Development of reference case for precision medicine and piloting its application in Thailand

A PM-RC WORKSHOP REPORT

28th-30th June, 2023

Khao Yai, Thailand

HITAP Health Intervention and Technology Assessment Program

NUS National University of Singapore

Contents

List of acronyms

AAR	After Action Review
ACE	Agency of Care Excellence
ACMG	American College of Medical Genetics and Genomics
AI	Artificial Intelligence
ASHG	American Society of Human Genetics
BIA	Budget Impact Analysis
BRCA	Breast Cancer Gene
BREATHE	Breast Screening Tailored for HEr
CEA	Cost Effectiveness Analysis
CIP	Clinical Implementation Pilot
CT	Cascade Testing
DCEA	Distributional Cost Effectiveness Analysis
EE	Economic Evaluation
FDRs	First Degree Relatives
FHCARE	Familial Hypercholesterolemia
HC	Hereditary Cancer
HIPER	Health Intervention and Policy Evaluation Research (HIPER)
HITAP	Health Intervention and Technology Assessment Program
HSRI	Health System Research Institute
HTA	Health Technology Assessment
IDSI	International Decision Support Initiative
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
LMIC	Low- or Middle-Income Country
MCDA	Multiple-criteria decision analysis
NGS	Next Generation Sequencing
NTU	Nanyang Technological University - NTU Singapore
NUS	National University of Singapore
PDPA	Personal Data Protection Act
PGx	Pharmacogenomic testing
PGD	Primary Glomerular Disease
PICOTEAM	Population, Intervention, Comparator, Time, Ethic/Equity, Adaptability and Modelling
PM	Precision Medicine
PRECISE	Precision Health Research, Singapore
PROSPERO	International Prospective Register of Systematic Reviews
QALY	Quality-Adjusted Life Year
RC	Reference Case
RWD	Real World Data
SJS	Steven Jhonson Syndrome
SLR	Systematic Literature Review
SSHSPH	Saw Swee Hock School of Public Health
TEN	Toxic Epidermal Necrolysis

Acknowledgements

This report provides an overview of the two- and half-day stakeholder consultation workshop conducted with the aim of developing a standard reference case for health technology assessment of precision medicine. This collaborative event, held from 28th June to 30th June 2023, was organized by the Saw Swee Hock School of Public Health, National University of Singapore (NUS) and the Health Intervention and Technology Assessment Program (HITAP), Ministry of Public Health, Thailand, under the aegis of the Health System Research Institute (HSRI), hosted at hotel U Khao Yai, Pak Chong, Thailand.

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It is essential to note that the findings, interpretations, and conclusions presented in this report do not necessarily reflect the views of the funding or participating agencies.

Executive summary

The rapidly evolving healthcare landscape is being shaped by cutting-edge technologies such as big data analytics, digital advancements, and genomics, leading to the emergence of Precision Medicine (PM). National genomics programs worldwide are embracing the potential of PM, signaling an imminent integration into healthcare systems.

However, PM interventions have considerable costs, fueling an ongoing discourse on their economic value to patients, society, and governments. To rationalize resource allocation for Research and Development (R&D) and healthcare reimbursement, a comprehensive health economic framework, encompassing both 'early economic evaluation' and 'traditional economic evaluation,' is essential.

Ensuring the accuracy and consistency of economic evaluations is pivotal. Addressing methodological challenges requires the establishment of reference cases (RC) that provide standardized guidance for the planning, execution, reporting, and assessment of economic evaluations. Building on previous work by research teams from the National University of Singapore (NUS) and the Health Intervention and Technology Assessment Program (HITAP) that performed a systematic review of cost utility analyses as well a narrative review of methodological recommendations for conducting economic evaluations on PM a beta reference case for PM was developed (PM-RC).

In order to receive feedback on the PM-RC and gather knowledge of existing work by different research teams, a two and a half-day workshop was held from June 28th to 30th, 2023, in Khao Yai, Thailand, organized by HITAP in collaboration with NUS and with support from the Health Strategy and Research Institute (HSRI) and the Ministry of Public Health (MoPH), Thailand.

Attended by distinguished health economists and clinical experts in PM from Singapore and Thailand, this workshop served as a platform to gather valuable feedback on the RC development process and generate interest among Clinical Implementation Pilot (CIP) teams to pilot their projects in Thailand for testing implementation of developed RC.

This report offers a concise overview of the workshop's key activities, in-depth discussions, and significant outcomes from the stakeholder consultation. The insights received from diverse participant groups will be thoughtfully integrated into the evolving reference case. Additionally, the feasibility and relevance evaluation of each domain and sub-domain on the beta PM- RC by the participants, will act as a guide for refining the RC further. This report serves as a foundation for the revision and enhancement of the reference case for Precision Medicine. It is expected to be an impactful, standardized approach to economic evaluations, thereby ensuring the responsible advancement of PM in the dynamic healthcare landscape.

Introduction

Background

Precision Medicine (PM) is a tailored medical approach that stratifies patients based on the characterization of individuals' phenotypes and genotypes (molecular profiling, medical imaging and lifestyle data) to personalize intervention decisions. PM is a fast-growing medical approach and typically associated with high developmental and implementation costs. Health technology assessment (HTA) is a systematic and multidisciplinary process to inform the value for money and provides guidance on how health technologies can be used across different health systems. Within HTA, “economic evaluation” (EE) in the broader sense is often used to denote the range of economic considerations, such as budget impact, and distributional effects of interventions within the health system and across the population.

Rationale for the workshop

While general approaches to EE are certainly applicable to PM, it may be argued that PM represents a unique class of health interventions distinguished by its complexity, lack of evidence, and the rapid evolution of “omics” technology. To date, there is no consensus on the most appropriate methods of EE in this context. And the existing methodologies for these "cure-based" health technologies may not be applicable to PM due to the complex decision-making space, lack of clinical evidence, and ethical and equity issues. New guidelines hereby referred to as reference case (RC) are needed for PM evaluations on a case-by-case basis across jurisdictions.

This workshop builds upon the completed work from research team from Saw Swee Hock School of Public Health of the National University of Singapore (NUS), the Health Intervention and Technology Assessment Program (HITAP) of the Ministry of Public Health Thailand and Precision Health Research Singapore (PRECISE) that jointly performed a systematic review and meta-analysis of 275 cost utility analyses on PM published from 2011- 2021 as well a narrative review of methodological recommendations for conducting economic evaluation[1]. This work laid the foundation in developing a beta version of “Precision Medicine - Reference Case” (PM- RC).

[1] Chen, W., Wang, Y., Zemlyanska, Y., Butani, D., Wong, N. C. B., Virabhak, S., . . . Teerawattananon, Y. (2023). Evaluating the Value for Money of Precision Medicine from Early Cycle to Market Access: A Comprehensive Review of Approaches and Challenges. *Value in Health, 26*(9), 1425-1434. doi:https://doi.org/10.1016/j.jval.2023.05.001

Workshop Aim

The workshop is aimed to develop a standard reference case for health technology assessment of PM in Thailand**.** This work is been conducted as part of the project titled "Development of reference case for precision medicine and piloting its application in Thailand" funded by Health System Research Institute (HSRI), Thailand.

Workshop Objectives

This workshop aimed to bring together health economists, clinicians, and researchers, from Singapore and Thailand to:

1. Share knowledge, experiences and lessons learnt from the past and on-going economic evaluations of various PM applications.
2. Engage experts to develop a reference Case for PM-RC with a focus on relevance and feasibility.
3. Generate interest from the Clinical Implementation Pilot (CIP) teams in Singapore piloting their study for testing the implementing of RC in Thailand.

Workshop Structure

To realize these objectives, a two-and-a-half-day agenda was crafted. The key topics covered each day are provided below:

Day One:

The focus of the first day was to introduce participants and share knowledge, experiences and challenges gained from conducting economic evaluations of PM. Commencing with an overview of the workshop, the session then delved into the presentation of findings from a systematic review of 275 HTA studies that evaluated the value for money of PM technologies. These findings highlighted the heterogeneity in value for money across diverse application types, contexts, and conditions. Furthermore, the drivers contributing to value for money were elaborated upon. Subsequently, the spotlight shifted to five Clinical Implementation Pilot (CIP) teams, who presented their experiences and findings on health economic evaluations of different PM technologies. Structured presentations highlighted the challenges faced in both the clinical and economic aspects of their studies, particularly when compared to national guidelines like Singapore's ACE.

Day Two:

The second day began by sharing insights from Thailand's experiences and the challenges encountered while utilizing Thai HTA guidelines for PM technology studies. This was illustrated through two case studies conducted by research teams. Following this, the findings from a narrative review that outlined the methodological challenges in conducting economic evaluations on PM applications were

presented. Participants were then introduced to a beta-version of reference case (RC) for the economic evaluation of PM through a dynamic world café-style session. Here, participants rotated through various domains of the proposed reference case, contributing insights and offering input. The day continued with participants evaluating the relevance and feasibility of the draft RC within the context of their respective study settings. This phase involved group surveys based on team affiliations. Additionally, an introduction to Early HTA was given, addressing its challenges within the realm of PM technologies. The day concluded with an interactive session on the draft RC for Early EE of PM, during which participants discussed their understanding and application of the concept, and group surveys on the relevance and feasibility of the Early EE RC.

Day Three:

The final day commenced with sessions focusing on suggesting best practices and relevant use cases pertinent to the reference case. Participants were divided into groups, tasked with addressing questions such as enhancing the success of the RC, improving it to tackle challenges and dilemmas, enhancing its utilization as a tool, and identifying areas for improvement. Subsequently, a brainstorming exercise ensued, aimed at generating potential solutions and tools applicable to the reference case. Here, participants considered the possibility of borrowing tools from other areas of HTA, as well as exploring unique research opportunities within the domain of PM or its subdomains. The session culminated with the announcement of the selected CIP team's study to conduct the implementation pilot in Thailand. Participants were once again reminded of their forthcoming roles as co-authors of the finalized Reference Case.

Workshop Participants:

The workshop drew a diverse gathering of clinical and economic experts from both Singapore and Thailand. The attendees were grouped into three distinct categories:

a) Clinical Implementation Pilot (CIP) Team: At the forefront of the workshop were five CIP teams awarded by **PRECISE**. These teams operated across various domains including ***Breast Cancer, Hereditary & Familial Cancers, Familial Hypercholesterolemia, Primary Glomerular Diseases, and Pharmacogenomics***. The core objective of these CIP team is to embed the clinical application of genetic/genomic tests in diagnosing, managing, and treating specific patient cohorts and populations for distinct conditions or disease phenotypes. A total of 11 participants graced the event, with an equal representation of health economists and clinical experts coming together to contribute their expertise.

b) Thai Research Teams: Two research teams from Thailand showcased their study findings, centering around Pharmacogenomic testing, Exome sequencing, and Next Generation Sequencing. Their presentations outlined the potential limitations encountered while adapting the Thai HTA guidelines to their research studies. This segment saw a total of 6 participants, comprising four health economists and two clinical experts.

c) Individual Experts: Beyond the teams engrossed in the economic evaluation of PM technologies, the workshop welcomed individual experts who boasted extensive experience in the economic evaluation as well clinical experts with experience in the implementation of genomics in Thailand. This cohort consisted of six eminent experts who enriched the discourse with their invaluable insights and comprehensive understanding.

Detailed information regarding each group's composition can be found in Table 1 of the Annex 3.

Workshop Highlights

Mapping the value of Precision Medicine

Precision medicine is a medical approach separating people into groups to optimize efficiency or therapeutic benefits. Categorized based on application type, broadly two types of PM exist **a) Test guided PM and b) Therapeutic PM**. A large body of evidence suggests that the value for money of PM applications is concentrated in established technologies, disease domains, markets, which is mainly influenced by incremental effectiveness in favor of early intervention over treatment stratification at diseased stages. It takes time for PM in new innovations, new indications, and new markets to accumulate evidence to affirm its value of money. Moreover, current cost effectiveness analysis (CEA) of PM is prone to study manipulation and systematic bias. Thus, it is difficult to make an overall conclusion on PM's value for money across application types and disease areas. To enable meaningful comparisons for truly informed decision making, policy makers and stakeholders should conduct local studies, with appropriate consensus approaches to standardize the conduct and report of CEA of PM.

Key Challenges in Economic Evaluation of Precision Medicine research

The five CIP teams and two Thai research team were asked to present their findings by sharing the methodological challenges encountered while conducting their study. To ensure a comprehensive and balanced discussion of these challenges, the research teams were asked to present their findings around the clinical and economic aspects of methodology, as well as any additional concerns such as equity, ethics and adaptability that have arisen**.** A presentation template with pre-defined scope within the three domains was shared with participants in advance. A total of eighteen items were identified and the table 1 in annexure 3 1) summarises the challenges reported by each research team around all three clinical, economic, and additional aspects of their study. In the subsequent sections,

we delve into a more detailed exploration of these challenges and, where relevant, offer potential recommendations and solutions to address them effectively. Detail of each team is summarised is Table 2 Annexure 2.

1. **Defining the Target Population and Addressing Patient Heterogeneity**

One significant challenge lies in defining the target population and addressing patient heterogeneity. For example, in breast cancer research (CIP Team 1), identifying high-risk groups can be complex, as they don't entirely overlap with intermediate or low-risk groups. Additionally, genetic risk profiles vary among different ethnicities, such as Chinese, Indian, and Malay populations in Singapore, leading to questions about how to cluster susceptibility genes. Moreover, assumptions about patients' ages may not account for the pediatric population, which complicates the capture of quality-of-life data. It's also essential to avoid double-counting in cascade testing (CIP Team 4) and decide whether to test everyone or specific groups for pharmacogenomics testing (CIP Team 5). Furthermore, the rarity of certain conditions like Steven Jhonson Syndrome/ Toxic Epidermal Necrolysis (SJS/TEN) poses' challenges, making the study less representative of the total population (Thai Team).

2. **Setting the Intervention Scope and Addressing Clinical Decision Complexity**

Defining the scope of interventions and addressing clinical decision complexity is another critical area. For example, in breast cancer research (Team 1), determining risk thresholds can be challenging, as changing screening frequencies for high-risk individuals is often subject to policy regulation that's hard to modify. Additionally, considerations for disutility and intergenerational effects need to be made when promoting mammogram use over genetic testing. Similarly, in primary glomerular disease (PGD) (CIP Team 4), questions arise regarding the representativeness of cascade testing for genotype/phenotype in monogenic genetic diseases.

3. **Identifying an Appropriate Comparator (or Policy Choice)**

Selecting an appropriate comparator or policy choice can be a complex task, as seen in the Thai Team's research on exome sequencing and rapid next generation sequencing (rNGS). The feasibility of the study's comparator and the lack of availability of randomized-controlled trials are concerns that may require using expert elicitations to control confounding factors, although relying solely on expert opinion may not be entirely reliable.

4. **Measuring Disease-Specific Outcomes**

Measuring disease-specific outcomes poses significant challenges, especially when context-specific data is hard to obtain (CIP Team 2). In healthcare contexts like Singapore, gathering Singapore-specific data can be essential for accurate research findings.

5. **Measuring and Extrapolating Long-Term Clinical Outcomes**

Extrapolating long-term clinical outcomes is challenging, as the natural history and progression of chronic diseases can be complex, as seen in PGD research (CIP Team 4). Addressing these difficulties may require advanced modeling techniques.

6. **Identifying Counterfactual Evidence for Intervention Effectiveness**

Identifying counterfactual evidence for intervention effectiveness is a crucial aspect of healthcare research. Teams such as PGD (Team 4) use propensity score matching (PSM) models to estimate effects from electronic medical record data. In pharmacogenomics testing (CIP Team 5), it's easier to focus on adverse effects, but modeling dosing efficacy is a challenging task.

7. **Economic Aspects**

In healthcare economic modeling, categorizing risk groups without a golden standard reference (CIP Team 1) and modeling cascade testing complexity (CIP Team 2) can pose significant challenges. Furthermore, dealing with various health states, treatment effectiveness, quality-adjusted life years (QALYs), and costs in PGD research (CIP Team 4) adds complexity to economic assessments.

8. **Additional Issues:**

Beyond these core challenges, several additional factors must be considered. Equity concerns may arise, such as ensuring equitable access to healthcare (CIP Teams 1, 2) or addressing disparities in insurance reimbursements for genetic tests (CIP Team 2). Ethical considerations, including patient privacy and consent, must be carefully managed (CIP Team 2 & 3). The adaptability of research findings to other hospital settings and healthcare systems is also a key consideration (CIP Team 1 & 2). Implementation issues can be significant, including low screening attendance, limited availability of genetic experts, and challenges in referral systems (CIP Teams 1, 2, 3).

Additional challenges and potential solutions related to cascade testing (CT) were discussed during the plenary sessions.

Challenges for economic evaluation of Cascade Testing

Reluctance of Family Members: One significant challenge in cascade testing is the reluctance of family members to undergo genetic testing. This reluctance varies depending on the specific genetic condition, such as auto-recessive diseases.

Health Insurance Coverage: Concerns about health insurance coverage create barriers to testing. Some individuals fear that their testing may not be covered, especially in cases where they have already been diagnosed by a molecular test. Additionally, predictive testing may come with upfront costs.

Economic Challenge: The main economic challenge revolves around how to quantify and attach the extra value of expanded family member testing to the cascade testing model. While cascade testing is often cost-effective and offers value for money, the uptake can be challenging, particularly for diseases with no cure and low perceived value for cascade testing, like Huntington's disease.

Solutions Proposed for Low Uptake of Cascade Testing

Improved Communication: One suggested solution is for clinicians to better communicate test results to patients. This communication can help reduce the disutility associated with receiving potentially bad news through testing, which may impact an individual's productivity.

Quantifying Patient-Reported Outcomes: Another proposed solution involves quantifying patient-reported outcomes to determine the value of knowing one's genetic status. This approach considers not only those who test positive or negative but also individuals who decline to be tested.

Patient Education: Educating patients about the importance of genetic testing and ensuring sufficient coverage by health insurance can influence uptake positively.

Subgroup Analysis: Currently, cascade testing is primarily offered to first-degree relatives. Conducting subgroup analyses to determine the most appropriate family members to receive cascade testing may help improve uptake and the overall effectiveness of the testing strategy.

In summary, cascade testing faces challenges related to patient reluctance, health insurance coverage, and the economic value of expanded testing. Addressing these challenges may require improved communication, quantifying patient-reported outcomes, patient education, and refining the selection of family members eligible for cascade testing. These measures aim to enhance the uptake and effectiveness of cascade testing, particularly in cases where its value might not be immediately apparent.

Introduction to Precision Medicine - Reference Case (PM-RC)

As mentioned above the methodological challenges observed across all the stages of an evidence-based research:

Population- Defining target population, Patient heterogeneity, Evolving patient characteristics, expanding target population, stratified sub-groups

Intervention- Uncertain scope of intervention, complex test-treatment pathways, PM validity and reproducibility, complex decision space, Multiple evolving pathways, Incidental findings

Comparator- Appropriate comparator; “treat-all" and "test-and-treat" or “new treatment versus standard of care”.

Outcome- Dat gap, limited counter-factual evidence, inconsistent reporting, varying unit costs, defining clinical utility, Life Years and Quality adjusted life years, surrogate outcomes, long-term spillover effect.

Other challenges **for modelling** an EE for PM include constructing a model, using correct perspective, determining the timeframe benefit, choice of discount rate, accounting for life-long or intergenerational effect, collecting unit cost data, structural and decision uncertainty, reporting and interpretation of findings. In addition, challenges around **equitable access, adaptability** (generalizability of study) and **ethical implication** such as privacy persist in determining the appropriate methodology of an EE for PM study. The persistence of several methodological challenges highlights a need for development of standard framework recommendations for conducting and reporting economic evaluations on PM. A reference case provides insights for helping clinicians and policy makers to make informed choices in a consistent way.

To make it easier for the users to remember the eight key elements of the recommended practices, the PM-RC proposes the first letter of every word to create an acronym to read: **PICOTEAM** (Figure 1). The acronym stands for Population, Intervention, Comparator, Outcomes (Health outcomes & Cost), Timeframe, Equity and ethics, Adaptability and Modelling.

Detailed beta version of PM-RC is provided in Table 2 & 3 Annexure 3

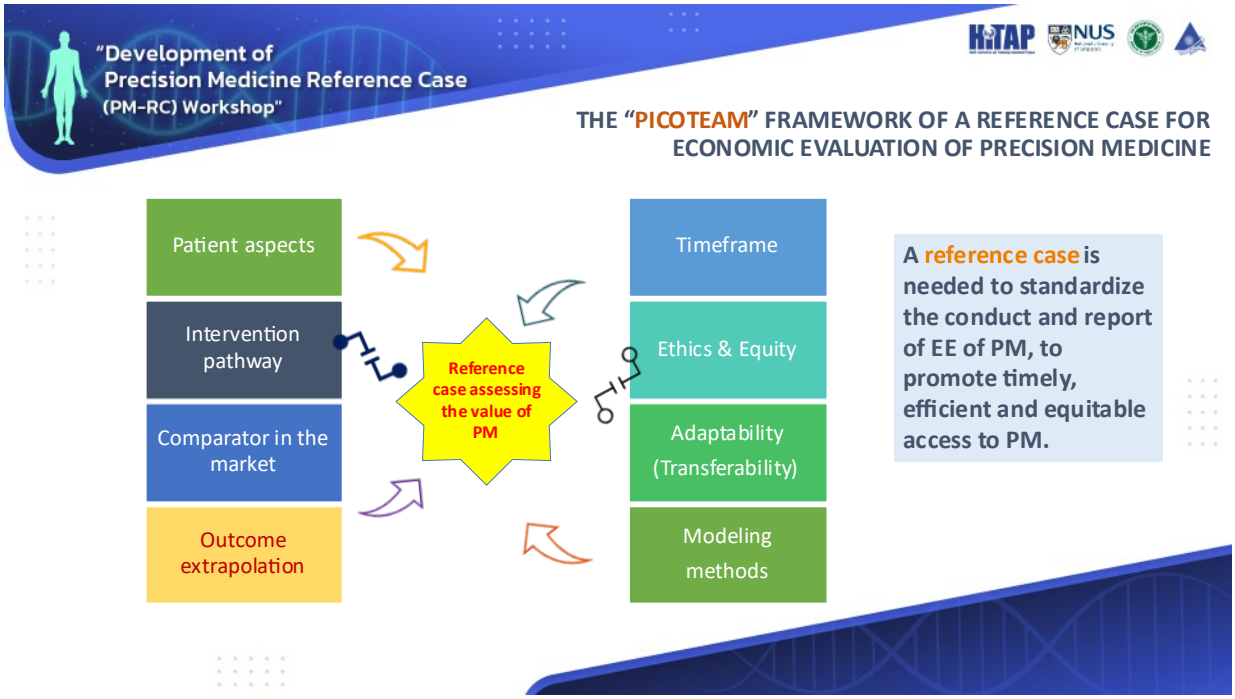


Figure 1Descriptive diagram of the PM-RC

Feedback on PM-RC for Traditional EE

The reference case was then tested for its clarity and understanding, a world café session was conducted to summarize the general feedback on the eight domains of PICOTEAM. Participants were divided into four groups randomly and asked to rotate around the four corners of the room. Each corner had a different domain from the beta reference case, and each group were asked to read and discuss the recommendation. Table 2 summarizes the feedback received on PM-RC for Traditional economic evaluation.

Table 2: Feedback on PM-RC for traditional RC

Term	Feedback
Population	• Clarify the choice of population and provide the rationale for population stratification. • Address the uncertainty of the target population, including re-classification. • Elaborate on the definition of "updating target population."
Intervention	• Clearly state the choice of interventions with rationale and link them to outcomes. • Provide guidance on defining objectives and rationale for PM. • Acknowledge that many PM scenarios involve multiple clinical applications and avoid over-specifying interventions. • Simplify and clarify complex statements related to clinical pathways and their assessment.

Term	Feedback
Comparator	• Offer information on comparator options (e.g., gene panel vs. exome/genome sequencing) and guidance for choosing fair comparators. • Clearly state the choice of comparators with rationale, ensuring they encompass the entire treatment pathway. • Provide guidance on defining the spectrum of variation in standard care.
Outcome	• Simplify and shorten the outcomes section for better understanding. • Define outcomes, including the methodology for data collection and analysis. • Ensure clarity of terminology and consider revisions or additional explanations/examples. • Separate costs from outcomes and consider a new name like "PIC**C**OTEAM" for clarity. • Rearrange recommendations on outcomes, starting with primary data collection. • Address the challenge of measuring emotional changes in PM. • Consider moving cascade testing to the outcomes section. • Define different types of PM (screening, diagnosis, prognostic, pharmacogenomic, therapeutic) before assessing outcomes. • Specific recommendation to this section are presented in Box 1 of Annexure 3.
Time horizon	• Explore modeling future benefits of cascade testing beyond the patient's lifetime. • Investigate the potential impact of genetic diseases on fertility rates. • Distinguish between program-only and program-plus-cascade testing. • Account for changing recommendations and guidelines over time. • Consider differential discounting for genetic components with varying price changes.
Equity	• Consider intergenerational effects on family members, employment, and insurance. • Emphasize prevention over treatment. • Replace the term "ethnicity" with "ancestry and heritage."
Adaptability	• Ensure recommendations consider different geographical regions and racial disparities in prevalence.
Modeling	• Tailor recommendations based on the type of PM and target populations. • Address the importance of cascade testing in the reference case and provide recommendations (e.g., separation or combination with other PM). • Include model scope and conceptualization in the RC. • Explain how to accurately model the disutility and utility of test results. • Consider dynamic uptake of PM over time in the model. • Explore the application of the RC to segregation testing. • Account for uncertainty in model performance (e.g., Area Under the Curve). • Justify health states in the model, considering validation. • Consider the use of patient-level state transition microsimulation models or discrete event simulation models when appropriate.

Term	Feedback
Overall comments	• Include clear definitions of both PM and EE terminology. • Incorporate more practical examples of PM applications. • Clarify the purpose of the RC (e.g., checklist or grading) and tailor it to different types of PM. • Seek insights from teams working on various forms of PM beyond diagnostics, such as gene therapy, to ensure broader applicability.

Following this activity, the participants were asked to rate the relevance and feasibility of each items from the eight domains. To accomplish this, each research team (comprising five CIP teams and two Thai research teams) completed the draft RC form, assigning rankings to relevance and feasibility based on their ongoing studies—thus, one team equated to one survey form. Expert individuals were solicited to complete the draft RC form based on their professional experience. The outcomes of this survey are set to undergo a separate analysis and results will be presented in form of manuscript.

Introduction to Early HTA & Feedback on PM-RC for Early HTA

Based on the health technology assessment (HTA) definition of the International Network of Agencies for Health Technology Assessment is “early assessment of medical devices” can be defined as the early examination of the medical, economic, social, and ethical implications of the medical device to determine the potential for incremental value in healthcare.

It includes all methods used to inform industry and other stakeholders about the potential value of new medical products in development, including methods to quantify and manage uncertainty.

Inform decisions on **early stage of product development, public investment in R&D, and features in new medical products or decisions on minimal clinical performance** to be able to compete with existing products.

Many decisions taken at the concept stage are **reversible** and will be reconsidered later before the product is brought to market.

Early-stage health economic evaluations differ from this, as they aim to support decisions on **allocation of the research and development (R&D) resources** from a business perspective in early product development stages.

Similar to challenges with traditional HTA of PM technologies, early HTA has also its own challenges. These includes, difficult to define target population, defining the comparator, scarce evidence, high uncertainty of test validity, expert elicitation & difficulty to measure downstream impact. Other challenges include exclusion of equity consideration in value of information analysis as well as adaptability which often focuses on the potential value but ignores the possibility to reach this value under real world practice. Hence, reference case that can address all these challenges.

The draft RC for Early EE was shared with participants, and they were asked to fill the information out similar to above. The outcomes of this survey are set to undergo a separate analysis.

Suggestion on good practice and use case example relevant to reference case

On the last day of the workshop, the participants were asked for suggestions on good practice that would help in advancing the overall development of the PM-RC. On the last day of the workshop, the participants were asked for suggestions on good practice that would help in advancing the overall development of the PM-RC. The findings of this are summarized in Table 3 below.

Table 3: Summary of suggestion on good practice and use case example relevant to reference case.

How to Improve RC	Suggestion on good practice
How to Make the Best Use of the RC	• Collaborate with journals to make the RC a mandatory checklist. • Ensure the RC is understandable for non-health economists (provide definitions/examples). • Identify channels to reach diverse audiences and stakeholders. • Generate patient decision aids. • Clearly communicate the benefits of the RC for improved health outcomes. • Consider introducing the RC in educational curricula. • Promote understanding and appreciation of the RC among the general population. • Explore international recognition for the RC. • Consider naming the RC project to make it more relevant (e.g., PANDAN).
How to improve the RC to address challenges and dilemma (e.g. good practice guidelines, use case etc.)	***Format and contents*** • Revise the RC to reduce jargon and provide detailed explanations of terminology, along with practical examples for each recommendation. • Consider creating a one-page summary of the RC tabulated by Precision Medicine domains to offer a quick overview. • Provide lists of appropriate methods and propose their usage for measuring outcomes. • Expand the RC's coverage of cascade testing. ***Development of the RC*** • Validate the RC with clinician groups, especially those focusing on prognosis and treatment pathways. • Involve a diverse range of stakeholders, including clinicians, geneticists, economists, and payers, in the development process. • Enhance the definition of "updating target population." • Use the RC for study planning and publish protocols, rather than using it solely as a report checklist. • Ensure continuous development of the RC as a "living document" with a flow chart for different types of Precision Medicines. • Consider translation into other languages, such as Thai. • Initiate editorial publications discussing the pros and cons of the RC in PM

Suggestions to Improve RC Tool Utilization	***Social media*** • Utilize social media platforms, such as Podcasts, YouTube, TikTok, and existing websites like HIPER/HITAP, to publicize the RC. • Incorporate patient narratives on social media platforms, potentially compiling them into short videos. ***Policy Advocacy Programme*** • Meetings with health economists. • Get endorsement from policymakers. ***Academic activities*** • Engage in academic activities, including providing more use case examples and organizing plenary sessions at international conferences. • Consider offering incentives to medical doctors to attend conferences. • Organize workshops and community working groups as a feasible alternative to modules. • Collaborate with journal editors to promote the RC. • Publicize the RC within genomics societies, oncology communities, and rare disease networks in faculties or hospitals. ***Other recommendations*** • Explore the possibility of providing financial incentives to encourage the use of the RC. • Simplify and enhance the RC's comprehensibility. • Provide translated versions of the RC. • Consider adopting a catchier acronym than "PICOTEAM." • Emphasize public and participant involvement, including patients in the RC's design. • Make the RC digitally accessible with features like color-coding and compulsory sections.
What's currently missing from the RC and how to make it flexible to adapt to future PM Evaluation	• Identify missing elements in the RC, such as recommendations on utility, elaboration of the modelling domain, and handling uncertainty. • Differentiate between minimum and optional requirements in the RC. • Offer recommendations for common challenges, including cascade testing, panel testing, and productivity loss. • Consider categorizing recommendations by types of PM (e.g., diagnosis and prognosis). • Address other types of PM, such as proteomic and omics approaches. • Enhance flexibility in the "Hierarchy of Evidence" within the RC.

	• Streamline cost-effectiveness recommendations for different types of PM. • Explore strategies to make the RC relevant to LMICs. • Develop the RC into a digital tool or website-based tool with customizable technology options. • Consider incorporating recommendations and tools for real-world data quality and analysis specific to PM. • Ensure future publications about the RC include discussions on limitations.

ACMG- American College of Medical Genetics and Genomics; ASHG- American Society of Human Genetics

Solutions and tools for future

Lastly, to capture the solutions and tools that could aid in improvement of this RC, the participants were asked to indicate solutions through an online mentimeter survey. These solutions aim to strengthen the evaluation and implementation of PM while leveraging tools and experiences from HTA and other relevant fields.

Table 4: Summary of solutions and tools for future improvement to reference case

Tools from Other HTA Areas	• REALISE - Real-world evidence framework. • CHEQUE - Criteria for Health Economic Quality Evaluation. • AdViSHE - Assessment of the Validation Status of Health Economic Decision Models. • SHEER - Spillovers in Health Economic Evaluation and Research, focusing on measuring spillover health effects. • GC0S24 - A specific tool or guideline. • ISPOR guideline for Real-World Data analysis. • IDSI RC guideline. • Expert elicitation guidelines. • Productivity guidelines.
Research Opportunities Unique to PM Domains or Sub-Domains	**Utility and disutility value** • Utility and disutility value quantification (e.g., negative testing for family mutations). • Examining the utility and disutility value of knowing genetic risk and its impact on behavior. **Cascade testing** • Cascade testing-focused research, including Cost Utility Analysis (CUA) and statistical methods. • Developing unbiased methods to count costs and impacts of cascade testing for monogenic screening. • Identifying generic health states unique to cascade testing. **HTA** • Investigating policymakers' attitudes and knowledge towards HTA in PM compared to other health technologies. • Early HTA considerations.

	General comments on PM • Streamlining Cost-Effectiveness Analysis (CEA) for similar PM applications. • Prioritization methods for PM interventions. • Distributional Cost-Effectiveness Analysis (DCEA) for PM. • Multicriteria Decision Analysis (MCDA) for prioritizing high-cost PM. • Addressing ethical concerns related to privacy and discrimination. • Statistical methods for patient simulation in rare genetic diseases. • Exploring newborn screening implications. • Identifying major risk factors contributing to declining genetic testing. • Addressing bias in AI targeting advertising and awareness. • Measuring spillover health and non-health effects from PM. • Capturing intergenerational benefits and productivity.

AI- Artificial Intelligence; CUA- Cost Utility Analysis; DCEA- Distributional cost effectiveness analysis

Outcomes of the PM-RC workshop

1. The immediate outcome of this workshop is a narrative summary of the feedback received on the beta version of PM-RC, which is presented in detail within this report. The subsequent step involves summarizing and analyzing the survey results related to relevance and feasibility, leading to the drafting of a revised PM-RC guided by insights from this consultative workshop.
2. Post this workshop, an expert **Core Working Group** has been established, primarily aimed at providing strategic advisory support and contributing to the ongoing refinement and development of the Precision Medicine Reference Case. Comprising representatives from the CIP team and individual experts specializing in the field of economic evaluations, this working group is expected to play a pivotal role in the continued enhancement of the PM-RC.
3. Another pivotal objective of this workshop was to garner interest from a CIP team for conducting a study in the Thai context while selecting the most suitable study based on the research question. After hearing from all the CIP team's presentations and consulting on applicability with Thai stakeholders, the decision was made to utilize the **FHCARE CIP** team's study as the testing ground for implementing the PM-RC in Thailand.

This study, led by A/Prof Wee Hwee Lin from NUS and A/Prof Tavintharan Subramaniam from the Department of Medicine at Khoo Teck Puat Hospital, Singapore, focuses on addressing challenges in case identification, cascade screening, genetic testing, and treatment within the context of Familial Hypercholesterolemia (FH). The study aims to tackle the prevalent issues of underdiagnosis and undertreatment among FH patients in Singapore by introducing interventions that span various stages, from enhancing case identification to maximizing cascade screening of First-Degree Relatives (FDRs) and adopting a registry-based approach to address treatment adherence and gaps.

Critical feedback to finalize the RC

The finalization of the PM-RC for economic evaluation across the Early and Market Access stages involved a comprehensive process of feedback collection and revision. Involving 24 survey respondents from five Singapore CIP teams, Thai PM research teams, and individual stakeholders, the relevance and feasibility of each RC recommendation item were evaluated using a Likert scale ranging from 1 (least) to 5 (most). Additionally, participants provided valuable input on the most critical recommendations and identified missing elements through free-text responses.

Considering the survey results and insights garnered during workshop discussions, several critical revisions were made to the RC. Notable modifications include the removal of therapeutic PM applications, as they differ fundamentally from genetic tests, and the customization of the RC to cater to various types of PM applications, such as screening tests, diagnostic tests, and pharmacogenomic tests. The recommendation for defining the target population was enhanced and tailored to specific PM types, while a two-step systematic approach was adopted for defining intervention pathways and comparators. Furthermore, the RC was refined by segregating the outcomes and costs domains and expanding recommendations for modeling practices, encompassing aspects like model perspective, structure, selection, validation, data extrapolation, and uncertainty analysis. Specific guidance on addressing ethics and equity concerns in PM economic evaluations was incorporated, providing detailed considerations and suitable evaluation methods.

In addition to these revisions, it was decided that a web-based tool would be developed to facilitate the utilization of the PM-RC, making it more accessible and user-friendly. The dissemination of the PM-RC will also be supplemented by presenting the work at academic conferences, including side meetings, to ensure that the broader academic community is informed about this valuable resource.

Future directions

Looking ahead, the research team plans to revise and update the RC based on the feedback received during the beta version evaluation. An expert Core working group has been established to provide advisory support during the revision process.

Following this, a pilot study, following the methodology of the FHCARE CIP team, will be conducted in Thailand to test the implementation of the revised RC. Finally, upon completion of the pilot study, the development of the PM-RC will be finalized, and the findings will be disseminated in the form of a manuscript. All workshop participants will be invited to co-author this manuscript, ensuring collaborative and comprehensive insights are incorporated into the final PM-RC.

Annexures

Annex 1: Agenda on development of reference case for precision medicine and piloting its application in Thailand.

Aim: To develop a standard reference case for health technology assessment of PM

Workshop Objectives:

This workshop aims to bring together health economists, clinicians, and researchers, from Singapore and Thailand:

1. To share experiences and lessons learnt from the past and on-going economic evaluations of PM
2. To collect inputs for the development of the Reference Case for PM (RC) focusing on relevance and feasibility
3. To gather information supporting publication of RC
    - Whether your countries HTA methods and process guidelines are sufficient and compatible with economic evaluation of PM
    - What are the barriers to using these guidelines?
4. To get interest from the Clinical Implementation Pilot (CIP) teams, in piloting a study for testing the implementation of RC in Thailand

Structure: Two- and half-day workshop.
Date: June 28-June 30, 2023
Venue: U Khao Yai, Pak Chong, Nakhon Ratchasima 30130

Target audience: We invite five CIP teams from Singapore working on PM technologies to participate in this workshop. In addition, there will be participation of health economists and clinicians working in PM research in Thailand. **Total participants that attended the workshop were thirty-one**.

Organizations:

Health Intervention and Technology Assessment Program (HITAP)
The Health Intervention and Technology Assessment Program is a semi-autonomous research unit under Thailand's Ministry of Public Health. HITAP is renowned for its expertise in HTA that generates evidence to define the benefits package for Thailand's Universal Coverage Scheme, the National List of Essential Medicines, and the National List of Essential Vaccines. In addition, HITAP has a diverse set of skills in the sphere of health systems research and collaborates with partners globally to promote the use of evidence in healthcare decision-making. It has conducted economic evaluations of health technologies such as vaccines, drugs, and devices. As part of its international work, HITAP has supported the development of HTA in countries in Asia and Africa. HITAP has also developed resources for HTA researchers, particularly in low-and-middle income countries and reference case for conducting economic evaluation.

Contact Person:

1. Dr. Yot Teerawatanon, a senior researcher at HITAP
   Contact- yot.t@hitap.net

2. Dr. Dimple Butani, Project Associate, HITAP
   Contact- dimple.b@hitap.net

Saw Swee Hock School of Public Health, National University of Singapore (SSHSPH NUS)

The Saw Swee Hock School of Public Health at the National University of Singapore (SSHSPH NUS) is at the forefront of public health knowledge discovery and practice in Asia. SSHSPH NUS aims to continually foster healthier communities in Singapore and the region, and impact public health programmes and policies through translational cross-disciplinary research work on cohort studies and life course epidemiology, infectious disease research, health technology assessments, health promotion, workplace safety and health, health systems evaluation and health services research. SSHSPH has been co-hosting the Vaccinology for Clinical and Public Health Practice course since 2013.

Contact Person

1. Dr. Wenjia Chen, Assistant Professor, SSHSPH NUS
   Contact- wenjiach@nus.edu.sg

Workshop Day 1, 28th June 2023

Objective:

1) Introductions and sharing experiences on lessons learnt from conducting economic evaluations of PM.

Time	Duration	Session Title	Responsible person
9:00 - 9:30	30 min	Arrival and registration of participants	Organizing team
9:30 – 9:40	10 min	Welcome	Dimple Butani
9:40 -10:10	30 min	Workshop objectives and overview	Dr. Wenjia Chen
10:10 – 10:50	40 min (20+20)	Presentation from 1st CIP team Breast Cancer Screening CIP team Discussion – moderated by another CIP team	**Presenter:** Dr. Li Jingmei & Asst Prof Wang Yi **Moderator:** Dr. Lou Jing
10:50- 11:10	20 min	Coffee Break	
11:10-11:50	40 min (20 + 20)	2nd team Improving access for clinical hereditary cancer genetic testing in Singapore ("HC") Discussion – moderated by another CIP team	**Presenter:** A/Prof Joanne Ngeow & Dr. Sara Tasnim **Moderator:** Prof Wee Hwee Lin
11:50-12:10	20 min	Plenary discussion 1st & 2nd team	**Moderator:** Prof. Alec Mortan
12:10-1:10	60 min	Lunch	
1:15- 1:55	40 min (20 + 20)	Presentation from 3rd team Familial Hypercholesterolemia (FHCARE) Discussion – moderated by another CIP team	**Presenter:** Dr. Lou Jing & Dr. Sharon Pek Ling **Moderator:** Asst Prof Wang Yi
2:00-2:40	40 min (20 + 20)	Presentation from 4th team NGS Primary Glomerular Diseases in Singapore ("PGD") Discussion – moderated by another CIP team	**Presenter:** A/Prof Ng Kar Hui & Dr. Naline Gandhi **Moderator:** A/Prof Joanne Ngeow
2:40- 2:50	15 min	Coffee break	
2:50- 3:30	40 min (20 + 20)	Presentation from 5th team Pharmacogenomic testing (PGx) Discussion – moderated by other CIP team	**Presenter:** Prof Wee Hwee Lin & Jamaica Briones **Moderator:** Dr. Naline Gandhi
3:30-3:55	25 min	Plenary discussion 3rd, 4th, & 5th team	**Moderator** - Prof. Vorasuk Shotelersuk
3:55-4:00	5 min	Instruction and Close	Dimple Butani
20:00 – 22:00	120 min	De-brief	Organizing team

Workshop Day 2, 29th June 2023

Objective:

1. To inform the CIP teams about development of reference case
2. Map the challenges form the case studies (Day1) and fit into our narrative reference case.
3. Collect inputs on proposed reference case- Relevance and Feasibility

Time	Duration	Agenda	Description	Responsible Person	Note taking
9:00 – 9:15	15 min	Welcome & Recap	• Recap from Day 1 • Introducing PRECISE Singapore funded SLR projects & our progress & Reference case	Dimple Butani	
9:15 – 10:05	25 mins 20 mins	Thai Research teams Discussion	• Structured presentation • Lessons learned from Thailand in using generic version of HTA guidelines to guide PM evaluations for public reimbursement • Moderated discussion	**Presenter**- Waranya Rattanavipapong, Thamonwan Dulsamphan, Parntip Juntama & Chotika Suwanpanich **Moderator**- Dr. Wanrudee Isaranuwatchai	**DB, YR, WC, LL**
10:05 – 10:10	5 min	Wenjia introduce RC	• Methodological challenges • Reference Case	**Presenter**- Dr. Wenjia Chen	**SP, YR**
10:10-11:10	60 mins	World Café Interactive session – Traditional HTA	You are divided to move across the four corners (cities) Each corner will have a different "Domain" from the Beta Reference case. You will read and discuss the recommendation from each domain (15 minutes per round) Clarify with your facilitator if any doubts and engage in active participation. Rotate- At the end of 15 minutes, you rotate to next corner and repeat the discussion but for different domain.	Facilitator- PIC- Dr. Yot & Dr. Pritaporn Kingkaew O- Wenjia Chen & Waranya Rattanavipapong TEA – Dimple Butani & Dr. Wanrudee Isaranuwatchai M – Alec Morton & Wang Yi *PI- Population, Intervention CO- Comparator, Outcome TEA- Time, Equity and Adaptability M- Modelling Issue	**YR, LL**
11:10-11:20	10 mins	Coffee Break			
11:20 – 12:00	40 mins	Reflect and Rank	Based on discussion from the morning session, please fill out the RC Beta version		
12:00-1:00	1 hr	Lunch			
1:10-1:30	20 min	Introduction to Early HTA	• What is Early HTA • Different challenges for Early vs Conventional HTA for PM	Dr. Yot Teerawattananon & Dr. Wang Yi	**YR, SP**

1:30-1:45	15 min	Present Early HTA Methodological Challenges	• PICO-TEAM (Challenges & reference case)	Dr. Wenjia Chen	**YR, SP**
1:45-2:45	1 hr	Interactive session on Early HTA	Open Ended – • Are you involved in any early-stage development of PM? • Experience on conducting early HTA. • Do you think Early HTA would be helpful to PM to the domain of your project? • Do you think our RC will help with the early HTA of the domain of your project – Why/Why not?	**Presenter**- Dr. Wang Yi **Moderator**- Yah Ru	**WR, YR, SP,BH**
2:45-3:00	15 min	Coffee Break			
3:00-3:30	30 min	Discussion on future plans	• Summarise the reference case based on their input • Announce and invite to be co-authors • Information on Pilot case study	Dr. Wenjia Chen & Dr. Yot Teerawattananon	**DB, SP**
3:30-3:45	15 mins	Closing	Conclude and Close	Dr. Jate Ratanachina	
20:00-21:00	60 min	De-brief	Core team to summarize the exercise on relevance and feasibility	Organizing team	

Note takers - DB- Dimple Butani, YR- Yah Ru, LL- Laura Lim, WC- Wenjia Chen, SP- Sakdichod Petsom, PK- Pritaporn Kingkaew, WR- Waranya Rattanavipapong, BH- Brendon Zhou Hui

World Café format

World Café	Participant Name	Facilitator	Co-Facilitator
City 1 (PI)	Li Jingmei, Peh Joo Ho, Naline Gandhi, Ng Kar Hui, Janewit Wongboonsin	Yot Teerawattananon	Pritaporn Kingkaew
City 2 (CO)	Joanne Ngeow, Sara Tasnim, Namfon Sribundit, Chotika Suwanpanich, Parntip Juntama	Wenjia Chen	Waranya Rattanavipapong
City3 (TEA)	Lou Jing, Sharon Pek, Thamonwan, Nattiya Kapol, Jate Ratanachina	Dimple, Wanrudee Isaranuwatchai	Laura Lim
City 4 (M)	Wee Hwee Lin, Jamaica Briones, Vorasuk Shotelersuk, Brendon Zhou Huijun, Bhoom Suktitipat	Alec Morton & Wang Yi	Yah Ru

Workshop Day 3, 30th June

Objective:

1. Discuss on solutions and tools
2. Future plan
3. registering expression of interest of CIP team to pilot their case study for implementing PM-RC in Thailand

Time	Duration	Agenda	Responsible Person
9:00-9:30	30 mins	Welcome & Recap- Day 2	Yah Ru
9:30- 10:30	60 min	Suggestion on good practice and use case examples relevant to the reference case	Dr. Wenjia Chen
10:30-10:45	15 min	Coffee break	
10:45-11:15	30 min	Brainstorm on solutions and tools relevant to the reference case	Prof Alec Mortan
11:20-11:30	10 min	Future plan	Dr. Wenjia Chen
11:30-11:40	10 min	Closing remark	Dr. Yot Teerawattananon
11:40-11:50	10 min	Feedback and survey	Yah Ru
11:50-12:00	10 min	Conclusion & Travel instruction	Dimple Butani
13:00-14:00	60 min	Debrief AAR	

Annex 2: List of Participants

No.	First Name	Last Name	Organization	Country
1	Li	Jingmei	Genome Institute of Singapore	Singapore
2	Wang	Yi	Saw Swee Hock School of Public Health	Singapore
3	Lou	Jing	Saw Swee Hock School of Public Health	Singapore
4	Sharon	Pek Ling	Khoo Teck Puat Hospital	Singapore
5	Ng	Kar Hui	National University of Singapore	Singapore
6	Naline	Gandhi	Duke - National University Singapore Medical School	Singapore
7	Wee	Hwee Lin	Saw Swee Hock School of Public Health	Singapore
8	Jamaica	Briones	Saw Swee Hock School of Public Health	Singapore
9	Joanne	Ngeow	Lee Kong Chian School of Medicine	Singapore
10	Sara	Tasnim	Nanyang Technoloical University	Singapore
11	Alec	Mortan	National University of Singapore	Singapore
12	Peh	Joo Ho	Genome Institute of Singapore	Singapore
13	Brendon	Zhou Huijun	Precision Health Research	Singapore
14	Wenjia	Chen	Saw Swee Hock School of Public Health	Singapore
15	Laura	Lim	Saw Swee Hock School of Public Health	Singapore
16	Yah Ru	Juang	Saw Swee Hock School of Public Health	Singapore
17	Yot	Teerawattanon	Health Intervention and Technology Assessment Program	Thailand
18	Wanrudee	Isaranuwatchai	Health Intervention and Technology Assessment Program	Thailand
19	Pritaporn	Kingkaew	Health Intervention and Technology Assessment Program	Thailand
20	Waranya	Rattanavipapong	Health Intervention and Technology Assessment Program	Thailand
21	Thamonwan	Dulsamphan	Health Intervention and Technology Assessment Program	Thailand
22	Parntip	Juntama	Health Intervention and Technology Assessment Program	Thailand
23	Chotika	Suwanpanich	Health Intervention and Technology Assessment Program	Thailand
24	Sakdichod	Petsom	Health Intervention and Technology Assessment Program	Thailand
25	Dimple	Butani	Health Intervention and Technology Assessment Program	Thailand
26	Nattiya	Kapol	Faculty of Pharmacy, Silpakorn University	Thailand
27	Namfon	Sribundit	Faculty of Pharmacy, Silpakorn University	Thailand
28	Vorasuk	Shotelersuk	Faculty of Medicine, Chulalongkorn University	Thailand
29	Wongboonsin	Janewit	Brigham and Women's Hospital, Harvard University	Thailand
30	Jate	Ratanachina	Faculty of Medicine, Chulalongkorn University	Thailand
31	Bhoom	Suktitipat	Faculty of Medicine, Siriraj Hospital	Thailand
32	Jidapa	Planuson	Health Intervention and Technology Assessment Program	Thailand
33	Kanokporn	Srivarom	Health Intervention and Technology Assessment Program	Thailand
34	Chotirat	Wongseejan	Health Intervention and Technology Assessment Program	Thailand

Table 2: Categorization of Participants into Three Groups, Along with Team Name, Organization, and Research Study Details

S.No.	Team	Participant Name	Age	Position	Organization	Country
CIP101	***Familial Hypercholesterolemia Cross-cluster program (FHCARE)***	Lou Jing	32	Senior research fellow	SSHSPH, NUS	Singapore
CIP102		Sharon Pek	41	Principle research officer	Khoo Teck Puot Hospital	Singapore
CIP201	***Primary Glomerular Disease (PGD)***	Ng Kar Hui	40	Assoc professor	NUS	Singapore
CIP202		Gandl Naline	35	Research fellow	Duke-NUS	Singapore
CIP301	***Hereditary & Familial Cancers (HC)***	Sara Tasnim	30	PhD student	NTU	Singapore
CIP302		Joanne Ngeow	47	Assoc professor	NTU	Singapore
CIP401	***BREAst Screening Tailored for HEr (BREATHE)***	Ho Peh Joo	33	Research Associate	Genome Institute of Singapore	Singapore
CIP402		Wang Yi	33	Assoc professor	NUS	Singapore
CIP403		Li Jingmei	40	group leader	Genome Institute of Singapore	Singapore
CIP501	***Pre-emptive Pharmacogenomic Testing (PGx)***	Wee Hwee Lin	44	A/P	NUS	Singapore
CIP502		Jamaica Briones	32	Research Associate	NUS-HIPER	Singapore
TH101	***Rapid Next Generation Sequencing (rNGS) in critically ill patient with unknown etiology***	Namfon Sribundit	51	Associate Professor	Faculty of Pharmacy, Silpakorn University	Thailand
TH102		Nattiya Kapol	52	Associate Professor	Faculty of Pharmacy, Silpakorn University	Thailand
TH201	***Exome sequencing for infantile intractable epilepticus in Thailand***	Thamonwan Dulsamphan	35	Health economist	HITAP	Thailand
TH202		Parntip Juntama	31	Health Economist	HITAP	Thailand

TH203		Chotika Suwanpanich	25	Health Economist	HITAP	Thailand
IND1	***Individual Expert***	Waranya Rattanavipapong	39	Researcher	HITAP	Thailand
IND2	***Individual Expert***	Janewit Wongboonsin		Rel genetics	Harvard University, Siriraj Hospital	Thailand
IND3	***Individual Expert***	Bhoom Suktitipat	43	Assistant professor	Mahidol University	Thailand
IND4	***Individual Expert***	Vorasuk Shotelersuk	54		Faculty of Medicine, Chula	Thailand
IND5	***Individual Expert***	Jate Ratanachina	33	Lecturer, Doctor	Faculty of Medicine, Chula	Thailand
IND6	***Individual Expert***	Wanrudee Isaranuwatchai		Researcher, Health Economist	HITAP	Thailand
IND7	***Individual Expert***	Pritaporn Kingkaew	39	Head of research unit	HITAP	Thailand
IND8	***Individual Expert***	Alec Morton	49	Professor, Health Economist	NUS	Singapore
IND9	***Individual Expert***	Zhou Huijun	47	Senior health economist	Precision Health Research	Singapore

NUS- National University of Singapore, HITAP- Health Intervention and Technology Assessment Program, SSHSPH- Saw Swee Hock School of Public Health

Annex 3: Analysis Supplement

Table 1: Challenges Reported by CIP and Thai Research Teams in Conducting Economic Evaluation

Clinical Aspects
1. Defining the target population and addressing patient heterogeneity • [TEAM 1 Breast Cancer] The high-risk group does not entirely overlap between intermediate-risk group and low-risk group (difficult to identify exact proportion and relative/absolute risk in the 3 groups) • [TEAM 2 HC] Prevalence of genetic risk profile varies across Singaporean ethnicities (BRCA1/2 PALB2, MLH1 for Chinese/Indian/Malay populations); Numerous breast cancer susceptibility genes apart from single gene BRCA1 and BRCA2 – how can we group/cluster susceptible genes together • [TEAM 3 FHCARE] Assumption that all patients are 35 years of age, paediatric popularion is ignored (however hard to capture QoL) • [TEAM 4 PGD] Double counting of cascade testing • [TEAM 5 PGx testing] Consideration of whether to test everyone or just specific groups (e.g., those age >40) • [THAI TEAM] Rarity of SJS/TEN: Small/not representative of total population **2. Setting the intervention scope and addressing the complexity of the clinical decision space** • [TEAM 1 Breast Cancer] Defining risk threshold to maximize clinical capacity; hard to change screening frequencies for high risk individuals (policy regulation hard to change); disutility and intergenerational effect consideration (aggressive encouragement of using mammogram may increase mammogram use but not genetic test results) • [TEAM 4 PGD] How far cascade testing is representative for genotype/phenotype for monogenic GD **3. Identifying an appropriate comparator (or policy choice)** • [THAI TEAM Exome Sequenceing] Comparator and the feasibility of the study not clear • [THAI TEAM rNGS] Lack of availability of randomized-controlled trial => Used expert elicitations to control confounding factors (however, expert opinion may not be entirely reliable) **4. Measuring disease-specific outcomes** • [TEAM 2 HC] Hard to obtain Singapore-specific data **5. Measuring and extrapolating long-term clinical outcomes** • [TEAM 4 PGD] Difficulties in measuring long-term clinical outcomes due to natural history/progression of chronic kidney disease **6. Identifying counterfactual evidence for intervention effectiveness** • [TEAM 4 PGD] PSM model to estimate effects from electronic medical record data • [TEAM 5 PGx testing] It is easier to focus on adverse effects but very difficult to model dosing efficacy of PGx test

Economic Aspects

7. **Defining the use case and constructing the economic model**
    - [TEAM 1 Breast Cancer] Hard to categorize risk groups (no golden standard)
    - [TEAM 2 HC] Hard to define use case when newly diagnosed patients have several different types of cancer and relatives; Complexity of modelling cascade testing or pathways and development of complex model may lead to cost-ineffective conclusion
    - [TEAM 4 PGD] Classification of health states with different natural history, treatment effectiveness, QALYS, and costs

8. **Determining the timeframe of benefit**
    - [TEAM 3 FHCARE] 35 years old might be late for intervention

9. **Collecting and estimating costs**
    - [TEAM 1 Breast Cancer] Difficulty in estimating the national-level cost (economies of scale and scope) based on this small pilot study
    - [TEAM 2 HC] Determining test cost (whether a single gene test or panel test which is discouraged)
    - [TEAM 4 PGD] Downstream costs of handling new variants (e.g., cost of storing data for long-term) and additional benefits in other areas; How to evaluate PM in terms of the one-shot-whole-genome information?
    - [TEAM 5 PGx testing] NGS is not appropriate, for cost, it has to be genome cost

10. **Collecting and estimating utility**
    - [TEAM 1 Breast Cancer] Data on long-term health gain is not included in this short-term project (2 years) and how to capture the health gain that is out of context of the intervention
    - [TEAM 4 PGD] Challenge for economists to translate the moods of patients into a value
    - [THAI TEAM rNGS] EQ-5D-5L can't measure mobility dimension in pediatrics

11. **Selecting appropriate analysis methods, including uncertainty analysis**

12. **Conducting a budget impact analysis, if relevant**
    - [TEAM 1 Breast Cancer] Difficulty of the budget impact– budget and capacity constraints before reaching steady state

13. **Reporting and interpreting findings**
    - [TEAM 1 Breast Cancer] The appropriateness of reporting method and how to accurately report results from thousands of scenarios
    - [TEAM 5 PGx testing] Too many parameters from a panel test make the factors not prominent (alternatives are all generic)

14. **Usefulness of the ACE's guidelines in guiding your evaluation**
    - [TEAM 1 Breast Cancer] Screening not under ACE
    - [TEAM 2 HC] Productivity not under ACE

Additional Issues
15. Equity (e.g., equitable access to healthcare) • [TEAM 1 Breast Cancer] Consideration of free PRS testing and subsidy of mammogram cost and clinical consultation • [TEAM 2 HC] Only the rich will have access to genetic testing • [TEAM 3 FHCARE] Newer medications are not fully subsidized (injectables – PCSK9 inhibitors) **16. Ethics (e.g., patient's privacy)** • [TEAM 2 HC] Insurance concern from patients – different reimbursement across test (Breast Cancer Gene (BRCA) is preferred over lynch) • [TEAM 3 FHCARE] PDPA Act affects ability to contact family members directly **17. Adaptability (e.g., study generalizability for other hospital settings)** **18. Implementation issues (e.g., healthcare system readiness)** • [TEAM 1 Breast Cancer] Low screening attendance ~40% • [TEAM 2 HC] Limited number of genetic experts/ physicians specialized in genetic medicine in Singapore; Capacity for setting up genetic testing is not widely distributed across all hospitals; Referral system can be barrier as patients need to go through polyclinics before actual cascade testing • [TEAM 3 FHCARE] Requires specialists and practitioners to be trained; require readiness of primary care to receive families with FHCARE, challenges in cascade testing (referral process), insurance companies do not understand the importance of these tests

HC- Hereditary Cancer, FHCARE- Familial Hypercholesterolemia, PGD- Primary Glomerular Diseases, and PGx- Pharmacogenomics; rNGS- Next Generation Sequencing; SJS/TEN- Steven Jhonson Syndrome/ Toxic Epidermal Necrolysis.

Beta PM-RC for Traditional Economic Evaluation

Adobe Acrobat Document

Beta PM-RC for Early Economic Evaluation

Adobe Acrobat Document

Box 1 Recommendation on Outcome component of PICCOTEAM RC

- **Recommendation 1:** Follow established disease models to identify disease-specific health outcomes, in particular harmful outcomes and social values, to justify the choice of outcomes)
    - "Follow established disease models" should be renamed.
    - Some argue that PM model should incorporate a change in clinical/treatment management after the test result rather than disease model. For example, pharmacogenomics guided personalization of warfarin.
    - Sometimes researcher has not yet known the diseases so they cannot identify the disease-specific health outcomes.

- **Recommendation 2:** Follow guidelines and hierarchy of evidence on acceptable extrapolation of treatment effect.
    - "A hierarchy of evidence is not clear. The source of the outcome should be stratified. Suggestion for the revision is "Extrapolation" or "Extract data".

- **Recommendation 3:** Use appropriate parametrisation to account for long-term survival due to novel therapies.
    - Should be revised and add more example.

- **Recommendation 4:** Impact on labour force participation, social value (including intergenerational impact) should be included where feasible or discussed.
    - The wording labour force participation should be changed to "Productivity" or "Human capital".
    - There is an argument not to include the labour force participation because it may be double counting with the life years gained.
    - Many participants think that labour force participation is not easily measured.
    - The definition/example of social value should be explained.
    - The social value should be moved to the Ethic domain.

- **Recommendation 5:** Evidence that the technology improves the surrogate and the final outcome in several clinical trials

- **Recommendation 6:** Expand the scope of direct medical costs to cover costs of patient recruitment
    - Give more detail of scope of the costs on what to include in EE or BIA.

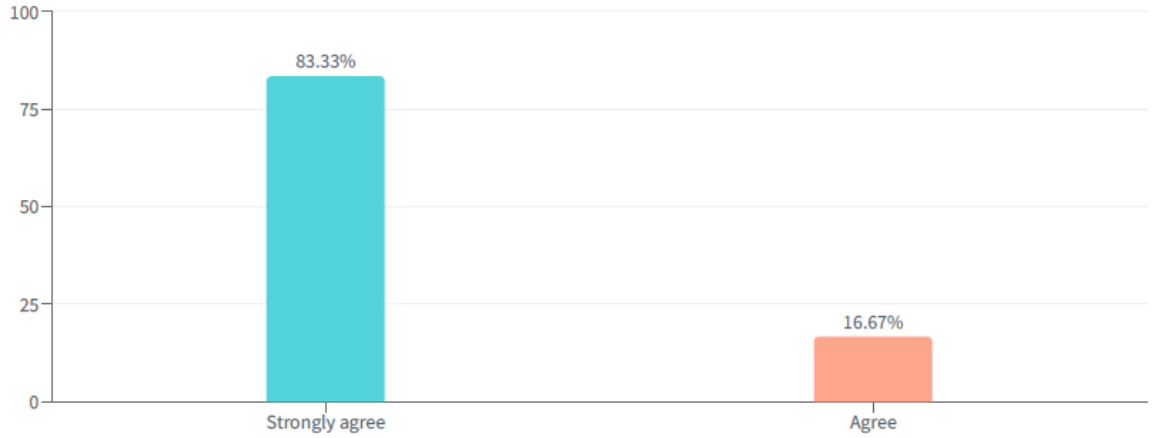
- **Recommendation 7:** "Consider costs associated with increased morbidity/mortality from time lags e.g., between tested vs treated".

Annex 4: Participant feedback

The overall feedback of workshop was received positively from the participants. We greatly appreciated the willingness of delegates to provide workshop feedback, crucial for enhancing future engagements. The anonymous feedback tool *Survey Sparrow* was employed to obtain rich and accurate insights into the perspectives and opinions of participants on aspects such as content, format, and overall satisfaction. The following section presents a concise summary of this invaluable feedback combining open-ended and quantitative responses.

Workshop Objective

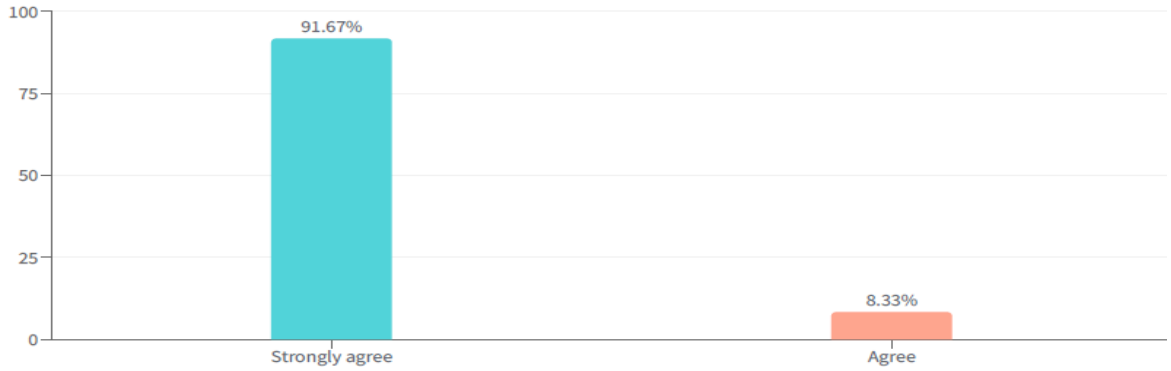
In response to question about meeting the overall objective of the workshop, ten out of 12 participants strongly agreed that the workshop met its objective and two agreed that it met its overall objective.



ANSWER CHOICES	RESPONSES	RESPONSE PERCENTAGE
Strongly agree	10	83.33 %
Agree	2	16.67 %

Workshop Content

The workshop content was liked by many, and most participants agreed that it added to what they already knew. When talking about the session that interested them the most, the World Café discussions on developing and improving RC were the top choice. After that, the debates at the end of each session and the talks about future plans were also popular. People also really liked the session where the Thai research team presented their findings.



ANSWER CHOICES	RESPONSES	RESPONSE PERCENTAGE
Strongly agree	11	91.67 %
Agree	1	8.33 %

Other reflections

Further thoughts were shared regarding the workshop. Some participants suggested that more time should be allocated for the discussion and World Café session. They also proposed the idea of incorporating a hybrid format to allow more experts to participate and recommended involving a greater number of genomic experts. Additionally, it was suggested that supplementary reading materials be provided in advance.

One participant raised an important point about the reference case. They noted that certain terminology was used interchangeably for both precision medicine and health economics, which led to varying interpretations among clinicians and health economics experts.

Technical glitches such as microphone and WiFi disruptions were noted by a few. However, despite these challenges, the workshop was generally deemed effective in conveying its message. There were also requests for the forthcoming steps and outcomes to be made accessible.

Annex 4: After Action Review (AAR)

After the conclusion of the workshop, an After Action Review (AAR) survey was dispatched to the organizing team, encompassing four key aspects: initial expectations, actual occurrences, successful elements, and potential improvements for future workshops. The collective reflection of the team revealed unanimous agreement regarding the workshop's purpose, centered on gathering feedback for the proposed reference case development and exchanging experiences and challenges in economic PM evaluation. The envisioned outcome aimed at refining the reference case and fostering collaboration with a research team from Singapore to implement a pilot study.

Regarding what truly transpired during the workshop, it was observed that the event achieved its objectives efficiently. The research team successfully elicited valuable feedback from all participants

to enhance the reference case. The active engagement of participants, investing wholeheartedly in the enriching discussions, significantly contributed to this outcome.

When addressing the factors that contributed to the workshop's success and its smooth proceedings, the team attributed it largely to meticulous preparation. Comprehensive arrangements, encompassing a detailed agenda, logistics, accommodation, and participant comfort, provided a conducive and secure environment for open engagement. The team's fexibility in accommodating last-minute changes played a pivotal role. Interactive sessions such as the world café format facilitated more participant involvement, enhancing the overall effectiveness of subsequent exercises.

For future workshops of a similar nature, the team proposed some improvements. Acknowledging the diverse backgrounds of participants, the suggestion was made to offer clearer presentation instructions, potentially through PowerPoint templates with explicit guidelines. It was recognized that certain teams did not contribute sufficient information relevant to RC development, possibly due to differing participant backgrounds, leading to challenges in effectively collating and analyzing inputs and feedback.

Lastly, the logistical team recommended strengthening on site support in terms of more personnel, to ensure smooth execution and swift adaptation to any unexpected changes, ensuring future such workshops go without any hinderance.

Annex 6: Snapshots from PM-RC workshop

Figure 1: Clinical Implementation Pilot (CIP) teams during their presentations


Development of
Precision Medicine Reference Case
(PM-RC) Workshop
Acknowledgements


"Development of Precision Medicine Reference Case (PM-RC) Workshop"
Genetic Testing For Kidney Diseases
Renal Alliance for Precision Diagnosis in Singapore
RAPIDS
Health and Economic Impact of Next Generation Sequencing in Primary Glomerular Diseases in Singapore
Ng Kar Hui
Senior Consultant
Paediatric Nephrologist
National University Hospital / NUS
David Matchar / Naline
Professor / Health Economist
Duke-NUS

Figure 2: Plenary discussions

Figure 3: Thai research team presentations


Methodological challenges and recommendations for RC
On cost

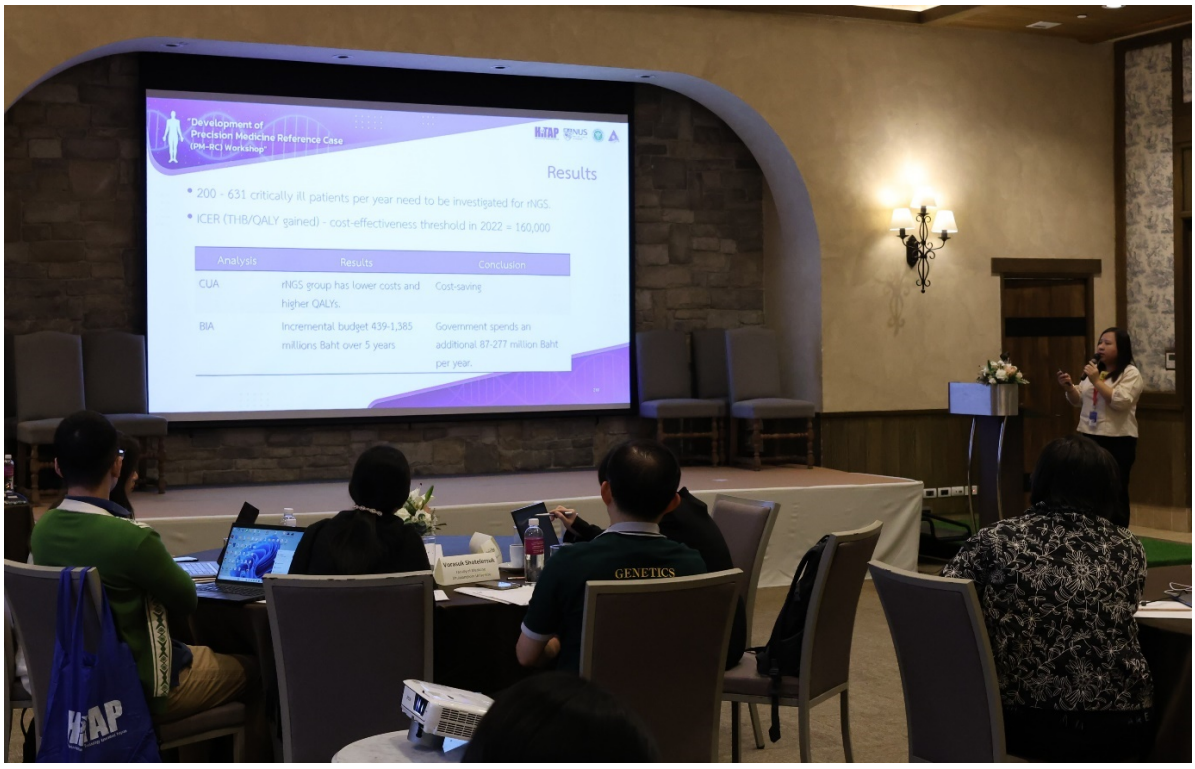
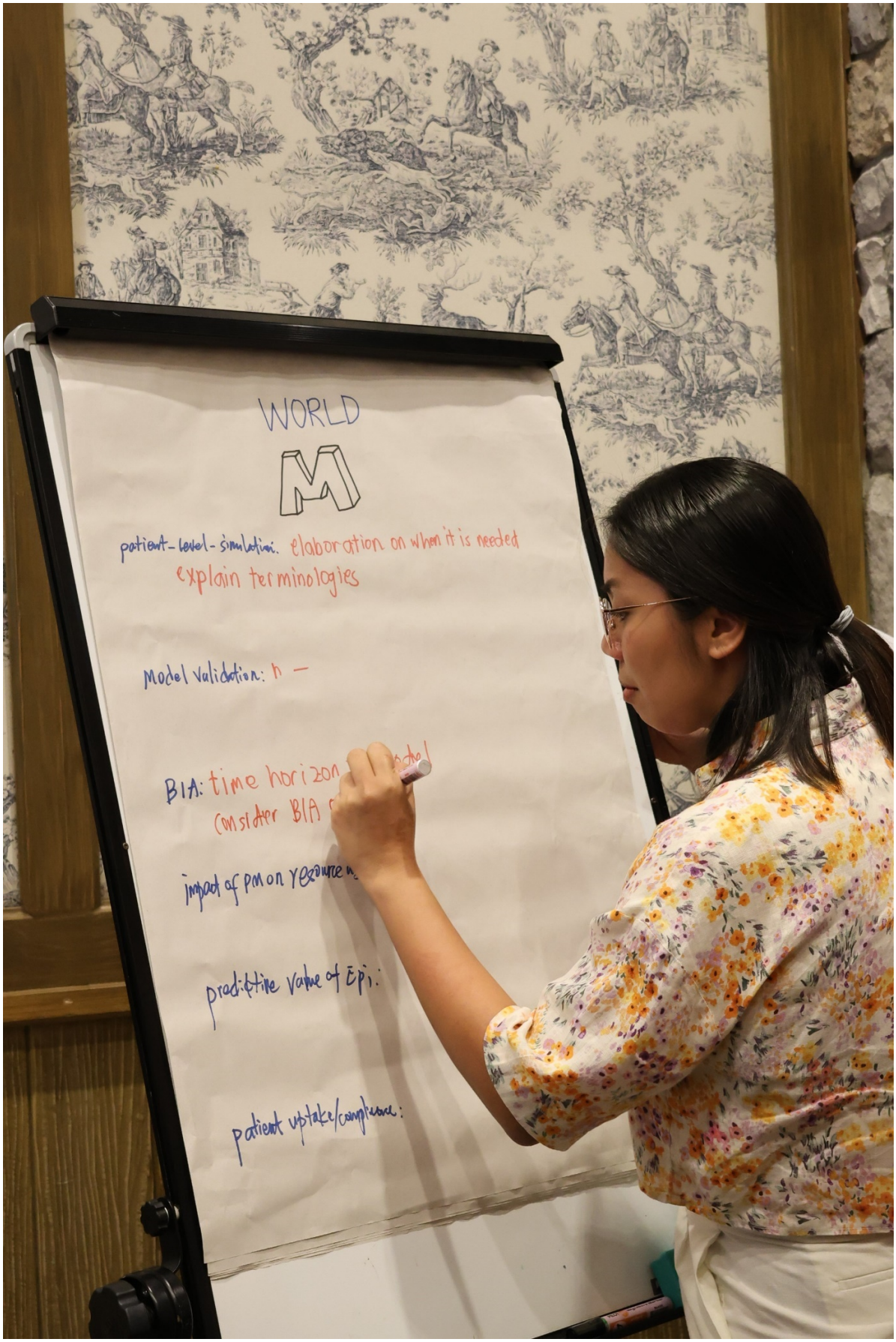

"Development of Precision Medicine Reference Case (PM-RC) Workshop"
Results
200 - 631 critically ill patients per year need to be investigated for rNGS.
ICER (THB/QALY gained) - cost-effectiveness threshold in 2022 = 160,000
Analysis
Results
Conclusion
CUA
rNGS group has lower costs and higher QALYs.
Cost-saving
BIA
Incremental budget 439-1,385 millions Baht over 5 years
Government spends an additional 87-277 million Baht per year.
GENETICS

Figure 4: Stakeholder engagement activities


WORLD
M
patient-level-simulation: elaboration on when it is needed
explain terminologies
Model validation:
BIA: time hori
consider BIA
impact of pm on
predictive value of Epi:
patient uptake/compliance:


Clarification
-To separate btw. plant 1 & 2
-Difficult to understand. Can it be simplified?
-Cost is not an outcome, but
Terminology "Out
(outcomes)


00:04:37
10:58 AM
input
output)
groups of
FR for lung
cancer

Figure 5: Group photos:

Figure 5: Fun activities


HiTAP


"Development of
Precision Medicine Reference Case
(PM-RC) Workshop"
Precision Medicine
Economic Evaluation
Reference Case

Annex 7: Attendance Sheet

Day 1: 28th June 2023

Development of Precision Medicine Reference Case (PM – RC) Workshop

Date: 28 June 2023 Time: 09:00 – 16:00 Venue: U Khao Yai

No.	Name	Organization	Signature
1	Li Jingmei	Genome Institute of Singapore	
2	Wang Yi	Saw Swee Hock School of Public Health	
3	Lou Jing	Saw Swee Hock School of Public Health	
4	Sharon Pek	Khoo Teck Puat Hospital	
5	Ng Kar Hui	National University of Singapore	
6	Naline Gandhi	Duke - National University Singapore Medical School	
7	Wee Hwee Lin	Saw Swee Hock School of Public Health	
8	Jamaica Briones	Saw Swee Hock School of Public Health	
9	Joanne Ngeow	Lee Kong Chian School of Medicine	
10	Sara Tasnim	Nanyang Technological University	
11	Alec Mortan	National University of Singapore	
12	Peh Joo Ho	Genome Institute of Singapore	
13	Brendon Zhou Huijun	Precision Health Research	
14	Wenjia Chen	Saw Swee Hock School of Public Health	
15	Laura Lim	Saw Swee Hock School of Public Health	
16	Yah Ru Juang	Saw Swee Hock School of Public Health	
17	Nattiya Kapol	Faculty of Pharmacy, Silpakorn University	
18	Namfon Sribundit	Faculty of Pharmacy, Silpakorn University	

19	Vorasuk Shotelersuk	Faculty of Medicine, Chulalongkorn University	
20	Janewit Wongboonsin	Brigham and Women's Hospital, Harvard University	
21	Jate Ratanachina	Faculty of Medicine, Chulalongkorn University	
22	Bhoom Suktitipat	Faculty of Medicine, Siriraj Hospital	
23	Yot Teerawattanon	Health Intervention and Technology Assessment Program	
24	Wanrudee Isaranuwatchai	Health Intervention and Technology Assessment Program	
25	Pritaporn Kingkaew	Health Intervention and Technology Assessment Program	
26	Waranya Rattanavipapong	Health Intervention and Technology Assessment Program	
27	Thamonwan Dulsamphan	Health Intervention and Technology Assessment Program	
28	Parntip Juntama	Health Intervention and Technology Assessment Program	
29	Chotika Suwanpanich	Health Intervention and Technology Assessment Program	
30	Sakdichod Petsom	Health Intervention and Technology Assessment Program	
31	Dimple Butani	Health Intervention and Technology Assessment Program	
32	Jidapa Planuson	Health Intervention and Technology Assessment Program	
33	Kanokporn Srivarom	Health Intervention and Technology Assessment Program	
34	Chotirat Wongseejan	Health Intervention and Technology Assessment Program	
35	Thapana Senrat	Health Intervention and Technology Assessment Program	

Day 2: 29th June 2023

HITAP Health Intervention and Technology Assessment Program

NUS National University of Singapore

Development of Precision Medicine Reference Case (PM – RC) Workshop

Date: 29 June 2023 Time: 09:00 – 16:00 Venue: U Khao Yai

No.	Name	Organization	Signature
1	Li Jingmei	Genome Institute of Singapore	
2	Wang Yi	Saw Swee Hock School of Public Health	
3	Lou Jing	Saw Swee Hock School of Public Health	
4	Sharon Pek	Khoo Teck Puat Hospital	
5	Ng Kar Hui	National University of Singapore	
6	Naline Gandhi	Duke - National University Singapore Medical School	
7	Wee Hwee Lin	Saw Swee Hock School of Public Health	
8	Jamaica Briones	Saw Swee Hock School of Public Health	
9	Joanne Ngeow	Lee Kong Chian School of Medicine	
10	Sara Tasnim	Nanyang Technological University	
11	Alec Mortan	National University of Singapore	
12	Peh Joo Ho	Genome Institute of Singapore	
13	Brendon Zhou Huijun	Precision Health Research	
14	Wenjia Chen	Saw Swee Hock School of Public Health	
15	Laura Lim	Saw Swee Hock School of Public Health	
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20	Janewit Wongboonsin	Brigham and Women's Hospital, Harvard University	
21	Jate Ratanachina	Faculty of Medicine, Chulalongkorn University	
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32	Jidapa Planuson	Health Intervention and Technology Assessment Program	
33	Kanokporn Srivarom	Health Intervention and Technology Assessment Program	
34	Chotirat Wongseejan	Health Intervention and Technology Assessment Program	
35	Thapana Senrat	Health Intervention and Technology Assessment Program	

Day 3: 30th June 2023

Development of Precision Medicine Reference Case (PM – RC) Workshop

Date: 30 June 2023 Time: 09:00 – 16:00 Venue: U Khao Yai

No.	Name	Organization	Signature
1	Li Jingmei	Genome Institute of Singapore	
2	Wang Yi	Saw Swee Hock School of Public Health	
3	Lou Jing	Saw Swee Hock School of Public Health	
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10	Sara Tasnim	Nanyang Technological University	
11	Alec Mortan	National University of Singapore	
12	Peh Joo Ho	Genome Institute of Singapore	
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20	Janewit Wongboonsin	Brigham and Women's Hospital, Harvard University	-
21	Jate Ratanachina	Faculty of Medicine, Chulalongkorn University	-
22	Bhoom Suktitipat	Faculty of Medicine, Siriraj Hospital	-
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25	Pritaporn Kingkaew	Health Intervention and Technology Assessment Program	
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27	Thamonwan Dulsamphan	Health Intervention and Technology Assessment Program	Thamonwan.
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35	Thapana Senrat	Health Intervention and Technology Assessment Program	