BMJ Open

Assessing the cost-effectiveness of precision medicine: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Precision medicine (PM) involves gene testing to identify disease risk, enable early diagnosis or guide therapeutic choice, and targeted gene therapy. We aim to perform a systematic review and meta-analysis to quantify the cost-effectiveness profile of PM stratified by intervention type, identify sources of heterogeneity in the value-for-money of PM.

Methods and analysis We will perform a systematic search in Embase, MEDLINE, EconLit and CRD databases for studies published in English language or with translation in English between 1 January 2011 and 8 July 2021 on the topic of cost-effectiveness analysis of PM interventions. The focus will be on studies that reported health and economic outcomes. Study quality will be assessed using the Biases in Economic Studies checklist. The incremental net benefit of PM screening, diagnostic, treatment-targeting and therapeutic interventions over conventional strategies will be respectively pooled across studies using a random-effect model if heterogeneity is present, otherwise a fixed-effect model. Subgroup analyses will be performed based on disease area, WHO region and World Bank country-income level. Additionally, we will identify the potential sources of heterogeneity with random-effect meta-regressions. Finally, biases will be detected using jackknife sensitivity analysis, funnel plot assessment and Egger’s tests.

Ethics and dissemination For this type of study ethics approval or formal consent is not required. The results will be disseminated at various presentations and feedback sessions, in conference abstracts and manuscripts that will be submitted to peer-reviewed journals.

PROSPERO registration number CRD42021272956.

INTRODUCTION

Precision medicine (PM) is a fast-growing medical approach that stratifies patients based on the characterisation of individual phenotypes and genotypes (molecular profiling, medical imaging and lifestyle data) to tailor intervention decisions. The goal of PM is to achieve more accurate predictions of predisposition to disease and/or to deliver timely and targeted prevention or treatment.5,6 The Council of the European Union defines PM as a medical model that bases therapeutic choice on the result of gene profiling or aims to correct pathogenic gene mutations via gene therapies.2,3 The concept of PM is translated into practice predominantly through the use of diagnostic tests and companion diagnostic tests; the latter refers to genetic tests that identify biomarkers correlated with treatment response and are connected to distinct molecular characteristics, such as the single gene testing to measure the human epidermal growth factor receptor 2 (HER2) protein expression for breast cancer pharmacotherapies,4 or the multigene panel testing to assess multiple genes and syndromes at one time for an individual whose personal and/or family history of cancer suggests risk for more than one hereditary cancer syndrome.6

Recently, a number of PM tools started using ‘omic’ based biomarkers, including proteomics, metabolomics and lipidomics to estimate disease prognosis and predict
treatment response, such as whole genome sequencing (WGS) and whole exome sequencing (WES). The ‘Omics’-based testing is expected to evolve in complexity and scope so that one can use a single ‘omics’ test to simultaneously inform treatment pathway, therapy choice or disease risk for multiple diseases. For instance, WGS is at the broadest end of this scale and could feasibly provide information on risks and treatment decisions for hundreds of diseases.

As governments around the world have initiated national genomics programmes to harness the benefits of PM, a sharp increase in dissemination of PM into the healthcare system is to be expected. In Singapore, PM has been identified as a priority by the Ministry of Health, with the ultimate goal of transitioning to individualised healthcare in a sustainable and cost-effective manner. In Thailand, an initiative is underway to implement a pharmacogenomic identity card to identify adverse risk for common drugs in a nationwide pharmacovigilance programme. Meanwhile, Australia, Belgium, Canada, France, Japan, Korea and the USA have each made a substantial effort and introduced initiatives to implement national PM programmes. To date, there are over 54,000 diagnostic tests available for over 16,000 genes, which enable early detection of disease risk or a severe disease variant. This, in turn, reduces the burden of disease through preventive interventions, reduces the costs and potential adverse events associated with inappropriate therapies and allows access to targeted therapy.

Nonetheless, some PM interventions come at a high cost, and there is always a debate about whether such interventions provide economic value to patients and/or governments. The benefits of PM should be captured in a health economic framework in order to justify the allocation of resources for investment in R&D, hereafter ‘early health economic evaluation’, or in healthcare reimbursement, hereafter ‘traditional health economic evaluation’. The value-for-money of PM depends on a variety of factors, including the prevalence of certain gene alleles, severity of disease, test accuracy or treatment effectiveness, related costs, availability of alternative technologies and so forth. These factors may vary across different disease areas, types of PM and even study settings.

Despite the many economic evaluations (EEs) of PM and a few reviews of EEs of PM in current literature, most of the recent reviews were narrative or systematic reviews without synthesis of outcomes, considering only methodology challenges without distinguishing between early and traditional EEs, research capacity constraints and described only the broad proportion of PM being cost-effective. Furthermore, there are a range of potential ethical and equity dilemmas in medical genetics that may influence decision-making in addition to their cost-effectiveness profiles, including patient autonomy, patient confidentiality, beneficence and non-maleficence as well as affordability and equitable access to available PM interventions, which are overlooked in these publications.

A critical step to advance PM in policy and practice is to understand the value-for-money of PM across disease domains, intervention types, technologies and country-income settings, the sources of heterogeneity in PM’s value-for-money and additional humanistic impacts on decision-making such as equity and other ethical values. In light of a lack of evidence for early-stage PM application or application of PM in resource-constrained countries, robust evidence on PM’s cost-effectiveness profiles may enable technology investors and R&D teams to better predict potential returns on investment in early-stage PM technology or returns on the adoption of developed PM in clinical practice, as well as to design pricing policies. Furthermore, the systematic review and meta-analysis of PM’s cost-effectiveness profiles can provide critical evidence for decision-makers and researchers to prioritise crucial topics for the assessment and appraisal of EE on PM, ensuring that such studies are policy relevant and accepted in decision-making.

OBJECTIVES
First, this study will perform a comprehensive systematic review and meta-analysis to summarise the magnitude of cost-effectiveness profiles of PM by intervention type, taking into consideration variation in value across disease domains, technology, epidemiological and geographical regions and country-income levels; and to identify other potential sources of heterogeneity using statistical approaches. Second, this review will explore whether and how equity and ethical issues have been incorporated into economic analysis of PM interventions when supporting policy decisions. Results from this review will inform the development of the Reference Case for conducting EE on PM in order to ensure that the future studies are conducted sensibly and reported accurately using a systematic framework.

METHODS AND ANALYSIS
Guideline
The review will be conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines. The review protocol is registered in PROSPERO International Prospective Register of Systematic Reviews (PROSPERO 2021).

Study selection
Embase, MEDLINE Ovid, EconLit and CRD databases will be searched to identify the relevant studies published between 1 January 2011 and 8 July 2021. In addition, we will search grey literature from the reimbursement dossier of health technology assessment agencies such as Asian Bioethics Review, National Institute for Health and Care Excellence and Institute for Clinical and Economic Review databases. Search terms must include ‘cost effectiveness OR cost utility OR cost benefit OR economic evaluation’ and ‘precision medicine OR genetic testing
OR gene profiling OR genome sequencing’. A detailed description of search strategies and search results of each database are presented in online supplemental appendix 1. The search is limited to studies published in English and/or with translation into English. The reason for the inclusion of studies published from 2011 onward is because the rapid pace of innovation in the field of PM and the improvement in the methodology of economic evaluation on PM rendering studies published more than 10 years ago to be less relevant.

Studies will be independently selected by two reviewers according to their titles and abstracts. Full articles will be reviewed if a consensus cannot be reached on title and abstract alone. Studies published in 2011 and later will be eligible for review if they meet all of the inclusion criteria listed below.

Inclusion criteria:

- The study type is an original research/systematic review of cost-effectiveness analysis of PM.
- The study’s population is human subjects.
- Interventions of interest are PM, defined as a medical intervention with gene profiling for diagnostic or prediction that have been used in a clinical setting for disease prevention or treatment.
- Outcomes of interest are costs and life-years (LYs) or quality-adjusted life years (QALYs) or disability-adjusted life years (DALYs), or incremental cost-effectiveness ratio (ICERs).

Exclusion criteria:

- Studies that report hypothetical (conceptual stage) PM technology will be excluded.

Data extraction

Data will be independently extracted by two reviewers, including:

- Characteristics of study including author’s name, publication year, setting according to WHO region and World Bank country-income level and types of funders.
- Characteristics of study’s population including types of target population, age, sex, types of disease, prevalence and mortality rate of disease.
- Characteristics of PM intervention including PM stage, type of intervention and PM technology.
- Characteristics of model used for analysis including model type, time horizon, discount rates used for costs and outcomes and perspective adopted.
- Consideration of equity in health burden, benefits and ethics in decision-making.

In particular, we will extract economic parameters including costs of PM and comparator (C), incremental costs (ΔC), effectiveness in terms of LYs, QALYs or DALYs of PM and comparator (E), incremental effectiveness (ΔE), ICER, incremental net benefit (INB), willingness-to-pay threshold or national Gross Domestic Product per capita as of 2021 (λ), as well as measures of dispersion (SD, SE and 95% CI) and uncertainty (range reported by sensitivity analysis). This step includes data extraction from the graph of cost-effectiveness plane using the WebPlotDigitizer software V.4.1. Extracted data will be validated using the Kappa statistics for agreement and solved in consultation with the senior author.

Risk of bias and quality assessment

Risk of bias will be assessed using the modified economic evaluations bias (ECOBIAS) checklist.19 ECOBIAS has two parts. Part 1 consists of 11 items that are used for assessment of overall bias in EEs (ie, narrow perspective bias, inefficient comparator bias, cost measurement omission bias, intermittent data collection bias, invalid valuation bias, ordinal ICER bias, double-counting bias, inappropriate discounting bias, limited sensitivity analysis bias, sponsor bias and reporting and dissemination bias). Part 2 is used for evaluation of biases of model-specific concerns, structure (ie, structural assumptions bias, no treatment comparator bias, wrong model bias, limited time horizon bias), data (ie, bias related to data identification, bias related to baseline data, bias related to treatment effects, bias related to quality-of-life weights (utilities), non-transparent data incorporation bias and limited scope bias) and bias related to consistency. Each item will be graded as ‘yes’, ‘partly’, ‘unclear’, ‘no’ or ‘not applicable’. Of note, we chose ECOBIAS over the alternative quality assessment tools such as the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist that are generic to all EE types,19 because we aim to assess sources of heterogeneity and bias in the structure and model of EEs in a PM-specific context that informs the development of PM-specific reference case for EE, rather than assessing to what extent the included EE had met the CHEERS criteria for peer-reviewed publication purposes.

Narrative assessment of ethics and equity issues

Ethics and equity issues will be summarised in three aspects: (1) inequity in benefits, including the presence of social disparity in the eligibility, uptake, short-term and long-term effects of PM; (2) inequity in cost and health burden including health insurance coverage; (3) any ethical consideration. Each aspect will be assessed as the percentage of included studies covering this topic and the summary of major issues that were raised in those studies.

Statistical analysis

All statistical analyses will be performed using Stata Software V.16. Results are considered statistically significant at p<0.05 (two-sided) for meta-analysis, and p<0.1 (two-sided) for subgroup analysis and meta-regression. We will apply the robust comparative efficiency research (COMER) to combine cost-effectiveness estimates by pooling INBs.20

Data preparation

The primary outcome, INB, is calculated as ΔE × λ – ΔC or ΔE (λ – ICER), comparing PM to conventional test/intervention. A positive INB indicates that the PM is cost-effective compared with conventional care, whereas a negative INB
favours conventional care. The variance of INB is calculated as $\text{Var}(\text{INB}) = \lambda^2 \sigma_{\Delta E}^2 + \sigma_{\Delta C}^2 - 2\lambda \text{Cov}(\Delta E, \Delta C) \approx \lambda^2 \sigma_{\Delta E}^2 + \sigma_{\Delta C}^2$. However, different EE report data differently. In the event a study reports incomplete data that are not ready for pooling, data will be simulated. Data are derived and imputed as follows.

**Scenario 1:** The EE compares PM to conventional intervention strategy

INB and its variance are calculated by directly comparing PM to conventional intervention strategy. In case of incomplete reporting, if the variance of ICER is not reported, whereas variances of $\Delta E$ and $\Delta C$ are reported, Monte Carlo simulation will be performed for 1000 replications with gamma and log-normal distributions of $\Delta C$ and normal distribution of $\Delta E$ and the variance of ICER will be derived; if the study only reports the means of $\Delta E$ but not the measure of dispersion, we will derive the variance of $\Delta E$ using Monte Carlo simulation of $E$ from both arms for 1000 replications with normal distribution. If $E$ is not reported, we will take the measures of dispersion of $\Delta E$ from another study of the same disease, where the model settings (ie, intervention, comparator, study time period, region, level of countries’ incomes, model inputs (discounting, time horizon, etc)) are similar. Meanwhile, we will take the range of ICER from sensitivity analysis, or the 2.5th and 97.5th percentile of ICER from probabilistic sensitivity analysis, as a proxy of 95% CI. Finally, we will derive the variance of INB based on the variance of $\Delta E$ and ICER as abovementioned.

Of note, the monetary units of intervention and comparators are dually reported as country-specific and time-specific currencies. To standardise costing data, all INBs in terms of costs are converted to 2021 US$ adjusted with purchasing power parity, according to the consumer price index obtained from the World Bank.

**Scenario 2:** The EE compares PM to another PM

We will extract $C$ and $E$ from both arms, and compare both PMs to the $C$ and $E$ of a conventional intervention strategy from another study, where the disease is the same and study settings are similar. $C$ and $E$ of both PE arms and the conventional intervention strategy will be separately simulated for 1000 replications with normal distribution to estimate INB and its variance.

**Scenario 3:** The EE compares PM to other new technology

We will extract $C$ and $E$ from the PE arm, take the $C$ and $E$ of conventional intervention strategy from another study, and calculate INB as described in Scenario 2.

**Scenario 4:** The EE compares PM and conventional intervention strategy to no intervention at all

First, INB and its variance will be calculated by directing comparing intervention to no intervention. Next, based on Bucher et al.’s theory of indirect treatment effect, the INB of PM vs conventional intervention strategy will be calculated as

$\text{Indirect INB (PM vs Con)} = \text{INB (PM vs None)} - \text{INB (Con vs None)}$

and the variance is

$\text{Var} \left[ \text{Indirect INB (PM vs Con)} \right] = \text{Var} \left[ \text{INB (PM vs None)} \right] + \text{Var} \left[ \text{INB (Con vs None)} \right]$

where Con refers to conventional intervention strategy.

**Meta-analysis**

Following the COMER methodology, we will calculate weighted-pooled summary estimates of INB, namely the total incremental net benefit (TINB), where a positive TINB indicates that a PM intervention is overall cost-effective. Of note, we will separately estimate TINB as stratified by the types of PM intervention, including screening tool (ie, risk stratification of genetic conditions that predispose to disease), diagnostic tool (ie, early diagnosis of disease such as the Galleri test for undiagnosed cancers), pharmacogenomic tool (ie, prediction of treatment response) and gene therapy (ie, addition or replacement of a gene to cure or improve immunity to fight against disease).

First, within each PM type, we will perform a fixed-effects model assuming there is no heterogeneity by weighting the inverse of the variance of INB ($\omega_i$), as follows

$\text{TINB}_f = \frac{\sum_{i=1}^{N} \omega_i \text{INB}_i}{\sum_{i=1}^{N} \omega_i^2},$ where $\omega_i = \frac{1}{\text{Var(INB)}}$

Next, we will test for heterogeneity with the Cochran $Q$ test and $I^2$ statistics. The degree of heterogeneity will be categorised as low ($I^2 <25\%$), moderate ($I^2=25\%–74\%$) or high ($I^2 \geq75\%$). In the presence of moderate-to-high heterogeneity, we will estimate TINB through a random-effects model based on the DerSimonian and Laird method, as follows

$\text{TINB}_r = \frac{\sum_{i=1}^{N} \omega_i \text{INB}_i}{\sum_{i=1}^{N} \omega_i + \frac{\text{Var(INB)}}{\sum_{i=1}^{N} \omega_i}},$ where $I^2 = \frac{Q - (N - 1)}{\text{Var(INB)}}$

**Subgroup analysis**

We will perform subgroup analysis to examine the internal consistency of TINB in relatively homogenous populations, that is, being epidemiologically and geographically alike, and identify better trade-offs between effectiveness and costs in clinically-relevant subgroups compared with the whole population. Within each PM intervention type, we will estimate TINB by subgroup of PM developmental stage (ie, early, first-clinical-use stage vs market access stage), PM technology (ie, single gene testing vs multigene panel testing, WGS and WES), 16 major disease areas as indicated by the diagnosis codes of the International Disease Classification, V.10 (ie, infectious and parasitic, neoplasms, blood and immunity, metabolic, mental, nervous system, eye and ear, circulatory, respiratory, digestive, skin, musculoskeletal, genitourinary, pregnancy/childbirth, perinatal, congenital malformations), WHO region (African, Americas, South-East Asia, Europe, Eastern Mediterranean, Western Pacific).
and World Bank country-income level (gross national income per capita (in 2020 US$), low income (<1036), lower-middle income (1036–4045), upper-middle income (4046–12 535) high income (>12 535)).

Sensitivity analysis and meta-regression
First, we will perform jackknife sensitivity analysis to assess the robustness and conclusiveness of results within each intervention type. In particular, we will omit the studies one at a time and repeat the comparative efficiency analysis based on the rest of the data, to examine whether the estimated TINB is excessively affected by any influential studies. Second, we will explore sources of heterogeneity using univariate random-effect meta-regressions, considering the impact of the following variables on TINB within each PM intervention type:

- Target population (paediatric, adult, senior, all-age), disease prevalence, disease mortality rate, the perspective of EE, year of publication and quality of study as indicated by bias score. Finally, to assess publication bias, we will perform funnel plot analyses by plotting the INB of individual studies against the variance, and use Egger’s test to objectively assess the funnel plot asymmetry. The asymmetric inverted funnel shape suggests an association between INB estimates and the absence of non-cost-effective studies.

Patient and public involvement
There was no patient or public involvement in the design and planning of this study.

ETHICS AND DISSEMINATION
Ethics approval and consent to participate is not applicable. The study findings will be disseminated at various presentations and feedback sessions, in conference abstracts and in manuscripts that will be submitted for publication in peer-reviewed journals.

DISCUSSION
To facilitate the decision-making of PM to move from evidence-based medicine to EE based on compatible clinical and economic evidence, we will perform the first, and possibly the most comprehensive systematic review and meta-analysis to quantify the magnitude of cost-effectiveness of genetic screening, diagnostic, pharmacogenomic tests and gene therapies, in general and across major disease areas, technology type, developmental stage, geographical location and country-income level. This study will assess the impact of key influences on the value-for-money of PM, including disease burden, target population, year of invention and the quality of study structure and EE model. The findings will provide decision-makers with a comprehensive picture of value-for-money of PM by synthesising all available evidence, which may allow stakeholders to better understand and predict the added value of investing in the R&D of a new PM technology or adopting an existing one.

Moreover, as EE results provide guidance for allocating resources and improving health outcomes, it is important to learn whether and how ethical issues were presented alongside economic evidence in such studies. Ethical considerations in economic evaluation of personalised medicines overlap with those of other medical research related to respect for persons, concern for individual welfare and justice, and extend beyond these to include those related to the generation of economic evidence, and to the use of this evidence by decision-makers. For example, consideration of ethical issues begins with the process of selecting a technology by researchers for assessment. EE promotes the maximisation of QALYs which may introduce inequity in how these benefits are distributed across subpopulations. Our study will provide deeper knowledge and better understanding of these issues, which is critical to sound development and implementation of PM interventions domestically and internationally.

A major strength of our study is that it provides quantitative, summary evidence in refined, clinically and economically relevant subgroups. In particular, our study overcomes the challenges of synthesising EEs by pooling INB, which is a valid measure of cost-effectiveness that integrates willingness-to-pay in the net monetary benefit of invention. In addition, our study standardises the extracted data by converting costs, incremental costs and INB to a common standard currency using the same base year. Furthermore, bearing in mind the varied healthcare and health delivery systems, perspectives of cost measurement, geographical regions, demographic and epidemiological features, our study will investigate the association between these potential sources of heterogeneity and the value-for-money of PM through meta-regressions. This may enhance the transferability of cost-effective data across regions worldwide.

Nonetheless, this study bears several limitations. The first is the quality and consistency of cost-effectiveness profiles of PM due to the heterogeneity of included EEs. Despite the rigorous statistical approach to address heterogeneity, our study may not capture the full spectrum of sources of heterogeneity. For instance, health resource uses vary across countries even after the standardisation of costs into US$ equivalents in the same year. Likewise, the effectiveness profile of PM is influenced by many causal variants, the preceding molecular diagnosis and the availability of a targeted therapy. Moreover, due to a lack of reference case for conducting EEs in PM interventions, the study design and modelling may vary greatly across studies, and study endpoints may be reported in various forms. Second, the exclusion of non-English language publications may affect the overall conclusions of evidence synthesis on WHO.
regions with non-English native languages. Last but not least, studies with negative outcomes (i.e., non-cost-effective profile) might be under-represented in the review given the likely reduced chance of publication, which will be assessed via the funnel plot analysis.

With global-scale data extraction and a robust statistical approach, our study will confer influential policy implications. First, countries lacking the capacity and data to conduct EEs or with budget constraints, in particular during the COVID-19 pandemic, can refer to the TINB of a PM type of interest in a particular disease area from similar epidemiological subregions and apply it to their own settings. Similarly, in instances where conducting an early EE is challenging due to data gaps, policymakers can use the study results to identify a PM technology in a disease area that has strong potential, and predict the added value of a new PM technology by comparing the TINB of a PM type of interest between early clinical stage and market access stage. This is likely to improve efficiency in R&D, economic assessment, appraisal, adoption and pricing design of PM. To our best knowledge, this is the first systematic review focusing on the issue of early EEs of PM. The results of the review may lead to better understanding of the similarities and difference between early versus late state health EEs of PM, which may then lead to the development of specific methodological guidelines. Our research team has expertise and experience in completing this challenging task.28

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Funding This study is funded by PRECISE Singapore (MOH-000588-01). WC receives National University of Singapore Start-up Funding (R-608-000-329-133).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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