	<u>Option 2</u>
	Current practice (No screening, CBZ)	HLA-B*1502 screening	No HLA-B*1502 screening (Alternative medicine)
Cost	1,203	1,668	3,016
Life years	20.167	20.188	20.188
QALYs	17.876	17.924	17.924
Incremental cost	-	465	1,812
Incremental QALYs	-	0.048	0.048
ICER (U.S. dollars/LY gain)		21,902	85,282
ICER (U.S. dollars /QALY gain)		9,717	37,834
<hr/>			
<u>Probabilistic</u>	<u>Baseline</u>	<u>Option 1</u>	<u>Option 2</u>
	Current practice (No screening, CBZ)	HLA-B*1502 screening	No HLA-B*1502 screening (Alternative medicine)
Cost	2,294	3,054	5,990
Life years	19.962	19.983	19.983
QALYs	17.746	17.794	17.794
Incremental cost	0	760	3,696
Incremental QALYs	0	0.048	0.048
Average ICER (U.S. \$ / LY gain)		36,249	176,060
Average ICER (U.S. \$ / QALY gained)		15,872	77,091
<hr/>			
<u>Number Needed to Screen and Cases Prevented</u>			
Cases prevented by screening 1 epilepsy patient			0.0089
Number needed to screen (NNS) to prevent 1 SJS/TEN			113

Incremental cost effectiveness analysis results for newly diagnosed adult epilepsy patients compare the baseline (current) practice of no screening and CBZ treatment to universal HLA-B*15:02 screening (option 1) and no screening with alternative VPA treatment (option 2).

Abbreviations: PGx: pharmacogenomics; HLA: human leukocyte antigen; CBZ: carbamazepine; VPA: Valproate acid; SJS/TEN: Stevens–Johnson syndrome/toxic epidermal necrolysis; LY: life year; QALY: quality-adjusted life year

Table 2:

Pharmacogenomic Use Case Generic Model Cross-Validation Comparisons^(a) to Country-specific Models using Country-specific input values (Base-case results)

Results	Baseline Current practice	Option 1 HLA-B*1502 screening	Option 2 No HLA-B*1502 screening	Baseline Current practice	Option 1 HLA-B*1502 screening	Option 2 No HLA-B*1502 screening
MALAYSIA MODEL ^(b)			GENERIC MODEL: MALAYSIA INPUT VALUES			
Cost (Currency: MYR)	31,643	34,555	48,645	19,881	20,132	20,192
QALYs gained	22.440	22.410	21.180	13.820	13.830	13.830
Incremental cost	-	2,912	17,002	-	251	310
Incremental QALYs	-	-0.026	-0.262	-	0.006	0.006
ICER (MYR/QALY)	-	Dominated	Dominated	-	42,471	52,473
THAILAND MODEL ^(c)			GENERIC MODEL: THAILAND INPUT VALUES			
Cost (Currency: THB)	17,915	26,006	61,104	16,425	24,752	61,212
QALYs gained	25.180	25.210	25.220	13.810	13.830	13.830
Incremental cost	-	8,091	43,190	-	8,327	44,787
Incremental QALYs	-	0.032	0.038	-	0.017	0.017
ICER (THB/QALY)	-	250,896	1,140,944	-	493,483	2,651,431
SINGAPORE MODEL ^(d)			GENERIC MODEL: SINGAPORE INPUT VALUES			
Cost (US Dollars)	4,110	4,680	6,780	1,203	1,668	3,016
QALYs	18.850	18.870	18.870	17.880	17.920	17.920
Incremental cost	-	570	2,100	-	465	1,813
Incremental QALYs	-	0.019	-	-	0.048	0.048
ICER	-	29,750	-	-	9,717	37,834

Generic and country-specific models compare three treatment strategies as follows:

- Baseline or current practice: all patients treated with CBZ without *HLA-B*15:02* screening;
- Option 1: *HLA-B*15:02* screening with patients testing positive treated with an alternative medicine (VPA) and patients testing negative offered CBZ; and
- Option 2: patients offered alternative medicine (VPA) without *HLA-B*15:02* screening.

^(a) More detailed cross-validation results are provided in Appendix B.

^(b) Malaysia model threshold ICER is 37,000 MYR/QALY; lifetime epilepsy treatment duration

^(c) Thailand model threshold ICER is 160,000 THB/QALY; 4 years epilepsy treatment duration

^(d) Singapore model threshold ICER is U.S. \$50,000/QALY; 7 years epilepsy treatment duration

Abbreviations: PGx: Pharmacogenomics; HLA: human leukocyte antigen; CBZ: carbamazepine; VPA: valproic acid; ICER: Incremental cost-effectiveness ratio; QALY: quality-adjusted life year; MYR: Malaysian ringgit; THB: Thai baht