NUS National University of Singapore

HITAP Health Intervention and Technology Assessment Program FOUNDATION

Health Technology Assessment for Precision Medicine in Asia:

Are We Ready?

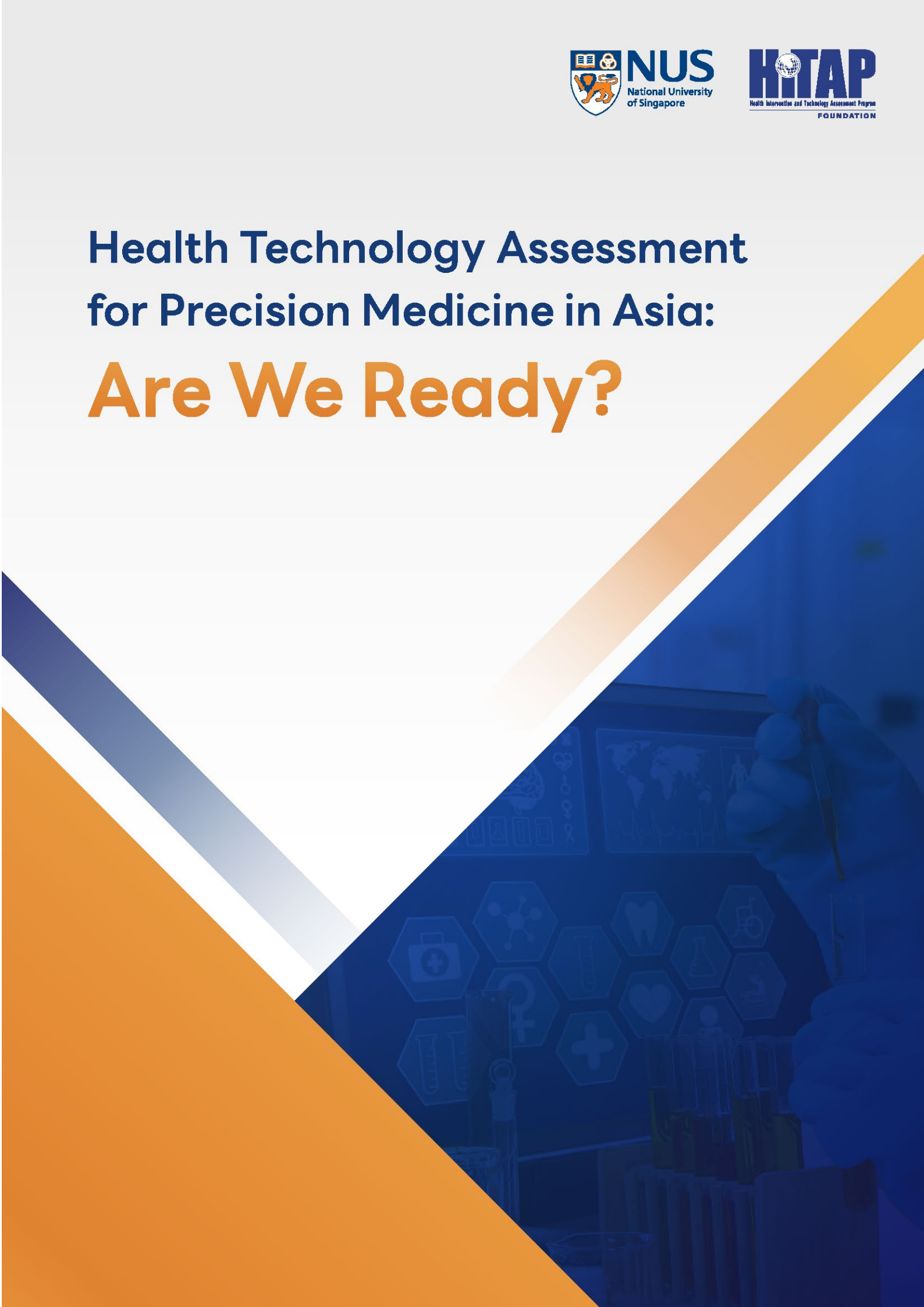

Table of Contents

EXECUTIVE SUMMARY **1**

INTRODUCTION **3**

METHODS **4**

PART 1: TARGETED REVIEW ON HTA IN PRECISION MEDICINE 4
PART 2: SURVEY ON HTA AGENCIES' PERSPECTIVES ON PM 6

PART 1: TARGETED LITERATURE REVIEW ON HTA FOR PRECISION MEDICINE **8**

(A) PUBLICATIONS FROM ENGLISH AND CHINESE SEARCH **8**

Methodological considerations in PM economic evaluations *9*
PM technology focus *11*

IN FOCUS: INSIGHTS FROM NATIONAL HTA AGENCIES **13**

AUSTRALIA 13
MALAYSIA 18
SINGAPORE 19
SOUTH KOREA 21
THAILAND 23
CHINA 25

PART 2: SURVEY ON HTA AGENCIES' PERSPECTIVES ON PM **26**

(A) Background information of survey respondents *26*
(B) HTA practices among countries of survey respondents *26*
(C) A focus on Precision Medicine *28*
(D) Country maturity level in assessing PMs *29*
(E) Challenges in assessing PM technologies *30*
(F) Stakeholder attitudes towards PM *32*

PM IN ASIA PACIFIC: CHALLENGES AND OPPORTUNITIES **35**

CHALLENGES IN HTA FOR PMS 35

REFERENCES **39**

Supplementary file 1: PRISMA flow diagram for the targeted literature search *49*

Health Technology Assessment for Precision Medicine in Asia, Are We Ready?

Jamaica Roanne Briones[1], Zin Nwe Win[2], Jiang Qian[3], Arwin Jerome Onda[4], Dimple Butani[2], Shiela Marie Selisana[2], Ryan Jonathan Sitanggang[2], Thittaya Prapinvanich[5], Asrul Akmal Shafie[6], Jeonghoon Ahn[6], Yue Xiao[7], Yot Teerawattananon[1,2], Wenjia Chen[1] and Alec Morton[1,9*]

1. Saw Swee Hock School of Public Health, National University of Singapore (NUS), Singapore
2. Health Intervention and Technology Assessment Program (HITAP) Foundation, Ministry of Public Health, Nonthaburi, Thailand
3. Department, Sichuan Clinical Research Center for Cancer, Sichuan Cancer Hospital &Institute, Sichuan Cancer Center, Affiliated Cancer Hospital of University of Electronic Science and Technology of China, Chengdu, 610041, China
4. Biomedical and Health Informatics, Mahidol University, Bangkok, Thailand
5. Yale-NUS College, Singapore, Singapore
6. School of Pharmaceutical Sciences, Universiti Sains Malaysia, Malaysia
7. Ewha Womans University, Seoul, South Korea
8. China National Health Development Research Center, People's Republic of China
9. Strathclyde Business School, University of Strathclyde, Glasgow, Scotland
**Corresponding author*

ACKNOWLEDGEMENTS

This report is the result of collaborative efforts between the Saw Swee Hock School of Public Health, the National University of Singapore (SSHSPH NUS), and the Health Intervention and Technology Assessment Program (HITAP) Foundation on behalf of the HTAsiaLink secretariat.

We extend our sincere gratitude to Saudamini Vishwanath Dabak and Panchanok Muenkaew from HITAP Foundation, as well as to Ankita Gaonkar, for their contributions to this report. We are also grateful to the Health Systems Research Institute Thailand for sharing their documents.

Our appreciation also goes to the survey participants, whose insights and feedback were essential in shaping the findings and recommendations presented in the report. Finally, we would like to thank all individuals and organizations that supported this study with their expertise, time, and resources.

FUNDING

This work was funded by Illumina to SSHSPH. The views expressed in this report are those of the authors and do not necessarily reflect the views of the funders.

ABBREVIATIONS

ACE	Agency for Care Effectiveness
ALK	Anaplastic Lymphoma Kinase
BGSI	Biomedical and Genome Science Initiative
BMI	Basic Medical Insurance
CEAs	Cost Effectiveness Analyses
CMA	Cost-Minimisation Analysis
CTGTP	Cell, Tissue, and Gene Therapy Products
DAC	Drug Advisory Committee's
EE	Economic Evaluations
EFC	Efficient Funding of Chemotherapy
EGFR	Epidermal Growth Factor Receptor
GART	Genotype-assisted Antiretroviral Resistance Testing
HER2	Human Epidermal Growth Factor Receptor 2
HIRA	Health Insurance Review and Assessment Service
HITAP	Health Intervention and Technology Assessment Program
HIV	Human Immunodeficiency Virus
HKSAR	Hong Kong Special Administrative Region of the People's Republic of China
HTA	Health Technology Assessment
HSDs	Highly Specialised Drugs
ICERs	Incremental Cost-Effectiveness Ratios
IHC	Immunohistochemistry
LQTS	Long QT Syndrome
LYs	Life-Years
MAF	Medication Assistance Fund
MAHTAS	Malaysian Health Technology Assessment Section
MAP	Managed Access Program
MBS	Medicare Benefits Schedule
MoH	Ministry of Health
MSAC	Medical Services Advisory Committee
NBS	Newborn Bloodspot Screening
NECA	National Evidence-based Healthcare Collaborating Agency
NHRA	National Health Reform Agreement
NHSA	National Healthcare Security Administration
NRDL	National Reimbursement Drug List
NUS	National University of Singapore
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PGD	Preimplantation Genetic Diagnosis
PICO	Population, Intervention, Comparator, and Outcomes
PM	Precision Medicine
PPV	Positive Predictive Value
QALYs	Quality-Adjusted Life Years
ROI	Return on Investment
SDL	Standard Drug List
SSHPH	Saw Swee Hock School of Public Health
TGA	Therapeutic Goods Administration
VN	Voretigene Neparvovec
WEA	Whole Exome Analysis
WTP	Willingness to Pay

EXECUTIVE SUMMARY

The rapid advancement of precision medicines (PMs) over the past decade has reshaped modern healthcare, but it has also introduced significant challenges for health systems. Unlike conventional therapies, many PMs lack the robust evidence necessary for confident assessments, creating uncertainty for Health Technology Assessment (HTA) agencies to make confident decisions about value, affordability, and reimbursement.

This paper examines the current landscape of PMs across the Asia-Pacific region and identifies the key challenges and opportunities for HTA systems. It draws on two main sources: (1) a targeted literature review of economic evaluations (EEs) of to identify emerging assessment methods and reimbursement models, and (2) a regional survey of HTA agencies from 12 of 20 invited countries, offering insights into their experiences and perspectives on PMs.

The survey findings reveal a wide variation in how countries are engaging with PMs. Countries such as Hong Kong SAR, India, and the Philippines, have yet to introduce HTA for PMs, while Bhutan has shown initial awareness. Vietnam has made early efforts on screening and diagnostic tools alongside targeted therapies. Indonesia has evaluated targeted therapies, while South Korea has progressed further by assessing both screening and diagnostic tools. In contrast, countries with more mature HTA systems—such as Australia, Malaysia, Singapore, Thailand and Taiwan—have conducted multiple evaluations of PM technologies, including diagnostic tools, targeted therapies, and screening tests. Across the board, targeted therapies are the most evaluated PM technologies.

In countries newer to PMs, stakeholders are eager to incorporate PM technologies, particularly when they demonstrate value for money and address pressing unmet needs. National investments in PMs are evident in Australia, China, Singapore, South Korea, Thailand, and Taiwan. However, concerns persist about safety, implementation challenges (e.g., workflow integration), and budget alignment.

Both the literature and survey results confirm that PMs—especially targeted therapies and diagnostics and screening technologies—are gaining ground in the region. Areas such as pharmacogenomics and gene therapies are emerging but remain less established. Despite application of methodological innovations, most assessments still rely on traditional HTA methods. The common challenge seen in evaluating PMs does not usually stem from their inherent complexity, but from gaps in real-world evidence, limited data availability and infrastructure, and the substantial budgetary impact.

As PMs increasingly enter the mainstream medicine, HTA capabilities and processes must evolve to meet the increasing demand for evaluation. To succeed, the emerging HTA systems must balance the need for confidence in outcomes, rising cost pressures on the system and the need for timely access to potentially transformative technologies. Proposed solutions include establishing post-HTA data collection systems, expanding HTA frameworks to account for PMs unique value propositions, and implementing risk-sharing agreements to navigate financial uncertainty.

PM adoption is advancing at different rates across the region. While some countries are prepared and moving forward, others face barriers related to resources or systemic factors. The sustainability of healthcare systems requires balancing affordability with stability.

Developing countries in the region face significant economic constraints, not only in adopting PMs but also in managing competing health priorities. Careful consideration of local contexts and broader systemic challenges is essential. This report indicates the scale of the HTA tasks ahead.

INTRODUCTION

In the era of a fully mapped human genome, individualising diagnostic and treatments for patients is advancing at an unprecedented pace.[1] While traditionally associated with pharmacogenetic and pharmacogenomic tests, precision medicine (PM) now encompasses a broader scope and is often used interchangeably with stratified medicine. It is gradually replacing the term "personalised medicine", as it includes technologies that provide unique treatment pathways tailored to individual patients.

There has been an expansion of PM's application across various fields such as oncology, cardiology, neurology, and rare diseases, with the aim of improving clinical outcomes, reducing side effects, and optimising healthcare resources.[2] In this report, we define a technology as a PM if it can stratify patients into specific treatment pathways or therapies based on their unique characteristics. [3 4]

Health Technology Assessment (HTA) for Precision Medicine

HTA plays a critical role in evaluating and introducing new healthcare interventions, including medicines, diagnostic tests, devices, and programmes using economic evaluations (EE) to inform decision-makers on resource allocation. [5] Over the past decade, HTA agencies have increasingly addressed PM interventions. However, PM introduces complexities that challenges traditional HTA frameworks. This includes dynamically evolving treatment pathways, significant cost implications, and inherent uncertainty around clinical benefits and harms. As such, evaluating PM demands methodological innovations that can capture its nuanced and individualised nature.[6]

The rise of PM presents significant challenges and opportunities for HTA bodies, policymakers, and guideline developers. As PM continues to advance, it raises critical questions regarding the ability of regulatory and reimbursement frameworks to balance broad access with the sustainability of the healthcare system. The high cost associated with developing therapies for small, targeted populations, along with the expense of companion diagnostic tests, create a pricing dynamic that raises concerns about affordability, access, and long-term sustainability.

This review offers a current overview of HTA activities related to PMs in the Asia-Pacific region. It maps the present state of PM evaluation, offers an overview of the growing portfolio of PM technologies, outlines emerging reimbursement pathways, and explores opportunities and systemic barriers into advancing the evaluation of PM technologies.

METHODS

This study was conducted in two phases to examine the evaluation and reimbursement of PMs in the Asia-Pacific region. The first phase comprised a targeted literature review to map the portfolio of PM technologies and identify reimbursement pathways within the region. The second phase involved a survey within the HTAsiaLink which is a network of organisational and individual members engaged in HTA research and evidence-based policy decision-making in the Asia-Pacific region. The survey aimed to evaluate the practices, challenges, and perspectives of network members regarding PM technologies.

Part 1: Targeted Review on HTA in Precision Medicine

The first phase involved identifying the landscape of PM technology to determine whether new methods or considerations are used to assess value of and determine reimbursement pathways of PMs. The targeted literature review was informed by three activities: (1) a systematic search of economic evaluations (EEs) of PMs, (2) input and study references from academic experts and HTA agency representatives; (3) a supplementary search focused on identifying local reimbursement pathways for PMs.

Systematic search of economic evaluations of PMs

The scoping review focused on studies conducted in the Asia-Pacific. The study selection process was carried out in several phases:

1. **Updating a previous study**: This builds upon the study titled *"Mapping the Value for Money of Precision Medicine: A Systematic Literature Review and Meta-Analysis".* [7] Searches were conducted in Embase, MEDLINE Ovid, EconLit, CRD, and Web of Science to identify studies published between 1 January 2011 and 8 July 2021. We updated the study to include those published until 30 September 2024. The systematic search and study selection process were managed using Covidence.
2. **Chinese Literature:** To capture a broader range of studies, a systematic search of EEs of PM published in China (PRC) was also included.
3. **Grey literature published by HTA agencies**: In addition to peer-reviewed articles, we also reviewed publicly available reports from HTA agencies in the region. Relevant reports were sourced from institutions such as the Agency for Care Effectiveness (ACE) in Singapore, Malaysian Health Technology Assessment Section (MAHTAS), Pharmaceutical Benefits Advisory Committee/Medical Services Advisory Committee (PBAC/MSAC) in Australia, and the National Evidence-based Healthcare Collaborating Agency (NECA) in South Korea, and Thai reports from the Health Systems Research Institute (HSRI) and the Health Intervention and Technology Assessment Program (HITAP) in Thailand. We also requested for studies from local academic and HTA representatives. Non-English reports from South Korea and Thailand were translated into English using Google Translate. An effort to identify any overlap between literature search and agency reports was made. While few overlaps were found, it was challenging to identify duplicates from agency reports as the author details for submissions are not provided.

Inclusion/Exclusion criteria

The inclusion criteria for the study were as follows:

1) **Study Type**: Original research focused on EE on PMs
2) **Population**: Studies involving human subjects
3) **Interventions of Interest**: PMs defined as medical interventions utilising human gene profiling for diagnosis or prediction, used in a clinical setting for disease prevention or treatment. Categories of interest include:
    a. **Screening Tools**: Tools for risk stratification and early identification of genetic conditions, such as genetic screening tests assessing disease risk.
    b. **Diagnostic Tools**: Tools for early disease diagnosis, identification of genetic subtypes with faster prognosis, or recognition of metastatic-prone genetic subtypes for treatment escalation.
    c. **Pharmacogenomic Tools**: Tools predicting an individual's treatment response based on genetic profiles, optimising drug efficacy while minimising adverse effects.
    d. **Targeted Therapy**: Treatments addressing specific genetic mutations or alterations, including targeted cancer therapies and therapies for rare genetic disorders.
    e. **Gene Therapy**: Interventions involving the addition, alteration, or replacement of genes to treat or prevent diseases, such as strategies to enhance immune function or correct genetic defects.

NOTE: Cancer-related technologies were identified to reflect the broader PM landscape but excluded from full text analysis. This is because cancer PM technologies have been widely used and evaluated since the 2000s, with standardised frameworks for assessing their clinical benefit and cost-effectiveness. We focus instead on new and emerging PM interventions, to identify whether there are new methodology or considerations taken to assess PM value.

Outcomes of Interest: Eligible studies must report outcomes such as life-years (LYs), quality-adjusted life years (QALYs), disability-adjusted life years (DALYs), or incremental cost-effectiveness ratios (ICERs).

Exclusion criteria

Studies were excluded if they focused on hypothetical or conceptual stage PMs without evidence of clinical application.

Part 2: Survey on HTA Agencies' Perspectives on PM

Study design

HTAsiaLink is a network of non-profit organisations dedicated to HTA research, making a significant contribution to the development of HTA in the Asia-Pacific region.[8] Since its establishment in 2011 with three founding members, the network has grown to include over 50 organisations from 20 countries. Its primary objectives are to (a) strengthen the capacity of individuals and institutions in HTA research and the utilisation of HTA evidence in policymaking, (b) promote collaboration while minimising research duplication, and (c) encourage the exchange of best practices among its members.[8]

The study adopted a self-administered survey approach to assess the perceptions of HTA agencies regarding the evaluation of PM technologies across multiple countries within the HTAsiaLink network. The survey, comprising both open- and closed-ended questions, was distributed online through email to network members, ensuring accessibility for respondents within their respective organisations.

Survey objectives

The primary aim was to understand the status of HTAsiaLink members in evaluating PM technologies, the challenges faced, and the perceived experience of stakeholders in conducting assessments in respective countries. Specific objectives include:

1. Assess the status and development level of HTAsiaLink members in the evaluation of PM technologies.
2. Identify challenges faced in evaluation of PM technologies.
3. Understand perceived attitude of stakeholders.

Questionnaire development

The survey consisted of 62 questions, validated internally and externally, and was organised into seven sections. Section 1 gathered background information on HTA agencies. Section 2 focused on the status of HTA in member countries, including assessment responsibilities and the influence on reimbursement decisions. Section 3 examined the evaluation of PM technologies since 2011, categorised into various types (e.g., diagnostics, gene therapies). Section 4 assessed agency maturity in applying HTA to these technologies, while Section 5 explored challenges in evaluating PM. Section 6 examined stakeholder support for PM implementation, and Section 7 allowed respondents to provide additional relevant information. The survey included multiple-choice, Likert scale, and open-ended questions.

Study participants and study collection

The survey was administered on 8 October 2024 and was sent to a total of 120 invitations via email, with additional promotion through HTAsiaLink newsletters. With the initial low participation, the original response deadline of 8 November was extended to 30 November 2024. To encourage greater engagement, weekly reminders were sent throughout the survey period to those who had not yet submitted their responses.

Sample and survey administration

The survey, conducted in English, was piloted internally to ensure clarity and alignment with research objectives. The content was revised based on the feedback received. Respondents were expected to complete the survey in 20–30 minutes.

Data analysis

Quantitative data were summarised using descriptive statistics, supplemented by relevant literature to contextualise the findings.

Ethics approval and disclosures

Members of HTAsiaLink were invited to participate in the survey on a voluntary basis. Participants were provided with information about the purpose and intended use of the survey results in the introduction. The questions were designed to be general and posed no harm to the respondents. Moreover, any personal data collected was reported in an anonymised format to ensure confidentiality and privacy. We have reached out to ethics board that ethics approval was not required given the general nature of the survey questions. Furthermore, no patients or members of the public were involved in the design, implementation, reporting, or dissemination of the research.

Part 1: Targeted Literature Review on HTA for Precision Medicine

(A) Publications from English and Chinese search

317 HTA studies were identified between 2011 and 2024, with a notable increase in activity in 2021 (Figure 1). Most studies originated from China (n= 202), reflecting substantial output in both English (n=111) and Chinese (n=91) publication streams. Australia (n=35) and Singapore (n=23) (Figure 2) also demonstrated consistent research activity. However, low- and middle-income countries (LMICs) remain underrepresented in the literature. Contributions include single studies from Iran, Israel, Malaysia, New Zealand, Qatar, Sri Lanka, and Vietnam; two from Indonesia; and four from India (Figure 2). The PRISMA flow diagram is attached at the Supplementary file 1.

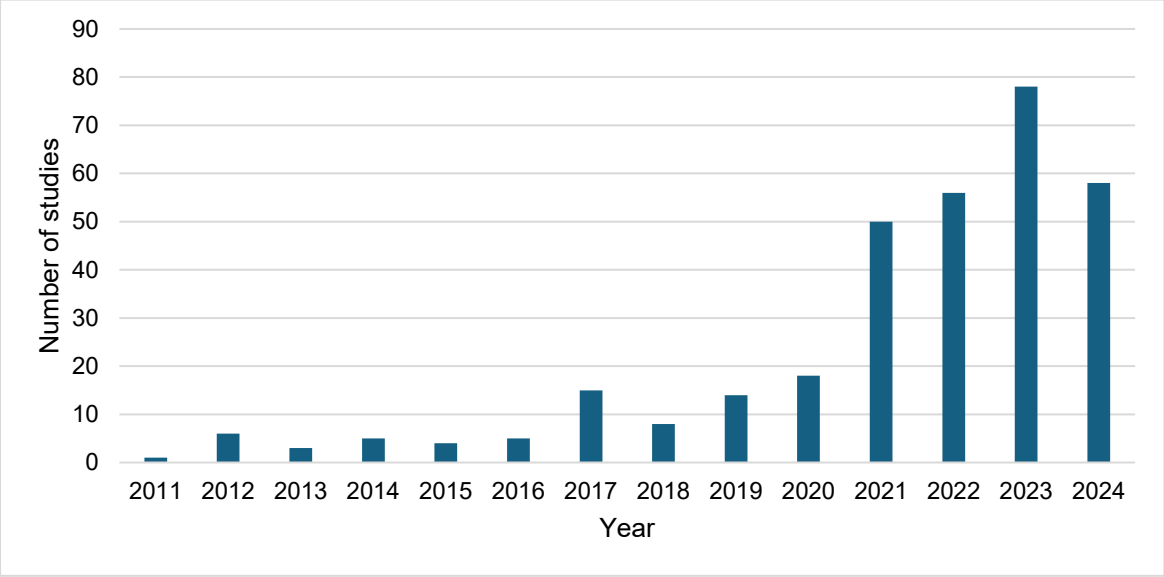

Figure 1. Number of published HTA assessments in the Asia-Pacific region

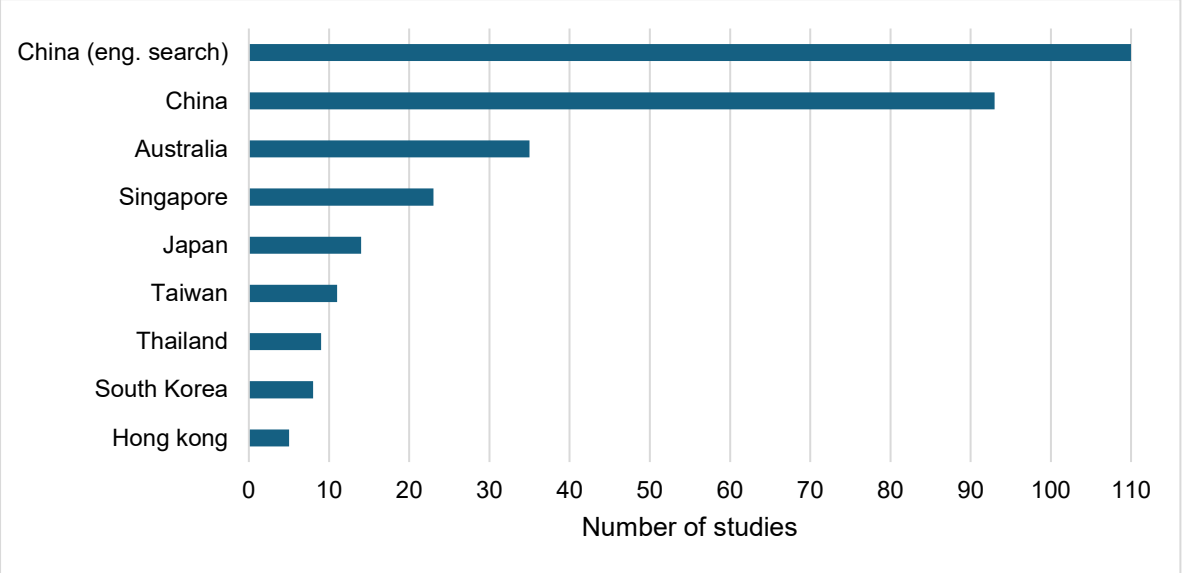

Figure 2. Number of published HTA assessments by country/setting in the Asia-Pacific region from 2012 to 2014

Cancer-related technologies dominate PM EEs, comprising 75% (n=242/321) of identified studies. Among all PM EEs, targeted therapeutics make up the largest share at 59% (190 studies). Pharmacogenomic tests (14%) and screening tests (13%) have a similar number of evaluations, while diagnostic tests account for 7%. Gene therapies remain the least studied, comprising only 5% of the total.

Table 1. Distribution of studies by type of PM technologies

Type of PM technologies	Number of studies
Targeted therapeutics	190
Pharmacogenomic test	46
Screening test	43
Diagnostic test	24
Gene therapy	18

Methodological considerations in PM economic evaluations

1. Modelling approach: Focusing on non-cancer related technologies, all studies used model-based analyses. Among the identified studies, Markov models were predominant (31 out of 79 studies), followed by hybrid approaches that combined Markov models with decision trees (27 studies). Decision trees as standalone models were used in 17 studies. More advanced modelling techniques were less common: only two studies used microsimulations, [9 10] while discrete event simulation[11] and systems dynamics modelling[2] were each used in one study. A detailed breakdown of modelling approaches across different PMs is found at table 2.

Table 2. Overview of modelling approaches in PM technologies

Modelling approach	Summary of PM technologies
Markov	**Screening:** Hepatitis B and C screening [12], hereditary haemochromatosis [13 14], Familial hypercholesterolemia (FH) [15], combined screening (FH, HBOC, and Lynch)[16] , polygenic risk profiling for open angle glaucoma [17], Isolated Congenital Hearing Loss [18] **Targeted therapeutics:** Hepatitis C (HCV) treatment [19-34] **Gene therapy:** SMA treatment [34-36] **Pharmacogenomics:** HLA-B*15:02 [37 38], CYP2C19 [39-41], ADRB2 [42], VKORC1/CYP2C9 [43], HLA-B*58:01 [44], CYP2D6*10[45], NAT2 gene [46]
Decision tree	**Screening:** chlamydia infection, Congenital deafness[47], preimplantation genetic testing [48], genetic testing for Maturity Onset Diabetes of the Young (MODY) [49] **Targeted therapeutics:** HCV treatment [50] **Pharmacogenetics:** CYP2C19[51], NUDT15[52], ADRB2 [53], UGT1A1*6/*28[54], HLA-B*58:01[55], HLA-B*1502 [55 56], HLA- B*58:01[57 58], HLA-B*5701 [59 60], TPMT/NUDT15 [61]
Hybrid (Markov + Decision tree)	**Screening:** Chronic ischaemic heart disease, cardiomyopathy[62-64], SMA newborn screening and treatment [65 66], FH [67 68], childhood mitochondrial disorders [11] **Targeted Treatment:** HCV treatment [33]

Modelling approach	Summary of PM technologies
	Pharmacogenomics: CYP2C19 [69-76], CYP2D6*10[77], HLA-B 13:01[78], HLA-B*15:02[79], HLA-B*5801[60 80-82], VKORC1/CYP2C9 [83 84], Multiple pharmacogenes [85]
Discrete event simulation	Childhood mitochondrial disorders[11]
Microsimulation	**Screening:** Expanded reproductive carrier screening for mendelian disorders [9], monogenic kidney disease[10 86 87]
Systems dynamics model	**Screening:** Polygenic risk score use in coronary artery disease [88]

2. Discount rate: Most studies adhered to national HTA guideline-prescribed discount rates, with 3% most applied rate across the region. This rate was consistently used in studies in Singapore (9/11 studies, 82%) as well as Indonesia,[37] Vietnam,[60] India,[27 32 46] Thailand,[35 78-80 84 89] New Zealand,[72] Hongkong, South Korea,[90] Malaysia,[81] Taiwan.[58] Studies from Australia uniformly applied 5%, while Chinese studies showed equal distribution between 3% (13/30 studies) and 5% (12/30 studies). Variations were observed in studies conducted in Qatar[76] and New Zealand[72] using 3.5%, and Japan[30] adopting 2%. Several studies either did not specify discount rates [51 91 92 93] or omitted them due to short timeframes.[48]

3. Perspective: Most studies aligned study perspectives with their country HTA guidelines, and a healthcare payer perspective was predominantly adopted across the region. This was particularly evident in China (26/30 studies, 87%), Australia (15/19 studies, 79%), and Singapore (9/11 studies, 82%) employing a payer perspective, with limited adoption of societal or patient perspectives. A payer perspective was also used in studies from Hong Kong (2 studies), Indonesia, Japan, New Zealand, South Korea, Qatar, and Taiwan (1 study each). In India, two studies used the payer perspective, and one adopted a societal perspective. Noteworthy exceptions included Thailand, where five of six studies (83%) adopted a societal perspective in line with Thai national guidelines, and Malaysia, where the only identified study also employed a societal perspective.

4. Budget impact analyses (BIA): BIA was not routinely performed, with only one out of 80 studies including a BIA. This study was conducted in Australia and assessed the financial impact of adding combined SCID and SMA screening to an existing newborn screening program and used a healthcare payer perspective. [65]

5. Sensitivity/scenario analyses: All identified studies incorporated sensitivity or scenario analyses. The majority (86%, 69/80 studies) employed multiple methods, most commonly combining one-way sensitivity analysis with probabilistic sensitivity analysis. Results were typically presented using tornado diagrams and cost-effectiveness planes.

6. Country settings, funding and conflict of interest: Most studies were conducted in upper-middle-income and high-income countries, with only four studies from LMICs (three from India [27 32 46], and one from Vietnam[60]). Public funding was the most common source (37 studies), followed by not-for-profit organisations (8 studies). Five studies received private sector funding, four reported mixed funding sources, and 20 did not disclose funding.

PM technology focus

Screening or diagnostic test studies (21 studies)

Among the screening and diagnostic studies, three evaluated whole exome sequencing, [11 18 63] while four examined targeted or multiple gene panel.[11 13 94 95] Several studies did not clearly specific the sequencing methodology, either omitting specific details, or broadly referencing next-generation sequencing. [49]

Most of the studies (18/21, 86%) demonstrated cost-effectiveness. Only three studies reporting unfavourable economic outcomes: two from China which were studies on preimplantation genetic testing for aneuploidy in in vitro fertilisation (IVF)[48] and pre-pregnancy genetic screening for deafness[94]; and one from Singapore evaluating genetic testing for Maturity Onset Diabetes of the Young (MODY). Both the Chinese studies employed short time horizons, although the exact durations were not specified. Notably, the deafness screening study indicated that considering future medical expenditures and family income loss could lead to potential cost savings, suggesting that longer time horizons may produce more favourable results. The Singaporean study identified high test pricing as the primary barrier to cost-effectiveness.

Time horizon varied across studies: four used 10-year horizons, two used 18-year timeframes,[18 96] and the remainder adopted lifetime horizons. Meanwhile, cascade screening strategies were evaluated in four studies, all conducted in Australia. These studies examined hereditary haemochromatosis,[13] dilated cardiomyopathy[63] and FH.[97 98] Notably, all studies involving cascades focused on adult populations and demonstrated cost-effective results.

Targeted therapies (12 studies)

All twelve studies evaluating targeted therapies focused on hepatitis C virus (HCV) treatments. The majority (11 out of 12) used a lifetime horizon in their analyses, while one study[33] did not clearly specify the timeframe. Most studies (75%, 9 out of 12) found targeted therapies to be cost-effective; however, outcomes were highly dependent on the choice of comparator.[28] Across these studies, three main factors influenced cost-effectiveness: age at treatment initiation, drug pricing, and treatment duration.[19 19 22 28] Most identified studies involved a lifetime horizon.

Pharmacogenetics study (43 studies)

Thirty three of the 43 (77%) pharmacogenetic (PGx) studies demonstrated cost-effectiveness. Among the ten studies reporting unfavourable results, several key factors contributed to the lack of cost-effectiveness: PGx test cost, [84 93 99 91] low carrier risk incidence in the population, [44 93 91] poor positive predictive value for adverse drug reactions (ADR),[99 100 81 91] lower alternative drug cost when PGx test was not used, [39 44 100] and less-severe ADRs.[84] Regarding time horizons, two studies did not specify their timeframe, two used a 10-year horizon, five adopted a 30-year horizon, and the remainder used lifetime horizons in their analyses.

Gene therapies (3 studies)

Three studies evaluated gene therapies, all using a lifetime horizon in their analyses. Two studies focused on treatments for spinal muscular atrophy (SMA), and one examined gene silencing therapy for FH and all reported unfavourable cost-effectiveness results. The Thai SMA analysis [101] study identified discount rates for costs and outcomes as the primary factor influencing ICER, while the Australian SMA study highlighted drug costs and health utility

values as the key determinants.[34] The FH gene silencing therapy study adopted an early HTA approach to inform pricing strategy and proposed an interim cost-effective price threshold for the intervention.[68]

In Focus: Insights from National HTA Agencies

This section provides a summary of HTA reports on PMs from six countries: Australia, Malaysia, Singapore, South Korea, Thailand, and China. These countries were chosen based on the availability of publicly accessible HTA reports on their official websites and the opportunity to gather insights from HTA practitioners familiar with their respective contexts.

Australia

Australia was an early adopter of HTA, first implementing it in 1992 to inform decisions on pharmaceutical reimbursement through Pharmaceutical Benefits Scheme (PBS). Over time, the scope expanded to include procedures, diagnostic tests, and medical devices under the Medicare Benefits Schedule (MBS).[102] Two central committees guide this process: the Pharmaceutical Benefits Advisory Committee (PBAC), which assesses medicines for PBS inclusion, and the Medical Services Advisory Committee (MSAC) which assesses medical services for MBS coverage.[102] [103] Both committees employ rigorous methodologies, beginning with an evaluation of whether the proposed technology's population, intervention, comparator, and outcomes are sufficiently justified before proceeding to full economic evaluations.

In recent years, PBAC and MSAC have seen an increase in PM technologies, with majority of these related to oncology. Of 134 PBAC PM assessment identified (Figure 4), 110 (82%) focused on cancer therapies, while 62% (n=67) MSAC PM assessments were related to cancer diagnostics or predictive tests (Figure 5).

Submissions often begin with narrow patient populations, with subsequent applications seeking broader indications. Deferrals are common, typically, due to evidence gaps, pricing concerns, or pending regulatory decisions. Other reasons include requests for price reductions, lack of adequate clinical or cost-effectiveness data, or dependencies between diagnostics and therapies (e.g., MSAC waiting for PBAC approval of a co-dependent therapy). Rejections usually stem from high or uncertain cost-effectiveness, insufficient evidence of added clinical benefit, unclear placement of the technology within the treatment pathway or inadequate justification for or target population.

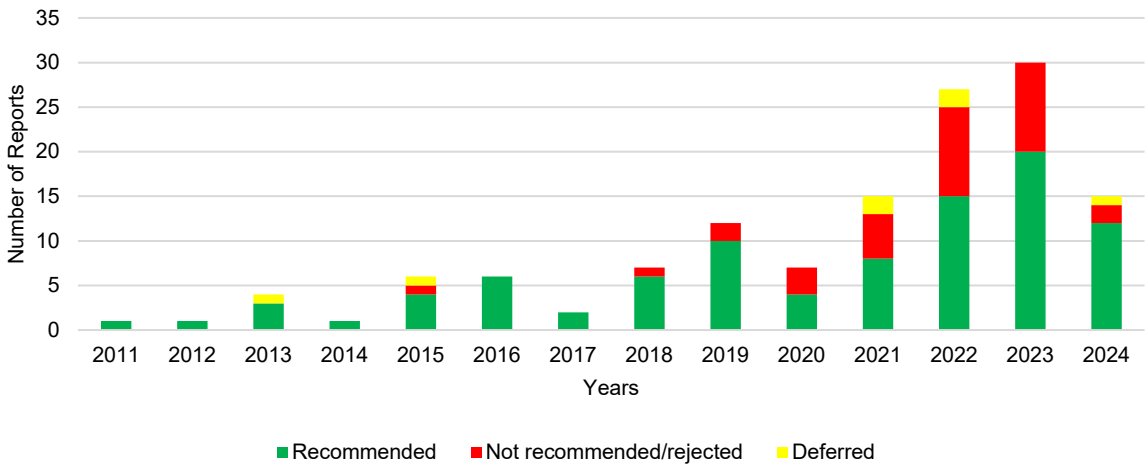

Figure 3. Portfolio of PM reviewed by PBAC

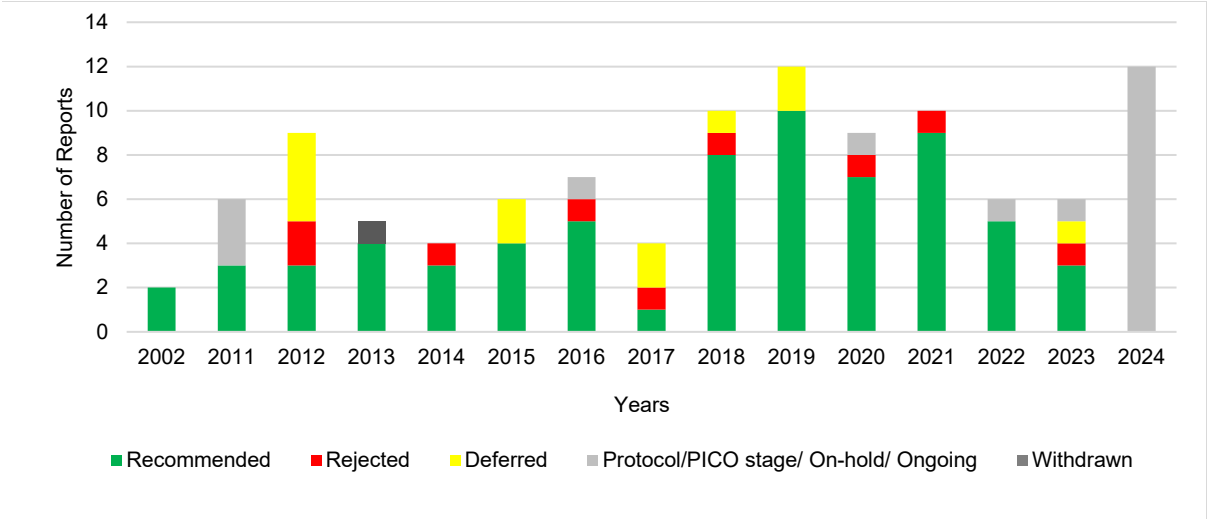

Figure 4. Portfolio of PM reviewed by MSAC

PBAC predominantly reviews therapeutics, while MSAC reviews diagnostics and gene therapies, which are frequently categorised as hybrid technologies or highly specialised therapies (Table 3). All 42 diagnostic tests reviewed by MSAC are co-dependent technologies and linked to PBAC-reviewed oncological therapeutics.

Table 3. Distribution of studies by type of PM technologies and reimbursement decision

Agency	Type of PM technologies	Technologies Accepted	Technologies rejected	Technologies deferred
PBAC	Therapeutic	91	34	7
PBAC	Gene therapy	2	0	0
MSAC	Gene therapy	8	1	0
MSAC	Diagnostic test	32	2	8
MSAC	Predictive test	27	6	4

Stakeholder Roles and Submissions

An in-depth review of 17 PBAC and 24 MSAC non-cancer assessments reveals distinct submission patterns. All PBAC submissions were initiated and submitted by industry, with government bodies appraising the dossiers. In contrast, MSAC received nominations from a broader range of stakeholders, including industry, professional groups, academia, and public authorities, reflecting its broader remit.

Evaluations for MSAC submissions, particularly for medical services and diagnostics, were often conducted by academic institutions, consultancies, or industry representatives. Final appraisals involved multi-sector panels including government, academic, and societal representatives. Both committees also prioritise stakeholder engagement, with formal input from policymakers, clinicians, and civil society groups.

Modelling approaches in economic evaluations

Economic modelling is integral to PBAC and MSAC submissions. Markov models were commonly used for chronic conditions, while decision trees were commonly seen with diagnostics. Hybrid models are used when both diagnostic and treatment components are involved. In addition, several unique approaches have been employed:

- **Cohort expected value models**: Rare diseases (e.g., hereditary angioedema, SMA)
- **Microsimulation**: Cystic fibrosis (CF) therapies
- **Partitioned survival models**: CF and SMA treatments

Six MSAC reviews included cascade screening into their analyses, specifically addressing genetic testing for Alport Syndrome, Long QT Syndrome, FH, and RET mutations.

Several submissions, particularly to MSAC, have incorporated cascade screening into their economic models and BIAs. Six MSAC reviews considered cascade screening or expanded family testing in conditions such as Alport syndrome, FH, RET mutations, and Long QT syndrome. These evaluations also extended to reproductive carrier screening for X-linked conditions and newborn screening for diseases like sickle cell anaemia.

PBAC evaluations were primarily conducted from the government or healthcare payer perspective, though a societal perspective is considered in certain cases, such as the nusinersen submission. For MSAC, a societal perspective was used in 10 out of 32 evaluations. A uniform discount rate of 5% was applied across assessments.

One-way sensitivity analysis was commonly used approach for uncertainty analyses. Additional methods, such as forest plots, was seen for evaluations on HCV treatment. BIA was also routinely performed as part of these evaluations.

Table 4. Modelling approaches used in PBAC submissions

Modelling approach	Technology reviewed
Markov	1. Targeted therapies • Familial Hypercholesterolaemia (FH): alirocumab, evolocumab, inclisiran • Hepatitis C Virus (HCV) treatments • Hereditary Amyloidosis: patisiran • X-linked Hypophosphataemia: burosumab • Achondroplasia: vosoritide 2. Gene therapies • SMA treatment: onasemnogene abeparvovec • Inherited Retinal Dystrophy: voretigene neparvovec • Haemophilia: etranacogene dezaparvovec 3. Screening/diagnostics • HIV testing • *Monogenic Disorders Genetic Testing:* Alport Syndrome, Heritable cardiomyopathies • Preimplantation Genetic Diagnosis (PGD) • Hereditary Angioedema
Decision tree	1. Screening/diagnostics • Hepatitis B virus (HBV) DNA testing

	• *Monogenic Disorders Genetic Testing:* FH, Long QT syndrome, Multiple Endocrine Neoplasia type 2 • *Population-level Screening*: Reproductive carrier testing for CF, SMA, and fragile X syndrome, Newborn bloodspot screening (NBS) for haemoglobinopathies
Markov + Decision tree	1. Screening/diagnostics • Alpha-1 antitrypsin deficiency (AATD) testing • heritable cardiomyopathies testing 2. Gene Therapies • Haemophilia: etranacogene dezaparvovec
Cohort expected value	Targeted therapies • Hereditary angioedema – lanadelumab • SMA: nusinersen
Microsimulation	CF treatment: Elexacaftor /tezacaftor /ivacaftor
Partitioned survival model	SMA: nusinersen, CF: tezacaftor /ivacaftor

Outcomes of analysis

In the PBAC and MSAC submissions reviewed, therapies with ICERs between A$30,000 to A$45,000/QALY) were generally approved for reimbursement. In contrast, therapies with ICERs above A$45,000 to A$75,000/QALY were typically rejected or deferred unless significant price reductions or risk-sharing agreements (RSAs) were proposed. Rejection or deferral was most often due to uncertainty about the magnitude of clinical benefit, limited supporting data, or concerns about the reliability of economic models.

For example, MSAC did not recommend genetic testing for alpha-1 antitrypsin deficiency stating that the benefits were modest and uncertain. Other therapies, such as alirocumab and inclisiran for FH, and HCV treatment like sofosbuvir, required multiple resubmissions because their ICERs exceeded acceptable thresholds. In some cases, decisions were deferred with MSAC citing reasons that the evidence did not demonstrate improved health outcomes from earlier diagnosis or intervention, such as in newborn screening for sickle cell disease and beta-thalassaemia.

However, PBAC often allows sponsors to resubmit applications in response to initial concerns. Common revisions included updating economic models and providing additional data to address uncertainties arising from small trial populations, limitations in study design, and uncertain long-term outcomes and cost-effectiveness. These revisions frequently involved stricter patient selection criteria and new clinical evidence to better assess the treatment's economic value.

For instance, sofosbuvir was resubmitted several times with price reductions, economic model updates, and capped pricing, eventually leading to approval. Similarly, evolocumab for FH was ultimately approved after multiple submissions addressed clinical uncertainties and simplified the economic evaluation, bringing its ICER within an acceptable range.

Notably, PBAC and MSAC demonstrates flexibility for therapies addressing rare diseases or high unmet clinical needs, even when ICERs far exceed conventional thresholds. Examples include nusinersen for SMA, treatments for CF, and genetic testing for heritable

cardiomyopathies, which were approved despite ICERs ranging from $65,000 to $355,000 per QALY gained. In these cases, substantial price reductions and robust RSAs, such as a 100% rebate for nusinersen if financial caps were exceeded, were critical to securing approval.

Reimbursement environment for PMs in Australia

The Australian Government supports a broad range of pharmaceuticals and health services with funding mechanisms such as the PBS and MBS. While the overall reimbursement landscape is complex, this discussion focuses on specialised pathways relevant to the PMs examined in our review.

In oncology, the Efficient Funding of Chemotherapy (EFC) is a key funding mechanism under Section 100 of the PBS. It is designed to support hospital-based administration of cancer therapies. Once approved for PBS listing through the HTA process led by PBAC, the EFC facilitates funding arrangements that account for the practical complexities of oncology care, including dose adjustments, compounding and specialised prescribing protocols. Originally implemented to support cytotoxic drugs, the EFC has since expanded to cover new classes of therapies, particularly immunotherapies and biologics.[104]

Meanwhile, highly specialised therapies (HSTs) refer to new, high-cost treatments—typically exceeding A$200,000 per patient—that are administered within selected public hospitals. These therapies undergo HTA assessment by MSAC and are jointly funded by Commonwealth and State and Territory health departments.[105] To support effective implementation, access is typically restricted to specialised tertiary hospitals and outcomes are monitored through registry-based systems. MSAC also mandates a comprehensive HTA reassessment within three years of initial public funding to ensure value for investment.[106]

Some of the HSTs are reimbursed through RSAs designed to manage uncertainty in clinical and economic outcomes. These may involve conditions such as price reductions, financial caps, or outcome-based payments. For example, voretigene neparvovec (for retinal dystrophy) and lumacaftor/ivacaftor (for CF) are reimbursed through a pay-for-performance model, where reimbursement is reduced if patients do not meet predefined clinical benchmarks. Likewise, ciltacabtagene autoleucel (for multiple myeloma) is reimbursed through an instalment-based payment model, with payments spread over four years and tied to the absence of disease progression, reflecting clinical evidence of potential relapse within this timeframe.

Malaysia

HTA within Malaysia's Ministry of Health (MOH) is led by two principal bodies with complementary mandates. The Malaysian Health Technology Assessment Section (MaHTAS), established 1995, conducts evaluation of a broad range of health technologies used in MOH facilities, including medical devices, diagnostics, clinical procedures, pharmaceuticals, and public health programs. In parallel, the Pharmacy Practice & Development Division (PPDD), established in 1985, is responsible for assessing pharmaceuticals for inclusion in the Ministry of Health Medicines Formulary (MOHMF).[107]

MaHTAS conduct Mini-HTAs, rapid assessments, and horizon scanning in response to requests from internal MOH stakeholders.[107] Our review of publicly available MaHTAS reports identified 13 assessments of PM technologies, 11 of which focused on cancer therapeutics (Figure 6). While MaHTAS does not typically issue explicit recommendations, it provides evidence-based reports to inform policy or decision makers. An exception occurred in 2008, when MaHTAS issues a formal recommendation for HER-2 testing for breast cancer.

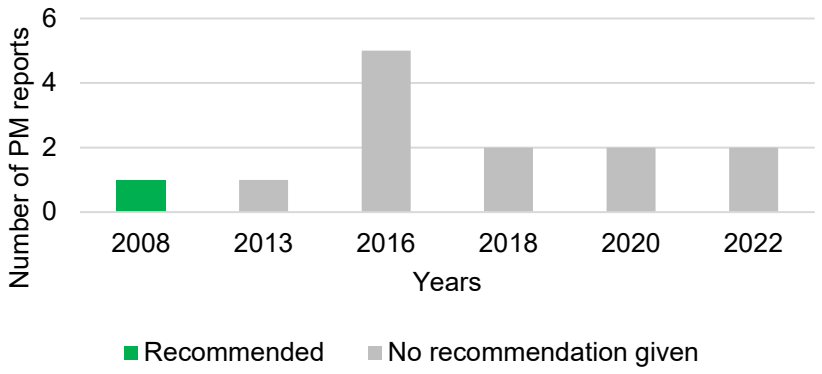

Figure 5. Portfolio of PM reviewed by MaHTAS

Assessment focuses on efficacy or effectiveness, safety, and cost or financial implication.[107] The majority of reviewed technologies (n=11) were therapeutics, with only two diagnostics—one using single-gene profiling for HER-2 and EGFR testing. All reports included systematic reviews of clinical and economic evidence.

Three cancer PM technologies—trastuzumab, pembrolizumab, and nivolumab—featured de novo economic evaluations, all employing Markov models. These evaluations mostly follow local HTA guidelines, applying a 3% discount rate to both costs and outcomes. Uncertainty was addressed through one-way sensitivity analyses, with tornado diagrams illustrating key drivers. Six reports also included BIA, estimating the costs of implementing these technologies over their intended treatment durations.

Reimbursement environment for PMs in Malaysia

Malaysia operates a two-tier healthcare system, with public services offered through MOH-run hospitals and clinics, and a growing private sector serving those who can afford out-of-pocket payments or insurance coverage.[108] Within the public sector, medications listed under the MOHDF are fully subsidised by the government. However, HTA is not yet consistently integrated into formulary listing decisions. [109 110]

Currently, early access to novel or high-cost therapies in public hospitals remains limited and is primarily facilitated through Patient Assistance Programs.[3] Proposals to implement managed access and early entry agreements are being explored. [111] [112] In this evolving landscape, HTA is expected to play an increasingly important role in supporting value-based decision-making and guiding sustainable integration of precision medicines into the public health system.

Singapore

The Agency for Care Effectiveness (ACE) was established in 2015[113] to support MOH Singapore Drug Advisory Committee's (DAC) in making evidence-based recommendations for public funding.[114] Request for subsidy evaluations can be initiated by public healthcare institutions (including hospitals and other health facilities managed by MOH Singapore), patient organisations and pharmaceutical companies, with companies typically responsible for evidence submissions.

Between 2020 to 2024, ACE reviewed 67 PM technologies, of which 88% were cancer therapies (Figure 7). Of these, 40% were not recommended for subsidy, citing reasons such as low clinical need, uncertain therapeutic benefits, or unfavourable cost-effectiveness compared to existing treatments.

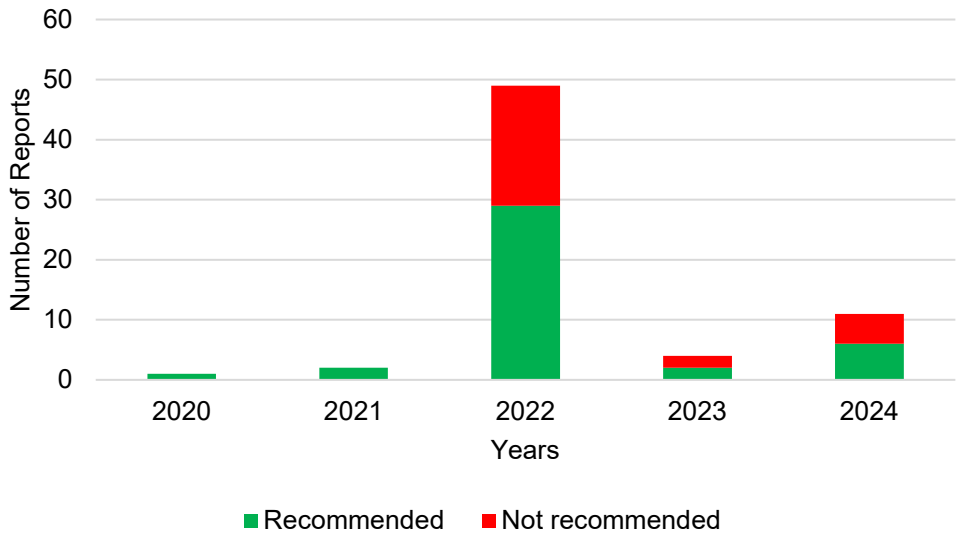

Figure 6. Portfolio of PM reviewed by ACE

Evidence used in PM reimbursement

ACE applies a tiered approach to evidence evaluation based on projected budget impact. Technologies with a high estimated budget impact exceeding over S$2 million annually are subjected to full economic evaluations. For lower-cost technologies, ACE adopts an expedited process, relying on published clinical data and international cost-effectiveness studies, and inputs from local clinical experts to inform the review.[115]

In the six studies reviewed in this work, including risdiplam and evolocumab, subsidy recommendations were based on both international cost-effectiveness studies and cost-minimisation analysis (CMA) of alternative available treatments.

Cost containment is a critical consideration in ACE's recommendations. Value-based pricing is applied to ensure that the reimbursement reflect both the technology's economic efficiency and clinical value. ACE also benchmarks proposed prices against international comparators and projects expected costs over a five-year horizon to assess long-term affordability within Singapore's health system.

Reimbursement environment for PMs in Singapore

Public subsidy for medicines in Singapore is channelled through two main mechanisms: The Standard Drug List (SDL) and the Medication Assistance Fund (MAF).[116] The SDL provides subsidies for low- to moderate-cost medicines routinely used in MOH institutions, with additional tested financial support for lower-income households through means-testing. While the SDL primarily covers common conditions, it also includes some low- to moderate-cost targeted cancer therapies and hormonal chemotherapies.

Technologies not funded by SDL may receive subsidies via MAF, which supports higher-cost drugs. MAF eligibility and level of subsidy are determined by clinical criteria and household income, ensuring that expensive yet necessary treatments remain accessible to those in need. Examples of those in the SDL are those second-generation targeted cancer therapies tyrosine kinase inhibitors (TKIs) for ALK-positive non-small cell lung cancer (NSCLC) and certain immunotherapies.

Recognising the emergence of high-cost, complex biologics, MOH Singapore also introduced a dedicated subsidy pathway for Cell, Tissue, and Gene Therapy Products (CTGTP). This scheme sets subsidy caps and eligibility criteria, with means-testing playing a central role. As of this review, tisagenlecleucel, a CAR-T therapy for certain haematological cancers, and axicabtagene ciloleucel for diffuse large B-cell lymphoma are the only gene therapies included under the CTGTP scheme. [117]

South Korea

South Korea enacted its HTA policy in 2006 following the institutionalization of the HTA process.[118] The Health Insurance Review and Assessment Service (HIRA) conducts HTA for pharmaceuticals, while National Evidence-based Healthcare Collaborating Agency (NECA) was established to evaluate non-drug technologies to strengthen evidence-based decision-making. [118]

NECA's reviews are the only publicly accessible HTA reviews in South Korea. Between 2008 and 2023, NECA assessed 104 PM technologies, with 59 (56.7%) focused on cancer-related technologies (Figure 8). Of these, 27.8% were not recommended for inclusion in the national healthcare system, mainly due to insufficient evidence regarding their safety, efficacy, or clinical utility.[119]

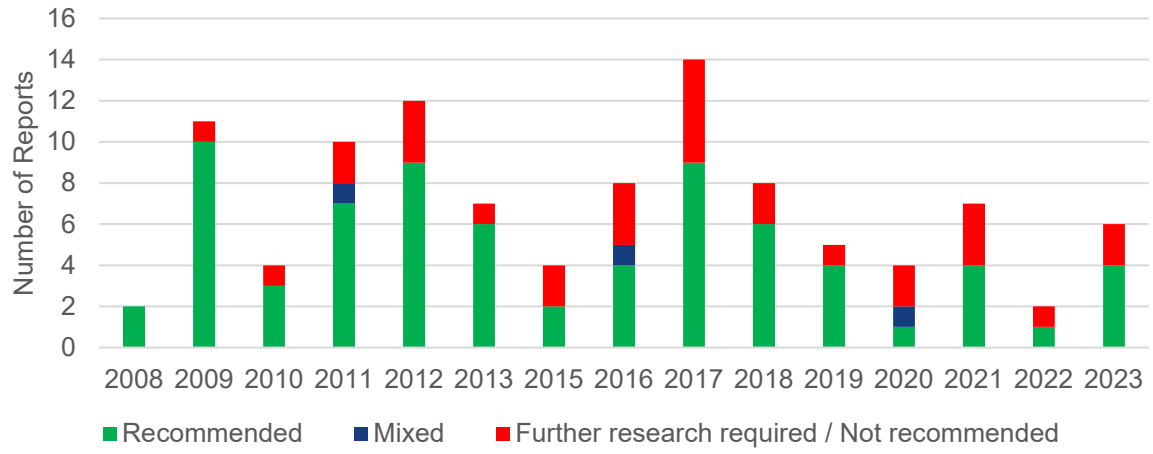

Figure 7. Portfolio of PMs reviewed by NECA
***Note:** Some technologies have more than one intervention type of PM (e.g. screening tool + other: predict prognosis) hence are counted separately*

Evidence used in PM reimbursement

NECA's review process places a strong emphasis on clinical evidence, particularly the safety and effectiveness of technologies, evaluated through literature review. The reports are typically endorsed by both the Committee and the Ministry. Rather than issuing outright rejections, NECA often concludes that "further research is required" before a technology can be considered for inclusion in the national healthcare system.

In terms of intervention types, more than half of the reviewed technologies were screening or diagnostic tools (Table 5). Approximately one-third served other purposes, such as predicting prognosis, survival, determining appropriate treatment, or monitoring response. Among the screening interventions, the majority (27 out of 34) were cancer related. Gene profile testing, also predominantly focused on cancer, was primarily conducted using single-gene or panel testing methods.

Table 5. Distribution of reports by type of PM technologies

Intervention type	Single Gene	Gene panel
Screening tools	18	15
Diagnostic tools	17	17
Pharmacogenomic tools	5	-
Other*	16	15

***Other:** predict prognosis or survival, determine appropriate treatment, monitor response, predict side effects, confirmatory/ verification test)

Reimbursement environment for PMs in South Korea

South Korea's reimbursement framework process begins with a two-step evaluation led by the HIRA and the National Health Insurance Service (NHIS). HIRA establishes reimbursement guidelines and recommends a maximum price based on cost-effectiveness analyses. Subsequently, NHIS negotiates the final Maximum Reimbursement Price (MRP) with pharmaceutical companies.[120]

To address challenges in funding high-cost therapies, South Korea introduced Risk-Sharing Agreements (RSAs) in 2013. These agreements target drugs for serious, life-threatening conditions (e.g., anticancer agents, orphan drugs) that lack alternatives. To qualify, drugs must meet two criteria: (a) Treat life-threatening conditions with no clinically equivalent alternatives (b) Receive approval from the drug review committee, which assesses disease severity, public health impact, and the necessity of additional risk-sharing terms. RSA eligible drugs undergo standard reimbursement evaluations, with RSA terms finalized during price negotiations. RSAs operate two primary models:[120-122]

1. Outcome-based agreements: Reimbursement is tied to predefined treatment goals (e.g., refunds if clinical outcomes are unmet).
2. Budget-capped models: Annual expenditure limits, per-patient utilization caps, or hybrid structures.

Despite RSAs, many drugs—including cell and gene therapies (CGTs), orphan drugs, and anticancer agents—struggle to demonstrate cost-effectiveness due to small patient populations and limited clinical data. To address this, South Korea introduced economic evaluation waivers in 2015. Drugs qualify for economic evaluation exemption if: it is approved in at least three of the A7 reference countries (USA, Japan, Germany, France, Switzerland, UK, Italy) and covered under an expenditure-capped RSA.[123] [124] Pricing for these drugs is benchmarked to the lowest adjusted price among A7 nations. [120]

Thailand

Thailand's HTA ecosystem comprises multiple institutions with evolving roles. The Ministry of Public Health (MOPH) initially established the Institute of Medical Research and Technology Assessment (IMRTA), affiliated with the Department of Medical Services (DMS), to support HTA activities. However, as demand for HTA evidence grew beyond IMRTA's capacity—other academic institutions and programs emerged to address this gap. The International Health Policy Program (IHPP), established in 1998, was created to support evidence generation and inform policy development. As HTA gained prominence in guiding benefit package decisions, institutional development progressed with the establishment of the Health Intervention and Technology Assessment Program (HITAP) in 2007 under IHPP. Funded by the Thai Health Promotion Foundation and the Health Systems Research Institute (HSRI), HITAP has since played a pivotal role in developing and revising HTA guidelines and providing regular capacity-building programs for a wide range of stakeholders. [125]

We identified 15 PM studies (Figure 9), either listed on the HITAP website or provided by HSRI through personal communications. Of the five studies identified from HITAP, the full texts were published in academic journals. [79 126-128] HITAP began assessing PM technologies as early as 2012, with its first evaluation on pharmacogenomic testing for HLA-B*1502 genotyping in carbamazepine treatment. [79]

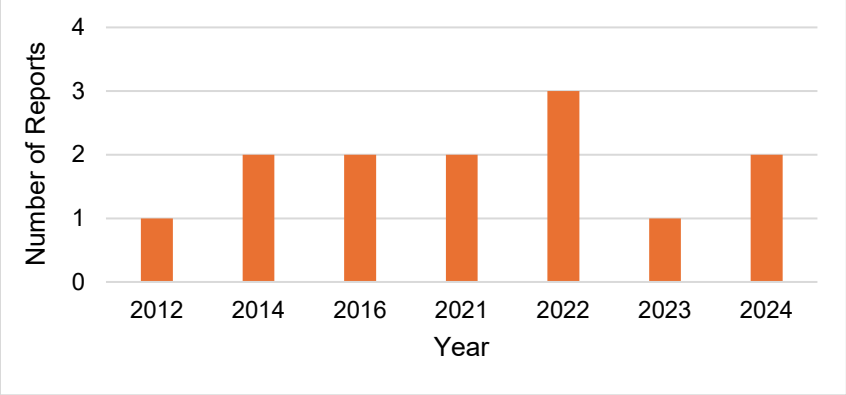

Figure 8. Portfolio of PM reviewed by HITAP or HSRI

Both HSRI and HITAP have reviewed a wide range of PMs (Table 7). HSRI has funded assessments include advanced approaches such as whole-exome sequencing for patients with undiagnosed illnesses and whole-genome sequencing for gestational diabetes. The distribution of evaluated PM technologies is as follows:

Table 6. Distribution of reports by type of PM technologies

Type of PM technologies	Technologies reviewed
Therapeutic	3
Pharmacogenomics	2
Diagnostic test	2
Screening test	8

For the studies where we could access either the abstract or full text (n=8), most evaluations employed either hybrid models combining decision trees and Markov models (n=3),

standalone Markov models (n=3), or decision trees (n=2). All studies demonstrated cost-effectiveness and adhered to Thailand's HTA guidelines and used a societal perspective in their analyses. [129]

Evidence used in reimbursement

In Thailand, HTA is used to guide the development of the National List of Essential Medicines (NLEM), a list of medicines that are reimbursed under all three public health insurance schemes, such as the the Civil Servant Medical Benefits Scheme (CSMBS), the Social Security Scheme (SSS), and the Universal Coverage Scheme (UCS).[130] Medicines not included in the NLEM are generally not reimbursable, though they remain available for patients to purchase out-of-pocket, through additional insurance,[131] or via CSMBS, which provides coverage for approximately five million government officials and their dependents.[132] The CSMBS is considered the most comprehensive public insurance scheme in Thailand and notably does not employ HTA in its coverage decisions.[129]

To explore the potential for reimbursing high-cost, cost-ineffective medicines, the National Health Security Office (NHSO) commissioned HITAP to provide recommendations to a Working Group on managing such medicines within the Universal Coverage Scheme (UCS) Benefit Package (UCBP). [131]

A new pathway for high-cost medicines has been proposed within the NLEM, primarily to address PM technologies, with implementation anticipated in 2025.[131] Medicines deemed cost-ineffective through EEs may still be considered for reimbursement if they are lifesaving, treat conditions with no alternatives, and are affordable in terms of budget impact. The final reimbursement decision is made by a sub-committee based on these criteria. If a medicine meets the requirements, it may be included in the NLEM and reimbursed under all three public health insurance schemes. Managed Entry Agreements (MEAs) may also be used in the negotiation process before a final decision is made. [131]

China

China's institutionalisation of HTA began with academic initiatives and pilot projects between 1990 and 2006. [133] A formal framework emerged in 2007 when the Ministry of Health established the Division of Health Policy Evaluation and Technology Assessment, signalling a commitment to evidence-based policymaking.[133] A landmark shift occurred in 2017 when HTA evidence was first used to update the National Reimbursement Drug List (NRDL),[134] with cost-effectiveness and BIAs becoming mandatory by 2018.[135]

The reimbursement process involves a two-stage evaluation. First, manufacturers submit dossiers outlining clinical and economic data. In the second stage, shortlisted drugs undergo HTA by independent experts, and uses the information to negotiate prices and make final inclusion decisions.[134] The National Healthcare Security Administration (NHSA) oversees this process, leveraging expert-reviewed evidence to finalize pricing and inclusion decisions.[135]

Initially focused on traditional chemotherapies, the NRDL evolved through successive revisions to prioritise targeted therapies and immunotherapies,[136] with 74 oncology agents by 2023.[1] Several provinces in China have also integrated genetic tests into their medical insurance coverage. For example, Beijing covers cancer tissue DNA sequencing, Jilin province includes EGFR gene testing, and Fujian province provides coverage for selected genetic tests.[1]

Reimbursement environment for PMs in China

Under China's Basic Medical Insurance (BMI) system, reimbursed drugs are classified into two categories: Category A (essential, cost-effective therapies) and Category B (innovative, higher-priced drugs). In an HTA review, clinical experts assigned a score to each drug (on a scale of one to five) according to its clinical value, patient benefit and level of innovation. The scores influence the willingness-to-pay (WTP) threshold. Exceptions to these thresholds exist for end-of-life care and rare or ultra-rare diseases, which may qualify for higher WTP values or direct inclusion without threshold limitations.[137]

The NRDL remains the main route of drug access and reimbursement for most patients in China.[137] Risk-sharing agreements are not currently implemented within the NRDL framework, although patients may access innovative treatments through other channels, such as commercial insurance and special access programs. [137]

[1]The information presented here is based on a presentation from the session titled "Prioritising Precision Medicine in Asia" at the Priorities Bangkok 2024 conference.

PART 2: Survey on HTA Agencies' Perspectives on PM

(A) Background information of survey respondents

A survey was distributed to HTAsiaLink members representing 55 organisations across 20 countries. From this, 25 responses were received, resulting in a 60% response rate at the country level and a 31% response rate at the organisational level. The respondents hail from 12 different countries in the Asia-Pacific region. Six of the respondents are in Southeast Asia (Indonesia, Malaysia, Philippines, Singapore, Thailand, and Vietnam), three from East Asia (Hong Kong Special Administrative Region of the People's Republic of China [HKSAR], South Korea, and Taiwan,China), two from South Asia (India and Bhutan), and one from the Pacific region (Australia).

Most of the survey respondents are researchers/analysts (88%, n=22) and have been employed in their current organisation for at least 5 years (n=12). Sixty percent work in a government agency (n=15), 36% work in the academia (n=9), while one respondent works in a not-for-profit research organisation. Two participating organisations from the 12 Asia-Pacific countries operate on an international level only while most work on the national and/or regional level (n= 18). Five organisations work on both international and national levels.

(B) HTA practices among countries of survey respondents

The status of HTA implementation per country is shown in Figure 10. According to the survey, 84% (n=21) said that national agencies conduct HTA research, while 68% (n=17) reported involvement of academic institutions. Moreover, 48% (n=12) noted that independent consultants or research teams perform HTA studies, and 44% (n=11) stated that pharmaceutical companies nominate or lead these studies. Seven respondents each said that payer agencies and hospitals also conduct HTA studies. Only the respondents from Thailand answered that regional or local authorities are additionally involved in HTA studies in their country but a review of HTA reports indicated similar involvement in Australia.

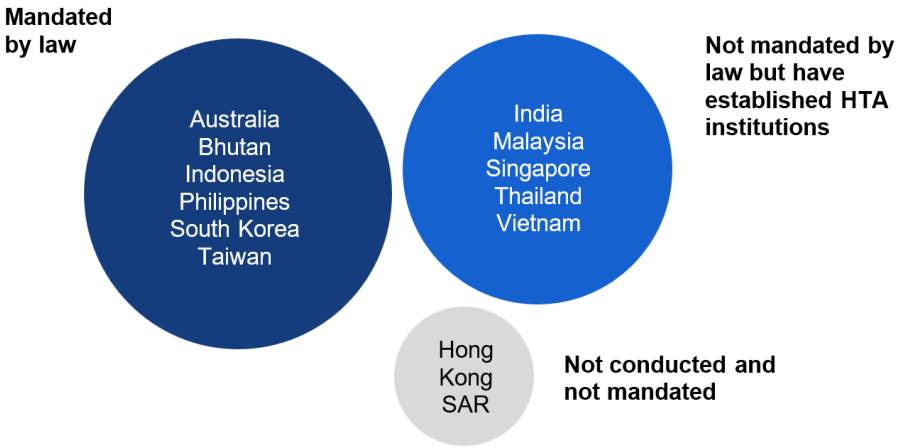

Figure 9. HTA implementation status per country

Among the many types of health technologies, participating HTA organisations mostly assess medicines (10 respondents including those from India, Indonesia, Singapore, Taiwan, Thailand, and Vietnam). In contrast, vaccines and medical devices, are the least assessed types (Figure 10).

New technologies considered for public reimbursement usually undergo assessment. Some respondents noted additional criteria from their guidelines before conducting HTA studies. For instance, in Vietnam, HTA is only compulsory for drugs. In Singapore, HTA studies are selected on factors such as disease severity, clinical need for the technology, claimed therapeutic benefit over alternatives, and budget impact. In Taiwan, HTA is only conducted for new drugs with annual cost exceeding NT$100 million in at least one of the 5 years following reimbursement. Hong Kong SAR does not currently mandate HTA but relies on budget impact and reference reimbursement recommendations from other countries to inform reimbursement decisions.

Around 90% of respondents indicate that HTA recommendations are communicated to public health payers, policy makers and relevant government agencies. Meanwhile, only 10% of respondents (n=3, from Australia, Malaysia, and South Korea) said that private health payers or agencies are also informed.

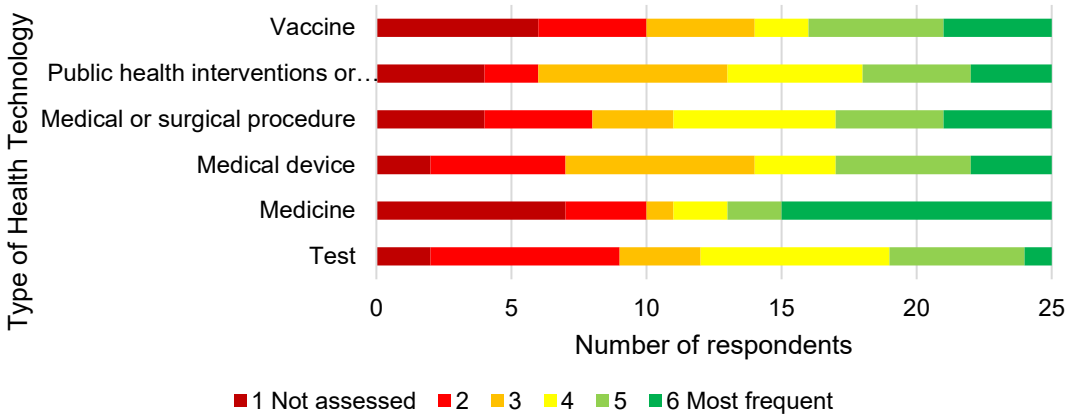

Figure 10. Ranking of different health technologies based on frequency of assessment by HTA organisations. Rank "1" is given to those with no assessment being done while "6" means that the HT is frequently assessed

(C) A focus on Precision Medicine

Ten countries represented by 19 survey respondents (76%) reported being involved in evaluating PMs. Respondents from organisations from India and Philippines noted they are not currently evaluating PMs. The primary reasons are lack of financial support (The Philippines) and absence of requests from relevant stakeholders (India).

Pharmaceutical industries and healthcare providers were the frequent nominators of PM technologies, followed by the Ministries of Health or National Health Services. Regarding the number of PM technologies evaluated since 2011, 28% of respondents (n=7) reported evaluating less than 5 PMs, 16% of respondents (n=4) evaluated 5 to 10 PMs, while 12% (n=3, from Malaysia, Singapore, and Taiwan) evaluated more than 20 PMs. Among these, diagnostic tools have been evaluated the most (50% of organisations), followed by targeted therapies (44%) and screening tools (44%) (Figure 11).

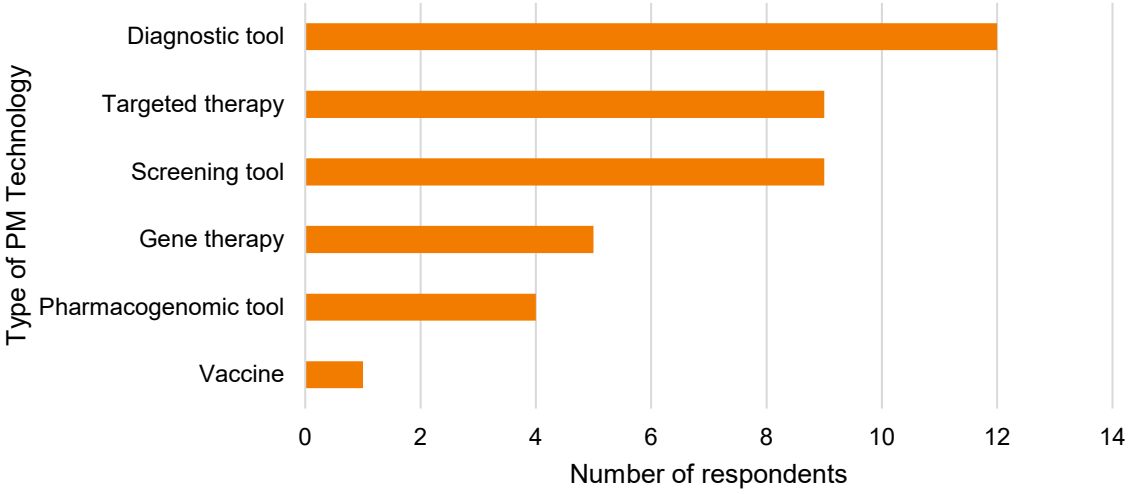

Figure 11. Types of precision medicine technologies that were evaluated by organisations involved in this study. Respondents from each organisation have multiple answers.

(D) Country maturity level in assessing PMs

The participating organisation's level of maturity in applying HTA to various PM technologies was self-assessed. Overall, 67% of the countries (n=8) assess themselves as being in mid to advanced stages of evaluating PMs. The remaining four countries (Bhutan, HKSAR, India, Philippines) either do not perform these studies or are still in the exploratory stage.

Most countries have their own local HTA guidelines; Singapore's ACE also refers to Australia's guidelines for evaluations. Among the respondents, 8 out of 14 considered their current HTA guidelines helpful for assessing PM technologies. Meanwhile, four respondents from Australia, Singapore and Taiwan expressed neutrality, and two respondents from Malaysia and Thailand disagreed.

The figure below shows respondents' self-assessment of their maturity level in applying HTA to PM technologies (Figure 12). Additional information from reports from HTA agencies or from literature review (marked in grey) were included to have a better sense of the current efforts in the region.

Targeted therapies, such as treatments targeting specific genetic mutations, are the most evaluated category, generally reported being in advanced implementation stage. For diagnostic tools such as genetic profiling and screening tools, most countries are in the initial to advanced implementation stage. Vaccine-related PMs are the least evaluated category, with Thailand reporting exploratory efforts in this area. Gene therapy also remain underexplored across the region.

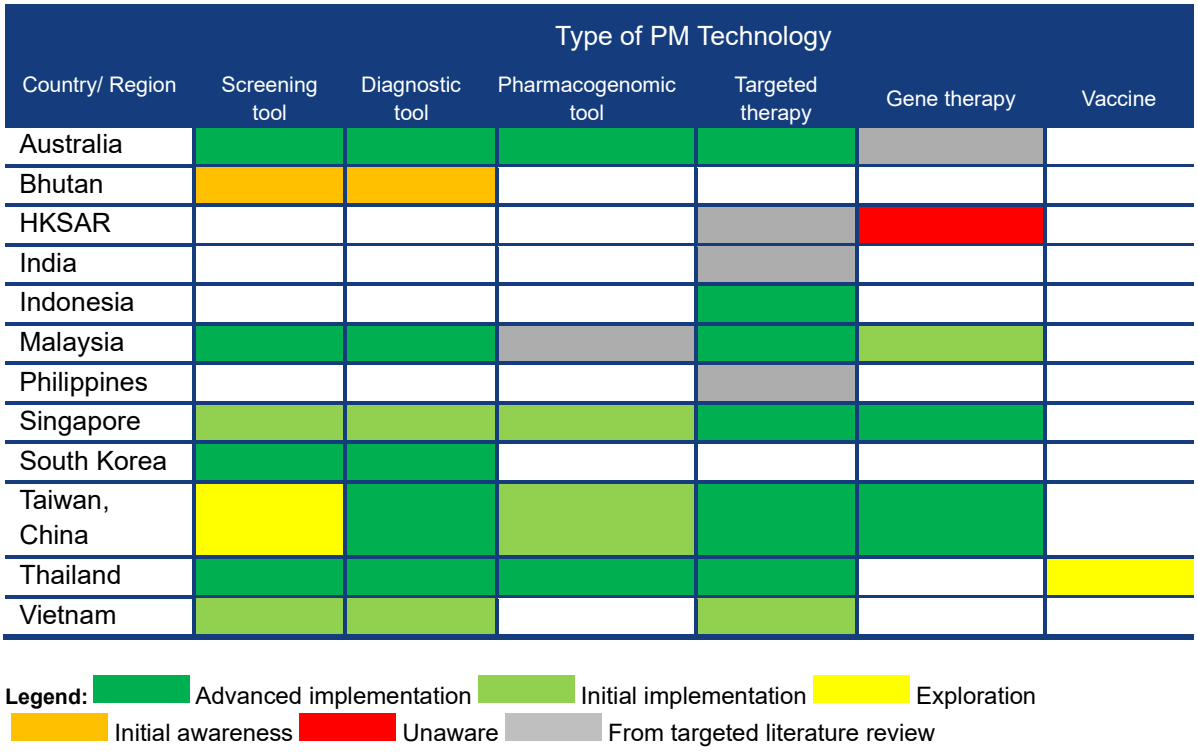

Figure 12. Self-assessment of maturity in applying HTA to PM technologies

(E) Challenges in assessing PM technologies

The survey respondents identified and classified the challenges that their organisation is facing when assessing PM technologies (Figure 13, Table 6). Generally, most organisations face technical (both modelling and clinical aspects) and human resources challenges. On the other hand, stakeholder engagement does not seem to be a challenge to most countries.

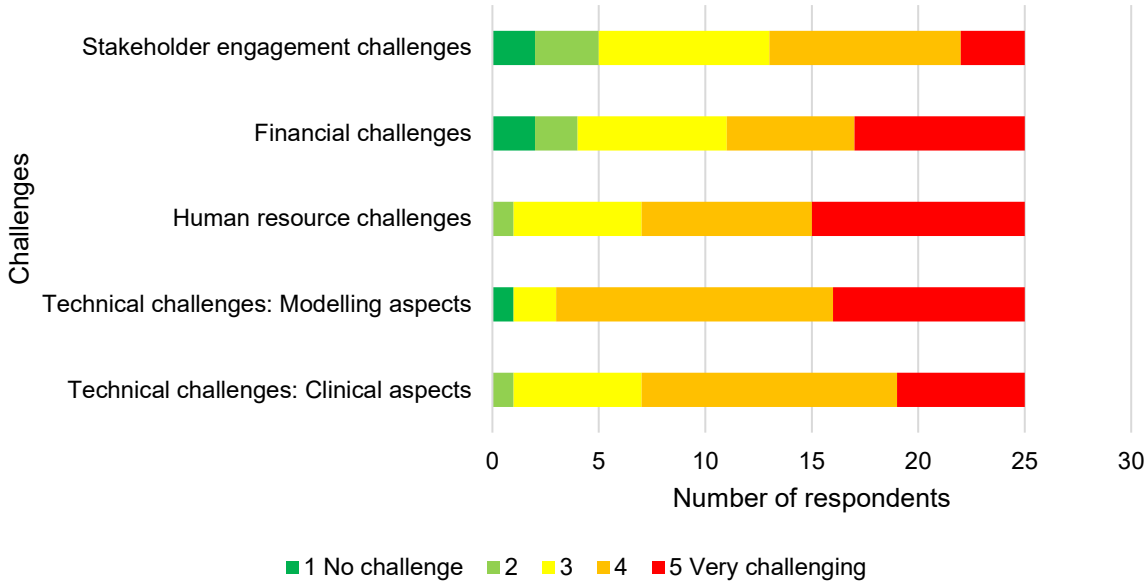

Figure 13. Severity of challenge faced by the organisation in assessing PM technologies is evaluated on a scale of 1 to 5, where 1 means "no challenge" and 5 is "very challenging".

Table 7. Description of the challenges faced by the agencies or organisation in assessing PM technologies.

Challenges	What did the responses note in the challenges?
Technical: clinical aspects	• Limited patient and genetic data • Difficulty in identifying patients and appropriate country-specific comparators • Uncertain intervention efficacy and long-term impact • Lack of consensus on outcomes measures • Complexity in understanding PM technology mechanisms
Technical: economic aspects	• Limited data for model parameters especially for developing countries • Challenges in model conceptualisation and analysis methods for capturing intergenerational outcomes (e.g., considerations for external factors) • Potential need for individual patient simulations with cohort model limitations, which increases required data. If not, researchers must rely on broad assumptions

Human resource	• Shortage of HTA researchers with PM expertise or interest
	  • High staff turnover in HTA agencies
	  • Existing training programmes focus on general topics, lacking PM-specific content.

Challenges	What did the responses note in the challenges?
	• Increased technical complexity raises demand for skilled personnel
Financial challenges	• No stable or dedicated fund for conducting HTA • Financial aspect is not a challenge for assessing PM technology but is a huge challenge for reimbursing PM technology and implementing PM technology in clinical practice due to the high budget impact • High budget impact makes PM technologies unaffordable for low-income countries. • Determining the appropriate professional fees for a study has been another significant issue, as it impacts the overall budgeting and resource allocation for HTA projects
Stakeholder engagement challenges	• Aligning stakeholder interests with evaluation outcomes can be challenging. There may also be conflicts of interest due to the specialised and limited pool of experts in PMs • Political will and competing priorities • PM technologies usually have a high budget impact. Even if deemed cost-effective, they often result in additional cost instead of savings, making payers reluctant to adopt the recommendation. • Unlike traditional medicine or procedures, PMs usually involve interdisciplinary approaches such as machine learning or gene testing, requiring more detailed communication with stakeholders • Limited data and understanding of technical aspects of PMs contribute to the distrust among stakeholders making it harder to build consensus and gain widespread acceptance

(F) Stakeholder attitudes towards PM

Survey respondents were asked to indicate their perceived level of support from the different stakeholders of the HTA system. Stakeholders—such as payers, healthcare providers, funders, academia, and industry—are generally seen as offering moderate to strong support (rated 3-4 on the scale) for the adoption of PM technologies, particularly technologies addressing significant unmet needs (Figure 14, Table 7). Countries such as Australia, Singapore, South Korea, and Taiwan have made national investments in this area. However, concerns persist regarding the safety, efficacy, cost, and ease of implementation of PMs, particularly with integrating these technologies into existing workflows, the need for additional training, and potential increased costs.

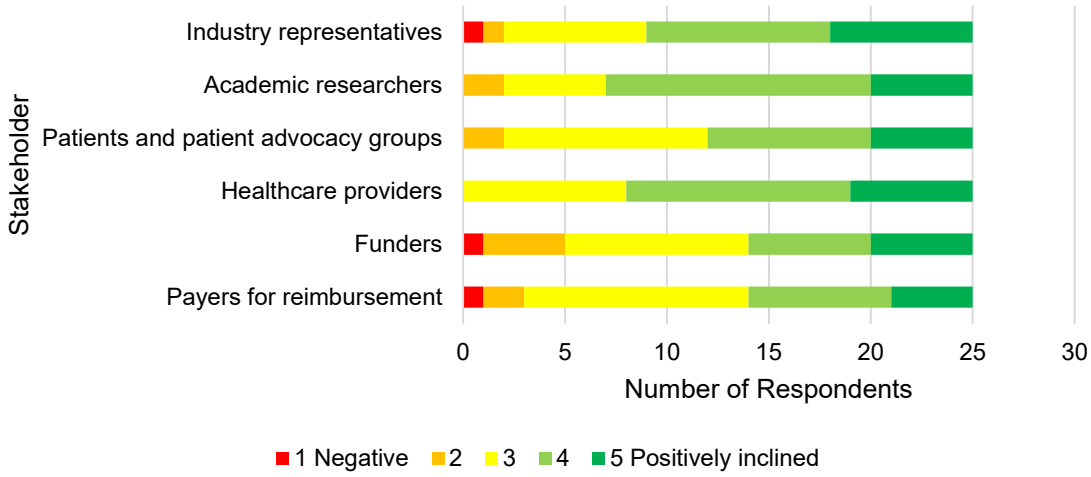

Figure 14. Perception of stakeholder attitudes towards implementation of precision medicine technologies. The perceived level of support was evaluated on a scale of 1 to 5, where 1 indicates "negative" and 5 indicates "positively inclined".

Table 8. Description of perceived level of support from different stakeholders of the HTA system towards the implementation and uptake of PM technologies.

Stakeholders	What did the responses note in the perceptions?
Payers for reimbursement	• Payers are very keen to assess whether a PM technology provides good value for money. They are encouraged to support genetic testing, as it offers significant benefits for patients with rare diseases. • Payers are often concerned about positive recommendations for PM technologies and would prioritise PMs that demonstrate clear benefit without excessive spending. • Some PM technologies have potential to reduce overall medical expenses for the payers; some PMs can be too expensive to pay from social health insurance funds.
Funders	• On a national level (i.e. Australia, Taiwan, Thailand, Singapore), there appears to be a large amount of funding (grant opportunities) that are poured into this area. In South Korea,

Stakeholders	What did the responses note in the perceptions?
	funders are more supportive of PM-HTA related to cancer and dementia, while Malaysia conducts PM trials and assessments through the Institute for Biomedical Research.
Healthcare providers	• Providers have an interest in PM as it has potential to help patients, but they also know about the limitations in available funding and budget as PM technologies often come with a high price tag • Younger providers are keener towards adopting newer science, while many still adhere to traditional treatments as they may have concerns in terms of efficacy and safety of novel therapies compared with empirical therapies. • They may view PM technologies as having significant potential for clinical benefits, as they can lead to more personalised treatment plans tailored to individual patient needs. However, providers may also express concerns about the ease of implementation, particularly regarding the integration of PM technologies into existing workflows, the need for additional training, and the potential for increased costs
Patients and patient advocacy groups	• Patients are generally excited about the potential benefits of PM but lack familiarity with these interventions. • Safety, efficacy, and cost are major concerns. Expensive therapies often face resistance, particularly if patients must pay out-of-pocket. • In Taiwan, patient opinions are underrepresented, being limited to select reimbursement committees.
Academic researchers	• Very likely interested in undertaking research on PM-HTA research but may require support on capacity building, data access, funding, and methodological guideline • One of the main challenges is whether there is buy-in from the implementers (MOH) for the evaluations. This can reduce the validity of the findings if there is a lack of support from public healthcare facilities. Studies might be limited to university hospitals only. • Despite the many challenges researchers face in conducting HTA for PM—including new clinical trial designs, unvalidated surrogate outcomes, uncertainty with one-time treatments, and innovative managed entry arrangements—there is continued support and dedicated effort to enhance the ability to assess PMs • May be biased since some are funded by pharmaceutical companies
Industry representatives	• Industry is generally very positive about the potential of PMs. However, in Malaysia, market potential is limited by the subsidised public healthcare sector, which makes the adoptions of very costly technologies less likely.

Stakeholders	What did the responses note in the perceptions?
	• Industry puts significant effort into ensuring that their product is listed in the government reimbursement list • There are challenges particularly for rare diseases where balancing return for investment, small population, unmet needs, and access. • Pharmaceutical companies can leverage PMs to identify target patients who will respond best to their technologies, reducing uncertainty and providing early market size insights, leading to increased investment, • The industry seeks clarity on reimbursement pathways on PM technologies in Indonesia, addressed in part by the Ministry of Health's (MoH) ongoing health transformation initiatives, including the Biomedical and Genome Science Initiative • In Taiwan, industries can submit reimbursement applications and present their perspectives in an expert committee

PM in Asia Pacific: Challenges and Opportunities

This report explores the landscape of HTA for PM across the Asia-Pacific region. While the maturity of HTA for PMs vary depending on healthcare systems, economic development, and spending priorities [138], common challenges and opportunities emerge.

Countries in the region are at varying stages of implementing HTA for PMs. Hong Kong SAR, India, and the Philippines have yet to introduce HTA for PMs, while Bhutan has shown initial awareness. Vietnam has made early efforts, focusing on screening and diagnostic tools alongside targeted therapies. Indonesia has evaluated targeted therapies, and South Korea has progressed in assessing screening and diagnostic tools. Countries with well-established HTA systems, such as Australia, Malaysia, Singapore, Taiwan, and Thailand, have conducted multiple evaluations across various PM technologies. Diagnostic tools have been evaluated most frequently, followed by targeted therapies and screening tools.

A key finding from the survey and targeted literature review is that many challenges in the methodological aspects of HTA for PM technologies stem from data limitations, uncertain evidence, and high budgetary impact, rather than the inherent complexity of PM technologies. These issues align with previously reported challenges in evaluating PMs [139] [140]. Below, we summarise key challenges and opportunities identified in the review.

Challenges in HTA for PMs

A key challenge in evaluating PMs lies in bridging the gap between evidence generation and synthesis and the stringent evidence requirements of payers and HTA bodies. While not an exhaustive list, the key issues identified in this review are summarised below:

a) Setting the analysis scope

A robust HTA assessment begins with a clearly defined scope of analysis. The PICO framework is instrumental to ensure that the evaluation is structured. However, PM technologies often challenge the traditional PICO framework with their broad and complex nature. For instance, cancer therapies with multiple indications may require separate assessments for each indication. Furthermore, screening and diagnostic tests may have broader applications than those specified in subsidy application and can serve as serve as platforms for addressing a range of health problems.

b) Evaluating co-dependent technologies

Diagnostics and their associated therapies present a unique challenge because of their interdependent nature. In Australia, for example, co-dependent diagnostics were only approved after their linked therapeutics have been recommended for public subsidy. To address this, efforts are being made to create a more streamlined and unified HTA process. The goal is to improve efficiency and reduce the increasing administrative burden on the HTA system.

c) Smaller evidence base resulting from trial designs and smaller populations

PMs targeting specific gene variants or expression profiles present significant evaluation challenges. While innovative trial designs offer promise, they introduce variability and are often seen as lower quality compared to traditional methods. [141] [142] For instance, small single-arm trials, commonly used for such therapies, lack long-term follow-up data, leading to uncertainty about their long-term effects and response durability.[139] This is particularly evident

in therapies like CAR-T cell treatments, which are sometimes regarded as curative but lack comprehensive longitudinal evidence to substantiate such claims.

Furthermore, disease stratification into narrower subgroups enhances treatment precision but reduces trial sample sizes and limits the generalizability of findings.[3] The complexity and variability of treatment pathways add another layer of uncertainty, making cost-effectiveness assessments more challenging.

d) Funding and implementation challenges

Emerging PMs carry substantial upfront and long-term costs, placing significant opportunity costs on funders. Their adoption often demands greater logistical and technical investments than conventional therapies, from specialised diagnostics to tailored care pathways. Addressing clinical uncertainties further necessitates comprehensive data collection—often via registries or real-world monitoring—which introduces operational burdens such as hospital-based administration or reliance on advanced care settings. These cumulative demands elevate both per-patient expenses and system-wide healthcare expenditures.

The situation is further complicated in low- and middle-income countries (LMICs), where resource constraints, fragmented health infrastructure, and competing public health priorities may hinder the establishment of foundational systems required to support PMs, such as genomic testing networks or integrated data platforms. These dynamic risks exacerbating global inequities in adoption, underscoring the need for context-sensitive strategies that align with local capacities and societal needs.

Mapping the Path in HTA for PMs

Below are some potential approaches to better manage PM uncertainties in HTA evaluations:

a) Data collection aligned with HTA needs

To ensure reliable and relevant HTA evaluations for PMs, generation of real-world data strategies are essential. This is particularly important for technologies that target small patient populations or rely on trial designs with limited follow-up. While such PMs claim lifelong benefits, they are typically supported by limited short-term trial data, which underscores the importance of post-HTA data collection. To support sound decision-making, data collection systems must be robust, well-designed, and tailored to the specific evidence needs of PM technologies.

Governments in countries like Singapore, Australia, and Taiwan are heavily investing in PMs through national strategies and grant opportunities could be a platform to do this. Australia, for example, has embedded post-HTA data collection within its HTA process. MSAC requires post-approval evidence gathering for highly specialised and costly PM interventions. These interventions are usually restricted to specialised tertiary centres and monitored through registry-based systems. MSAC also mandates a full HTA reassessment within three years of initial public funding to ensure ongoing value for investment.

In Singapore, initiatives such as the establishment of Precision Health Research, Singapore (PRECISE), and the broader National Precision Medicine (NPM) strategy demonstrate strong governmental commitment to PM research and system development. Although these initiatives do not currently focus on post-HTA RWE collection, they lay critical groundwork for building the data infrastructure needed to support such efforts in the future.

At the regional level, collaborative initiatives offer promising opportunities to address shared challenges in data collection and HTA assessments. For example, HTAsiaLink is initiating an HTA registry to track studies before implementation, simplifying joint evaluations and reducing unnecessary duplication.

b) Integrating PM into existing HTA value frameworks

Current HTA frameworks struggle to incorporate PM effectively due to their unique characteristics. With the increasing number of PM interventions, it is important to identify and integrate key components of PM that are often missing from current HTA value frameworks.

While this document does not propose specific frameworks or critique existing ones, it highlights ongoing efforts in this area. For instance, the ISPOR value flower framework proposed elements for consideration such as reducing uncertainty, addressing fear of contagion, insurance value, disease severity, the value of hope, real option value, equity, and scientific spill overs. [143] Progress has been made in establishing more robust theoretical and measurement foundations for these novel value elements. [144]

Between 2017-2019, China's CNHDRC led a project on health reimbursement decision on PMs to develop a path for HTA-informed listing decisions in PMs. A key insight from this work is the need to first pool and screen information on emerging PM technologies to determine which warrant formal evaluation. Importantly, the project advocates for defining evaluation criteria based on the specific context and decision needs, rather than applying a fixed set of dimensions across all technologies.

Several other country-level initiatives are also paving the way for more fit-for-purpose approaches. Australia's Health Technology and Genomics Collaboration is developing a framework for assessing and funding high-cost, highly specialised therapies. Similarly, Thailand's is advancing work on a reference case for EE of PM[145] for more standardised approaches. In Singapore, discussions are underway to expand beyond the traditional healthcare system perspective to a broader societal viewpoint, which is particularly important as countries age and prioritise protecting the working-age population. Moreover, relying solely on government or hospital perspectives often overlook the broader benefits of PMs, which can extend to relatives and future generations beyond the individual patient.

Other complementary solutions include disease-specific common models, reference case modelling, and whole-care pathway modelling, which can assess the cost-effectiveness of diagnostics and therapies across the care continuum. These are particularly useful in PMs for hereditary conditions, where screening and diagnostic confirmation often extend beyond individual patients to their families. On one hand, this allows for savings on unnecessary diagnostics tests,[146] on the other they also introduce ethical and emotional complexities, such as psychological burden from uncertain test results. A standardised yet flexible method is needed to capture these family-level effects incorporating, as current practices and methods vary widely.

Countries could also benefit from investing in disease-specific common models to better understand the current burden and potential impact of PM screening interventions. Ministries of Health should not have to develop new models for specific diseases. Instead, they could adapt existing robust models to incorporate PM considerations.

While designing unique value frameworks or creating new modelling techniques for each emerging PM technology may be impractical with the influx of new innovations, early engagement with decision-makers on the current issues and know what is an acceptable solution and expectation.[4] The region could leverage on HTAsialink, especially that this project was commissioned by the board and is well-positioned to understand and reflect the relative priorities and challenges faced by HTA agencies in the region. In parallel, academia can explore the feasibility and application of alternative analysis and modelling techniques that are both defensible and aligned with stakeholder expectations. [144]

(c) Managing high-cost PMs

To address the challenge of high-cost PMs, some countries in the region, such as Australia, Japan, South Korea, and Singapore, have introduced RSAs between suppliers and funders. These agreements are designed to manage risks such as therapy underperformance, use beyond the intended population, or higher-than-expected patient numbers. Further details on the HTA agencies involved in these efforts are provided in the text.

Thailand is also exploring policy options to support reimbursement decisions for high-cost interventions in its public healthcare system. For example, medicines deemed cost-ineffective through economic evaluations may still be considered for reimbursement if they are lifesaving, treat conditions with no alternatives, and are affordable in terms of budget impact.[131]

Despite these strategies, the substantial budgetary impact of PMs remains a significant concern for healthcare systems and payers. High-income countries are already struggling to meet the increasing demand for reimbursement of these medicines in their benefits packages. This challenge is even more pronounced in LMICs, which face considerable economic barriers and face greater difficulties in absorbing innovation and financing costly treatments, especially when balancing other competing health priorities.[131] Expensive PM technologies are unlikely to be integrated into routine care within publicly funded systems in these settings. While innovative financing schemes and governance models may help negotiate pricing and improve access to PMs, it will not be the sole solution.

Sustainability in healthcare systems requires balancing affordability with system stability. Early discussions and learning from neighbouring countries can help guide health system planning to support the introduction of PMs across the region. We acknowledge that the applicability of these strategies can vary significantly due to differences in financing models and healthcare delivery structures. For LMICs, these approaches must be carefully tailored to address resource constraints, healthcare system structures, and financing limitations, while also meeting the growing demand for PMs.

This report highlights the scale of the HTA tasks ahead. As PMs become an integral part of modern medicine, HTA capabilities and processes must evolve to keep pace. Strengthening HTA systems, fostering regional collaboration, and adopting innovative approaches will be crucial in ensuring that PMs fulfil their potential to transform healthcare while maintaining system sustainability.

References

1. Marques L, Costa B, Pereira M, et al. Advancing Precision Medicine: A Review of Innovative In Silico Approaches for Drug Development, Clinical Pharmacology and Personalized Healthcare. *Pharmaceutics* 2024;16(3) doi: 10.3390/pharmaceutics16030332 [published Online First: 20240227]
2. Collins FS, Varmus H. A New Initiative on Precision Medicine. *New England Journal of Medicine* 2015;372(9):793-95. doi: doi:10.1056/NEJMp1500523
3. Love-Koh J, Peel A, Rejon-Parrilla JC, et al. The Future of Precision Medicine: Potential Impacts for Health Technology Assessment. *Pharmacoeconomics* 2018;36(12):1439-51. doi: 10.1007/s40273-018-0686-6
4. Faulkner E, Holtorf A-P, Walton S, et al. Being Precise About Precision Medicine: What Should Value Frameworks Incorporate to Address Precision Medicine? A Report of the Personalized Precision Medicine Special Interest Group. *Value in Health* 2020;23(5):529-39. doi: https://doi.org/10.1016/j.jval.2019.11.010
5. Weinstein MC. Recent Developments in Decision-Analytic Modelling for Economic Evaluation. *PharmacoEconomics* 2006;24(11):1043-53. doi: 10.2165/00019053-200624110-00002
6. Ginsburg GS, Phillips KA. Precision Medicine: From Science To Value. *Health Aff (Millwood)* 2018;37(5):694-701. doi: 10.1377/hlthaff.2017.1624 [published Online First: 2018/05/08]
7. Chen W, Wong NCB, Wang Y, et al. Mapping the value for money of precision medicine: a systematic literature review and meta-analysis. *Front Public Health* 2023;11:1151504. doi: 10.3389/fpubh.2023.1151504 [published Online First: 20231124]
8. Teerawattananon Y, Luz K, Yothasmutra C, et al. Historical development of the HTAsiaLink network and its key determinants of success. *International Journal of Technology Assessment in Health Care* 2018;34(3):260-66.
9. Schofield D, Lee E, Parmar J, et al. Economic evaluation of population-based, expanded reproductive carrier screening for genetic diseases in Australia. *Genetics in Medicine* 2023;25(5) doi: 10.1016/j.gim.2023.100813
10. Wu Y, Jayasinghe K, Stark Z, et al. Genomic testing for suspected monogenic kidney disease in children and adults: A health economic evaluation. *GENETICS IN MEDICINE* 2023;25(11) doi: 10.1016/j.gim.2023.100942
11. Wu Y, Balasubramaniam S, Rius R, et al. Genomic sequencing for the diagnosis of childhood mitochondrial disorders: a health economic evaluation. *Eur J Hum Genet* 2022;30(5):577-86. doi: 10.1038/s41431-021-00916-8 [published Online First: 20210608]
12. SU S, Zhang Q, Wang P, et al. Cost-effectiveness analysis of nucleic acid screening for hepatitis B and C in hospitalized patients in China. *Chinese Journal of Laboratory Medicine* 2023:38-44.
13. de Graaff B, Neil A, Si L, et al. Cost-effectiveness of different population screening strategies for hereditary haemochromatosis in Australia. *Applied Health Economics and Health Policy* 2017;15:521-34.
14. Mundy L, Merlin T. Population genetic screening for haemochromatosis: identifying asymptomatic "at risk" homozygous individuals. Australia: Adelaide Health Technology Assessment (AHTA), 2003.
15. Marquina C, Lacaze P, Tiller J, et al. Population genomic screening of young adults for familial hypercholesterolaemia: a cost-effectiveness analysis. *European Heart Journal* 2022;43(34):3243-54.

16. Lacaze P, Marquina C, Tiller J, et al. Combined population genomic screening for three high-risk conditions in Australia: a modelling study. *eClinicalMedicine* 2023;66 doi: 10.1016/j.eclinm.2023.102297
17. Liu QQ, Davis J, Han XK, et al. Cost-effectiveness of polygenic risk profiling for primary open-angle glaucoma in the United Kingdom and Australia. *EYE* 2023;37(11):2335-43. doi: 10.1038/s41433-022-02346-2
18. Downie L, Amor DJ, Halliday J, et al. Exome Sequencing for Isolated Congenital Hearing Loss: A Cost-Effectiveness Analysis. *Laryngoscope* 2021;131(7):E2371-E77. doi: 10.1002/lary.29356
19. Zhou HJ, Wu G, Li JM, et al. Cost-effectiveness analysis of glecaprevir/pibrentasvir regimen for treating Chinese patients with chronic hepatitis C genotype 1 and genotype 2 infection. *Annals of palliative medicine* 2021;10(10):10313-26. doi: 10.21037/apm-21-863
20. Liu J, Guo M, Ke L, et al. Cost-effectiveness of elbasvir/grazoprevir for the treatment of chronic hepatitis C: A systematic review. *Frontiers in Public Health* 2022;10:836986.
21. Chen P, Jin M, Cao Y, et al. Cost-Effectiveness Analysis of Oral Direct-Acting Antivirals for Chinese Patients with Chronic Hepatitis C. *Appl Health Econ Health Policy* 2021;19(3):371-87. doi: 10.1007/s40258-020-00623-3 [published Online First: 20201119]
22. Zhou HJ, Cao J, Shi H, et al. Cost-Effectiveness Analysis of Pan-Genotypic Sofosbuvir-Based Regimens for Treatment of Chronic Hepatitis C Genotype 1 Infection in China. *Frontiers in public health* 2021;9:779215. doi: 10.3389/fpubh.2021.779215
23. Dan YY, Ferrante SA, Elbasha EH, et al. Cost-effectiveness of boceprevir co-administration versus pegylated interferon-α2b and ribavirin only for patients with hepatitis C genotype 1 in Singapore. *Antiviral Therapy* 2015;20(2):209-16.
24. Tasavon Gholamhoseini M, Sharafi H, Hl Borba H, et al. Economic evaluation of pan-genotypic generic direct-acting antiviral regimens for treatment of chronic hepatitis C in Iran: a cost-effectiveness study. *BMJ Open* 2022;12(6) doi: 10.1136/bmjopen-2021-058757
25. Zhao YJ, Khoo AL, Lin L, et al. Cost-effectiveness of strategy-based approach to treatment of genotype 1 chronic hepatitis C. *Journal of gastroenterology and hepatology* 2016;31(9):1628-37.
26. Yuen MF, Liu SH, Seto WK, et al. Cost-Utility of All-Oral Direct-Acting Antiviral Regimens for the Treatment of Genotype 1 Chronic Hepatitis C Virus-Infected Patients in Hong Kong. *DIGESTIVE DISEASES AND SCIENCES* 2021;66(4):1315-26. doi: 10.1007/s10620-020-06281-8
27. Chugh Y, Dhiman RK, Premkumar M, et al. Real-world cost-effectiveness of pan-genotypic Sofosbuvir-Velpatasvir combination versus genotype dependent directly acting antiviral drugs for treatment of hepatitis C patients in the universal coverage scheme of Punjab state in India. *PLoS One* 2019;14(8):e0221769.
28. Zhao YJ, Khoo AL, Lin L, et al. Cost-effectiveness of strategy-based approach to treatment of genotype 1 chronic hepatitis C. *J Gastroenterol Hepatol* 2016;31(9):1628-37. doi: 10.1111/jgh.13341
29. Zhou HJ, Cao J, Shi H, et al. Cost-Effectiveness Analysis of Pan-Genotypic Sofosbuvir-Based Regimens for Treatment of Chronic Hepatitis C Genotype 1 Infection in China. *Front Public Health* 2021;9:779215. doi: 10.3389/fpubh.2021.779215 [published Online First: 20211209]
30. Suenaga R, Suka M, Hirao T, et al. Cost-effectiveness of a "treat-all" strategy using Direct-Acting Antivirals (DAAs) for Japanese patients with chronic hepatitis C genotype 1 at different fibrosis stages. *PLoS ONE* 2021;16(4 April) doi: 10.1371/journal.pone.0248748

31. Chen P, Jin M, Cao Y, et al. Cost-Effectiveness Analysis of Oral Direct-Acting Antivirals for Chinese Patients with Chronic Hepatitis C. *Applied Health Economics and Health Policy* 2021;19(3):371-87. doi: 10.1007/s40258-020-00623-3
32. Goel A, Chen Q, Chhatwal J, et al. Cost-effectiveness of generic pan-genotypic sofosbuvir/velpatasvir versus genotype-dependent direct-acting antivirals for hepatitis C treatment. *Journal of gastroenterology and hepatology* 2018;33(12):2029-36.
33. Tu Y, Tang X, Zhou D, et al. Is it time for China to prioritize pan-genotypic regimens for treating patients with hepatitis C? *Cost Effectiveness and Resource Allocation* 2024;22(1) doi: 10.1186/s12962-024-00519-2
34. Wang TJ, Scuffham P, Byrnes J, et al. Cost-effectiveness analysis of gene-based therapies for patients with spinal muscular atrophy type I in Australia. *JOURNAL OF NEUROLOGY* 2022;269(12):6544-54. doi: 10.1007/s00415-022-11319-0
35. Khuntha S, Prawjaeng J, Ponragdee K, et al. Onasemnogene Abeparvovec Gene Therapy and Risdiplam for the Treatment of Spinal Muscular Atrophy in Thailand: A Cost-Utility Analysis. *Applied Health Economics and Health Policy* 2024 doi: 10.1007/s40258-024-00915-y
36. Wang T, Scuffham P, Byrnes J, et al. Cost-effectiveness analysis of gene-based therapies for patients with spinal muscular atrophy type I in Australia. *Journal of Neurology* 2022;269(12):6544-54. doi: 10.1007/s00415-022-11319-0
37. Yuliwulandari R, Shin JG, Kristin E, et al. Cost-effectiveness analysis of genotyping for HLA-B*15:02 in Indonesian patients with epilepsy using a generic model. *Pharmacogenomics Journal* 2021;21(4):476-83. doi: 10.1038/s41397-021-00225-9
38. Gu YR, Shih STF, Geevasinga N, et al. Economic Evaluation of HLA-B*15:02 Genotyping for Asian Australian Patients With Epilepsy. *JAMA DERMATOLOGY* 2024;160(6):631-40. doi: 10.1001/jamadermatol.2024.1037
39. Zhang Z, Bao Y, Cai L, et al. Cost-Utility Analysis of CYP2C19 Genotype Detection for Selection of Acid-Suppressive Therapy with Lansoprazole or Vonoprazan for Patients with Reflux Esophagitis in China. *Clinical Drug Investigation* 2022;42(10):839-51. doi: 10.1007/s40261-022-01188-w
40. Narasimhalu K, Ang YK, Tan DSY, et al. Cost effectiveness of genotype-guided antiplatelet therapy in Asian ischemic stroke patients: ticagrelor as an alternative to clopidogrel in patients with CYP2C19 loss of function mutations. *Clinical Drug Investigation* 2020;40:1063-70.
41. Narasimhalu K, Chan JRY, Ang YK, et al. Empiric treatment with aspirin and ticagrelor is the most cost-effective strategy in patients with minor stroke or transient ischemic attack. *INTERNATIONAL JOURNAL OF STROKE* 2024;19(2):209-16. doi: 10.1177/17474930231202374
42. Li XY, Cao YY. Cost-effectiveness of Arg16Gly in ADRB2 pharmacogenomic-guided treatment for pediatric asthma. *EXPERT REVIEW OF PHARMACOECONOMICS & OUTCOMES RESEARCH* 2023;23(8):891-99. doi: 10.1080/14737167.2023.2220966
43. You JH. Pharmacogenetic-guided selection of warfarin versus novel oral anticoagulants for stroke prevention in patients with atrial fibrillation: a cost-effectiveness analysis. *Pharmacogenet Genomics* 2014;24(1):6-14. doi: 10.1097/fpc.0000000000000014
44. Pruis S-l, Jeon YK, Pearce F, et al. Cost-effectiveness of sequential urate lowering therapies for the management of gout in Singapore. *Journal of Medical Economics* 2020;23(8):838-47.
45. Wei X, Cai J, Zhuang J, et al. CYP2D6* 10 pharmacogenetic-guided SERM could be a cost-effective strategy in Chinese patients with hormone receptor-positive breast cancer. *Pharmacogenomics* 2020;21(1):43-53.

46. Rens NE, Uyl-de Groot CA, Goldhaber-Fiebert JD, et al. Cost-effectiveness of a Pharmacogenomic Test for Stratified Isoniazid Dosing in Treatment of Active Tuberculosis. *Clin Infect Dis* 2020;71(12):3136-43. doi: 10.1093/cid/ciz1212
47. Lv YP, Wang ZL, Yuan L, et al. A cost-effectiveness analysis of pre-pregnancy genetic screening for deafness: an empirical study in China. *FRONTIERS IN PUBLIC HEALTH* 2023;11 doi: 10.3389/fpubh.2023.1081339
48. He X, Wang X, Shen J, et al. Cost-effectiveness of preimplantation genetic testing for aneuploidy for women with subfertility in China: an economic evaluation using evidence from the CESE-PGS trial. *BMC Pregnancy and Childbirth* 2023;23(1) doi: 10.1186/s12884-023-05563-z
49. Nguyen H, Finkelstein E, Mital S, et al. Incremental Cost-Effectiveness of Algorithm-Driven Genetic Testing Versus no Testing for Maturity Onset Diabetes of the Young (Mody) in Singapore. *Value in Health* 2016;19(7):A812-A13.
50. Chan VKY, Yang R, Wong ICK, et al. Cost-Effectiveness of Poly ADP-Ribose Polymerase Inhibitors in Cancer Treatment: A Systematic Review. *Frontiers in Pharmacology* 2022;13 doi: 10.3389/fphar.2022.891149
51. Kim JH, Tan DSY, Chan MYY. Cost-effectiveness of CYP2C19-guided antiplatelet therapy for acute coronary syndromes in Singapore. *Pharmacogenomics Journal* 2021;21(2):243-50. doi: 10.1038/s41397-020-00204-6
52. Wei XX, Zhuang J, Li N, et al. NUDT15 genetic testing-guided 6-mercaptopurine dosing in children with ALL likely to be cost-saving in China. *International Journal of Hematology* 2022;115(2):278-86. doi: 10.1007/s12185-021-03237-0
53. **林琦**, 张超凤, **林娟**, et al. **基于**ADRB2**基因**检测的汉族COPD**患者使用干粉吸入**剂治疗的成本效果分析. *中国现代应用药学* 2019;36(4):466-70. doi: 10.13748/j.cnki.issn1007-7693.2019.04.017
54. Wei X, Cai J, Sun H, et al. Cost–effectiveness analysis of UGT1A1* 6/* 28 genotyping for preventing FOLFIRI-induced severe neutropenia in Chinese colorectal cancer patients. *Pharmacogenomics* 2019;20(4):241-49.
55. Teng GG, Tan-Koi W-C, Dong D, et al. Is HLA-B* 58: 01 genotyping cost effective in guiding allopurinol use in gout patients with chronic kidney disease? *Pharmacogenomics* 2020;21(4):279-91.
56. Chen Z, Liew D, Kwan P. Real-world cost-effectiveness of pharmacogenetic screening for epilepsy treatment. *Neurology* 2016;86(12):1086-94.
57. Dong D, Tan-Koi W-C, Teng GG, et al. Cost–effectiveness analysis of genotyping for HLA-B* 5801 and an enhanced safety program in gout patients starting allopurinol in Singapore. *Pharmacogenomics* 2015;16(16):1781-93.
58. Ke C-H, Chung W-H, Wen Y-H, et al. Cost-effectiveness analysis for genotyping before allopurinol treatment to prevent severe cutaneous adverse drug reactions. *The Journal of rheumatology* 2017;44(6):835-43.
59. Kapoor R, Martinez-Vega R, Dong D, et al. Reducing hypersensitivity reactions with HLA-B* 5701 genotyping before abacavir prescription: clinically useful but is it cost-effective in Singapore? *Pharmacogenetics and genomics* 2015;25(2):60-72.
60. Duong KNC, Nguyen DV, Chaiyakunapruk N, et al. Cost-effectiveness of HLA-B*58:01 testing to prevent Stevens-Johnson syndrome/toxic epidermal necrolysis in Vietnam. *Pharmacogenomics* 2023;24(13):713-24. doi: 10.2217/pgs-2023-0095
61. Zeng D, Huang X, Lin S, et al. Cost-effectiveness analysis of genotype screening and therapeutic drug monitoring in patients with inflammatory bowel disease treated with azathioprine therapy: a Chinese healthcare perspective using real-world data. *Annals of Translational Medicine* 2021;9(14):1138.
62. Ingles J, McGaughran J, Scuffham PA, et al. A cost-effectiveness model of genetic testing for the evaluation of families with hypertrophic cardiomyopathy. *Heart* 2012;98(8):625-30.

63. Catchpool M, Ramchand J, Martyn M, et al. A cost-effectiveness model of genetic testing and periodical clinical screening for the evaluation of families with dilated cardiomyopathy. *Genetics in Medicine* 2019;21(12):2815-22.
64. Zischke J, White N, Gordon L. Accounting for Intergenerational Cascade Testing in Economic Evaluations of Clinical Genomics: A Scoping Review. *Value in Health* 2022;25(6):944-53. doi: 10.1016/j.jval.2021.11.1353
65. Shih STF, Keller E, Wiley V, et al. Modelling the Cost-Effectiveness and Budget Impact of a Newborn Screening Program for Spinal Muscular Atrophy and Severe Combined Immunodeficiency. *International Journal of Neonatal Screening* 2022;8(3) doi: 10.3390/ijns8030045
66. Shih ST, Keller E, Wiley V, et al. Modelling the cost-effectiveness and budget impact of a newborn screening program for spinal muscular atrophy and severe combined immunodeficiency. *International Journal of Neonatal Screening* 2022;8(3):45.
67. Ademi Z, Watts GF, Pang J, et al. Cascade screening based on genetic testing is cost-effective: evidence for the implementation of models of care for familial hypercholesterolemia. *Journal of clinical lipidology* 2014;8(4):390-400.
68. Burvill A, Watts GF, Norman R, et al. Early health technology assessment of gene silencing therapies for lowering lipoprotein(a) in the secondary prevention of coronary heart disease. *Journal of Clinical Lipidology* 2024 doi: 10.1016/j.jacl.2024.08.012
69. Xiao-fang A, Ya-jing Z, Huan-ping A, et al. Cost-effectiveness analysis of CYP2C19 genetic test in guiding antiplatelet therapy/CYP2C19 基因检测指导抗血小板治疗的成本-效果分析. *Xi'an jiao tong da xue xue bao Yi xue ban* 2018(6):853.
70. Fu Y, Zhang X-y, Qin S-b, et al. Cost–effectiveness of CYP2C19 LOF-guided antiplatelet therapy in Chinese patients with acute coronary syndrome. *Pharmacogenomics* 2020;21(1):33-42.
71. Sorich MJ, Horowitz JD, Sorich W, et al. Cost–effectiveness of using CYP2C19 genotype to guide selection of clopidogrel or ticagrelor in Australia. *Pharmacogenomics* 2013;14(16):2013-21.
72. Panattoni L, Brown PM, Te Ao B, et al. The cost effectiveness of genetic testing for CYP2C19 variants to guide thienopyridine treatment in patients with acute coronary syndromes: a New Zealand evaluation. *Pharmacoeconomics* 2012;30:1067-84.
73. Wang Y, Yan BP, Liew D, et al. Cost-effectiveness of cytochrome P450 2C19 *2 genotype-guided selection of clopidogrel or ticagrelor in Chinese patients with acute coronary syndrome. *The Pharmacogenomics Journal* 2018;18(1):113-20. doi: 10.1038/tpj.2016.94
74. Cai Z, Cai D, Wang R, et al. Cost-effectiveness of CYP2C19 genotyping to guide antiplatelet therapy for acute minor stroke and high-risk transient ischemic attack. *Scientific Reports* 2021;11(1):7383. doi: 10.1038/s41598-021-86824-9
75. Zhang ZL, Bao YW, Gu YJ, et al. Cost-effectiveness analysis of CYP2C19 genotype-guided antiplatelet therapy for patients with acute minor ischemic stroke and high-risk transient ischemic attack in China. *BRITISH JOURNAL OF CLINICAL PHARMACOLOGY* 2024;90(2):483-92. doi: 10.1111/bcp.15921
76. AlMukdad S, Elewa H, Arafa S, et al. Short- and long-term cost-effectiveness analysis of CYP2C19 genotype-guided therapy, universal clopidogrel, versus universal ticagrelor in post-percutaneous coronary intervention patients in Qatar. *International Journal of Cardiology* 2021;331:27-34. doi: 10.1016/j.ijcard.2021.01.044
77. Wei X, Sun H, Zhuang J, et al. Cost-effectiveness Analysis of CYP2D6*10 Pharmacogenetic Testing to Guide the Adjuvant Endocrine Therapy for Postmenopausal Women with Estrogen Receptor Positive Early Breast Cancer in China. *Clin Drug Investig* 2020;40(1):25-32. doi: 10.1007/s40261-019-00842-0

78. Kategeaw W, Nakkam N, Kiertiburanakul S, et al. Cost-effectiveness analysis of HLA-B*13:01 screening for the prevention of co-trimoxazole-induced severe cutaneous adverse reactions among HIV-infected patients in Thailand. *Journal of Medical Economics* 2023;26(1):1330-41. doi: 10.1080/13696998.2023.2270868
79. Rattanavipapong W, Koopitakkajorn T, Praditsitthikorn N, et al. Economic evaluation of HLA-B*15:02 screening for carbamazepine-induced severe adverse drug reactions in Thailand. *Epilepsia* 2013;54(9):1628-38. doi: 10.1111/epi.12325 [published Online First: 20130729]
80. Saokaew S, Tassaneeyakul W, Maenthaisong R, et al. Cost-effectiveness analysis of HLA-B*5801 testing in preventing allopurinol-induced SJS/TEN in Thai population. *PLoS One* 2014;9(4):e94294. doi: 10.1371/journal.pone.0094294 [published Online First: 20140414]
81. Chong HY, Lim YH, Prawjaeng J, et al. Cost-effectiveness analysis of 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. *Pharmacogenet Genomics* 2018;28(2):56-67. doi: 10.1097/fpc.0000000000000319
82. Hong Y, Chen X, Li Z, et al. A lifetime economic research of universal HLA-B∗58:01 genotyping or febuxostat initiation therapy in Chinese gout patients with mild to moderate chronic kidney disease. *Pharmacogenetics and Genomics* 2023;33(2):24-34. doi: 10.1097/FPC.0000000000000488
83. Hemati H, Nosrati M, Hasanzad M, et al. Cost-Effectiveness Analysis of Pharmacogenomics-Guided Versus Standard Dosing of Warfarin in Patients with Mechanical Prosthetic Heart Valve. *Iranian Journal of Pharmaceutical Research* 2024;23(1) doi: 10.5812/ijpr-143898
84. Chong HY, Saokaew S, Dumrongprat K, et al. Cost-effectiveness analysis of pharmacogenetic-guided warfarin dosing in Thailand. *Thromb Res* 2014;134(6):1278-84. doi: 10.1016/j.thromres.2014.10.006 [published Online First: 20141014]
85. Turongkaravee S, Praditsitthikorn N, Ngamprasertchai T, et al. Economic Evaluation of Multiple-Pharmacogenes Testing for the Prevention of Adverse Drug Reactions in People Living with HIV. *CLINICOECONOMICS AND OUTCOMES RESEARCH* 2022;14:447-63. doi: 10.2147/CEOR.S366906
86. Wu Y, Balasubramaniam S, Rius R, et al. Genomic sequencing for the diagnosis of childhood mitochondrial disorders: a health economic evaluation. *European Journal of Human Genetics* 2022;30(5):577-86. doi: 10.1038/s41431-021-00916-8
87. Mundy L, Hiller JE. 0.2-0.5 Tesla MRi for the detection of arthritis and musculoskeletal disease. Australia: Adelaide Health Technology Assessment (AHTA), 2009.
88. Vernon ST, Brentnall S, Currie DJ, et al. Health economic analysis of polygenic risk score use in primary prevention of coronary artery disease – A system dynamics model. *American Journal of Preventive Cardiology* 2024;18:100672. doi: https://doi.org/10.1016/j.ajpc.2024.100672
89. Turongkaravee S, Praditsitthikorn N, Ngamprasertchai T, et al. Economic Evaluation of Multiple-Pharmacogenes Testing for the Prevention of Adverse Drug Reactions in People Living with HIV. *ClinicoEconomics and Outcomes Research* 2022;14:447-63. doi: 10.2147/CEOR.S366906
90. Kim DJ, Kim HS, Oh M, et al. Cost Effectiveness of Genotype-Guided Warfarin Dosing in Patients with Mechanical Heart Valve Replacement Under the Fee-for-Service System. *Appl Health Econ Health Policy* 2017;15(5):657-67. doi: 10.1007/s40258-017-0317-y
91. Kapoor R, Martinez-Vega R, Dong D, et al. Reducing hypersensitivity reactions with HLA-B*5701 genotyping before abacavir prescription: clinically useful but is it cost-effective in Singapore? *Pharmacogenet Genomics* 2015;25(2):60-72. doi: 10.1097/fpc.0000000000000107

92. Vernon ST, Brentnall S, Currie DJ, et al. Health economic analysis of polygenic risk score use in primary prevention of coronary artery disease - A system dynamics model. *AMERICAN JOURNAL OF PREVENTIVE CARDIOLOGY* 2024;18 doi: 10.1016/j.ajpc.2024.100672
93. Chen Z, Liew D, Kwan P. Real-world cost-effectiveness of pharmacogenetic screening for epilepsy treatment. *Neurology* 2016;86(12):1086-94. doi: 10.1212/wnl.0000000000002484 [published Online First: 20160217]
94. Lv Y, Wang Z, Yuan L, et al. A cost-effectiveness analysis of pre-pregnancy genetic screening for deafness: an empirical study in China. *Frontiers in public health* 2023;11:1081339. doi: 10.3389/fpubh.2023.1081339
95. He X, Wang X, Shen JJ, et al. Cost-effectiveness of preimplantation genetic testing for aneuploidy for women with subfertility in China: an economic evaluation using evidence from the CESE-PGS trial. *BMC PREGNANCY AND CHILDBIRTH* 2023;23(1) doi: 10.1186/s12884-023-05563-z
96. Crawford SA, Gong CL, Yieh L, et al. Diagnosing newborns with suspected mitochondrial disorders: an economic evaluation comparing early exome sequencing to current typical care. *Genetics in Medicine* 2021;23(10):1854-63. doi: 10.1038/s41436-021-01210-0
97. Ademi Z, Watts GF, Pang J, et al. Cascade screening based on genetic testing is cost-effective: evidence for the implementation of models of care for familial hypercholesterolemia. *J Clin Lipidol* 2014;8(4):390-400. doi: 10.1016/j.jacl.2014.05.008 [published Online First: 20140612]
98. Marquina C, Lacaze P, Tiller J, et al. Population genomic screening of young adults for familial hypercholesterolaemia: A cost-effectiveness analysis. *European Heart Journal* 2022;43(34):3243-54. doi: 10.1093/eurheartj/ehab770
99. Dong D, Tan-Koi WC, Teng GG, et al. Cost-effectiveness analysis of genotyping for HLA-B*5801 and an enhanced safety program in gout patients starting allopurinol in Singapore. *Pharmacogenomics* 2015;16(16):1781-93. doi: 10.2217/pgs.15.125 [published Online First: 20151110]
100. Duong KN, Nguyen DV, Chaiyakunapruk N, et al. Cost-effectiveness of HLA-B*58:01 testing to prevent Stevens-Johnson syndrome/toxic epidermal necrolysis in Vietnam. *Pharmacogenomics* 2023;24(13):713-24. doi: 10.2217/pgs-2023-0095 [published Online First: 20230914]
101. Wang T, Scuffham P, Byrnes J, et al. Cost-effectiveness analysis of gene-based therapies for patients with spinal muscular atrophy type I in Australia. *J Neurol* 2022;269(12):6544-54. doi: 10.1007/s00415-022-11319-0 [published Online First: 20220818]
102. Kim H, Byrnes J, Goodall S. Health Technology Assessment in Australia: The Pharmaceutical Benefits Advisory Committee and Medical Services Advisory Committee. *Value in Health Regional Issues* 2021;24:6-11. doi: https://doi.org/10.1016/j.vhri.2020.09.001
103. Hailey D. The history of health technology assessment in Australia. *International Journal of Technology Assessment in Health Care* 2009;25(S1):61-67. doi: 10.1017/S0266462309090436 [published Online First: 2009/07/01]
104. Efficient Funding of Chemotherapy Program. 2025. https://www.pbs.gov.au/info/browse/section-100/chemotherapy.
105. High cost, highly specialised therapy (HST) applications Australia: Medical Services Advisory Committee; 2024 [cited 2025 June 2025]. Available from: https://www.msac.gov.au/apply/before-you-apply/suitable-services-technologies/hst-applications accessed June 20 2025 2025.
106. Framework for the assessment, funding and implementation of high cost, highly specialised therapies and services. 2024 April 2024. https://www.health.gov.au/sites/default/files/2024-04/framework-for-the-assessment-

funding-and-implementation-of-high-cost-highly-specialised-therapies-and-services.pdf.
107. Shafie AA, Chandriah H, Yong YV, et al. Health Technology Assessment and Its Use in Drug Policy in Malaysia. *Value in Health Regional Issues* 2019;18:145-50. doi: https://doi.org/10.1016/j.vhri.2019.03.003
108. Yadav H. The health care system in Malaysia. Health Care Systems in Developing Countries in Asia: Routledge 2017:110-30.
109. Roza S, Junainah S, Izzuna MMG, et al. Health Technology Assessment in Malaysia: Past, Present, and Future. *International Journal of Technology Assessment in Health Care* 2019;35(6):446-51. doi: 10.1017/S0266462319000023 [published Online First: 2019/03/13]
110. Kwong KS, Choo YW, Cheah HM. Power of 1 Malaysian Ringgit: A Low-Cost Prescription Cost-Sharing Model in Malaysia. *Value in Health Regional Issues* 2020;21:245-51. doi: https://doi.org/10.1016/j.vhri.2019.12.002
111. Shafie AA. Improving Access to Orphan Drugs in Malaysia. 2019. https://www.ideas.org.my/wp-content/uploads/2021/04/RD_PolicyPaper-V3.pdf.
112. Value-based Medicines for Improved Patient Access in Malaysia: White Paper. 2019. https://www.phama.org.my/view_file.cfm?fileid=111.
113. INAHTA. ACE – Agency for Care Effectiveness. 2024. https://www.inahta.org/members/ace/.
114. Pearce F, Lin L, Teo E, et al. Health Technology Assessment and Its Use in Drug Policies: Singapore. *Value in Health Regional Issues* 2019;18:176-83. doi: 10.1016/j.vhri.2018.03.007
115. Singapore AfCE. DRUG AND VACCINE EVALUATION METHODS AND PROCESS GUIDE. 2023. https://www.ace-hta.gov.sg/resources/process-methods#0d9c81f3eadc349e3be4f908d386862c (accessed June 2025).
116. Singapore AfCE. Update of MOH List of Subsidised Drugs to include treatments for various cancer condition. 2024. https://isomer-user-content.by.gov.sg/68/91736e4b-b8de-4c08-a4c6-200dfebd8b20/update-of-moh-list-of-subsidised-drugs-for-various-cancer-conditions-(2-sep-2024).pdf (accessed June 2025).
117. Singapore AfCE. Cell, Tissue and Gene Therapy Product (CTGTP) List. 2025 1 April 2025. https://www.moh.gov.sg/managing-expenses/schemes-and-subsidies/cell-tissue-and-gene-therapy/product-list-cell-tissue-gene.
118. Oh J, Min-Jeong K, Sujeong H, et al. Institutionalizing Health Technology Assessment and Priority Setting in South Korea's Universal Health Coverage Journey. *Health Systems & Reform* 2023;9(3):2338308. doi: 10.1080/23288604.2024.2338308
119. Agency NE-bHC. National Evidence-based Healthcare Collaborating Agency South Korea: NECA; 2017 [cited 2025 June 2025]. Available from: https://www.cancer.go.kr/eng/index.do.
120. Kim S, Hyunyoung C, Jinhong K, et al. The current state of patient access to new drugs in South Korea under the positive list system: evaluation of the changes since the new review pathways. *Expert Review of Pharmacoeconomics & Outcomes Research* 2021;21(1):119-26. doi: 10.1080/14737167.2020.1758559
121. Yoo S-L, Kim D-J, Lee S-M, et al. Improving Patient Access to New Drugs in South Korea: Evaluation of the National Drug Formulary System. *International Journal of Environmental Research and Public Health* 2019;16(2):288.
122. Lee S, Lee JH. Cell and gene therapy regulatory, pricing, and reimbursement framework: With a focus on South Korea and the EU. *Front Public Health* 2023;11:1109873. doi: 10.3389/fpubh.2023.1109873 [published Online First: 20230224]
123. Lee B, Bae EY, Bae S, et al. How can we improve patients' access to new drugs under uncertainties? : South Korea's experience with risk sharing arrangements. *BMC Health*

Serv Res 2021;21(1):967. doi: 10.1186/s12913-021-06919-x [published Online First: 20210914]
124. Kim H, Kim E, Kang J, et al. PNS37 Evalutaion of Time to Reimbursement for Rsa Drugs in Korea. *Value in Health Regional Issues* 2020;22:S87.
125. Leelahavarong P, Doungthipsirikul S, Kumluang S, et al. Health Technology Assessment in Thailand: Institutionalization and Contribution to Healthcare Decision Making: Review of Literature. *International Journal of Technology Assessment in Health Care* 2019;35(6):467-73. doi: 10.1017/S0266462319000321 [published Online First: 2019/06/13]
126. Rattanavipapong W, Anothaisintawee T, Teerawattananon Y. Revisiting policy on chronic HCV treatment under the Thai Universal Health Coverage: An economic evaluation and budget impact analysis. *PLoS One* 2018;13(2):e0193112. doi: 10.1371/journal.pone.0193112 [published Online First: 20180221]
127. Kapol N, Lochid-Amnuay S, Teerawattananon Y. Economic evaluation of pegylated interferon plus ribavirin for treatment of chronic hepatitis C in Thailand: genotype 1 and 6. *BMC Gastroenterol* 2016;16(1):91. doi: 10.1186/s12876-016-0506-4 [published Online First: 20160805]
128. Bussabawalai T, Thiboonboon K, Teerawattananon Y. Cost-utility analysis of adjuvant imatinib treatment in patients with high risk of recurrence after gastrointestinal stromal tumour (GIST) resection in Thailand. *Cost Eff Resour Alloc* 2019;17:1. doi: 10.1186/s12962-018-0169-9 [published Online First: 20190108]
129. Laichapis M, Thathong T, Kanjanaphrut S, et al. The process of listing prostheses and medical devices in Thailand's universal health coverage. *Value in Health Regional Issues* 2024;42:100990.
130. Hanvoravongchai P. Health financing reform in Thailand: toward universal coverage under fiscal constraints. 2013
131. Butani D, Faradiba D, Dabak SV, et al. Expanding access to high-cost medicines under the Universal Health Coverage scheme in Thailand: review of current practices and recommendations. *Journal of Pharmaceutical Policy and Practice* 2023;16(1):138. doi: 10.1186/s40545-023-00643-z
132. Bhoothookngoen P, Khansilarchaipak S. Comparing Thailand and UK's Reimbursement Policies: Focus on High-Value Drug List for Cancer. *Thai Journal of Public Health* 2024;54(2):937-51.
133. Chen Y, Zhao K, Liu G, et al. Health technology assessment to inform decision making in China: progress, challenges, and sustainability. *BMJ* 2023;381:e068910. doi: 10.1136/bmj-2021-068910
134. Chen Y, Dong H, Wei Y, et al. Using health technology assessment to inform insurance reimbursement of high technology medicines in China: an example of cancer immunotherapy. *BMJ* 2023;381:e069963. doi: 10.1136/bmj-2022-069963
135. Chen W, Zhang L, Hu M, et al. Use of health technology assessment in drug reimbursement decisions in China. *Bmj* 2023;381:e068915. doi: 10.1136/bmj-2021-068915 [published Online First: 20230615]
136. Liu S, Xia Y, Yang Y, et al. Mapping of health technology assessment in China: a comparative study between 2016 and 2021. *Global Health Research and Policy* 2024;9(1):4. doi: 10.1186/s41256-023-00339-6
137. Macabeo B, Wilson L, Xuan J, et al. Access to innovative drugs and the National Reimbursement Drug List in China: Changing dynamics and future trends in pricing and reimbursement. *J Mark Access Health Policy* 2023;11(1):2218633. doi: 10.1080/20016689.2023.2218633 [published Online First: 20230613]
138. Teerawattananon Y, Rattanavipapong W, Lin LW, et al. Landscape analysis of health technology assessment (HTA): systems and practices in Asia. *Int J Technol Assess*

Health Care 2019;35(6):416-21. doi: 10.1017/s0266462319000667 [published Online First: 20191009]
139. Hogervorst MA, Vreman RA, Mantel-Teeuwisse AK, et al. Reported Challenges in Health Technology Assessment of Complex Health Technologies. *Value in Health* 2022;25(6):992-1001. doi: https://doi.org/10.1016/j.jval.2021.11.1356
140. Trapani D, Tay-Teo K, Tesch ME, et al. Implications of Oncology Trial Design and Uncertainties in Efficacy-Safety Data on Health Technology Assessments. *Curr Oncol* 2022;29(8):5774-91. doi: 10.3390/curroncol29080455 [published Online First: 20220816]
141. Blagden SP, Billingham L, Brown LC, et al. Effective delivery of Complex Innovative Design (CID) cancer trials—A consensus statement. *British Journal of Cancer* 2020;122(4):473-82. doi: 10.1038/s41416-019-0653-9
142. Michel S. Do Payers Find Value in Innovative Trial Designs?
143. Lakdawalla DN, Doshi JA, Garrison LP, Jr., et al. Defining Elements of Value in Health Care—A Health Economics Approach: An ISPOR Special Task Force Report [3]. *Value in Health* 2018;21(2):131-39. doi: 10.1016/j.jval.2017.12.007
144. Neumann PJ, Garrison LP, Willke RJ. The History and Future of the “ISPOR Value Flower”: Addressing Limitations of Conventional Cost-Effectiveness Analysis. *Value in Health* 2022;25(4):558-65. doi: 10.1016/j.jval.2022.01.010
145. Development of the PICCOTEAM Reference Case for Economic Evaluation Of Precision Medicine. ISPOR Europe 2024 2024.
146. Kapol N, Kamolvisit W, Kongkiattikul L, et al. Using an experiment among clinical experts to determine the cost and clinical impact of rapid whole exome sequencing in acute pediatric settings. *Front Pediatr* 2023;11:1204853. doi: 10.3389/fped.2023.1204853 [published Online First: 20230703]

Supplementary file 1: PRISMA flow diagram for the targeted literature search