

ABSTRACT

Objectives

The objective of this paper is to describe the unique challenges and present potential solutions and approaches for economic evaluations of PM interventions using simulation modelling methods.

Methods

Given the large and growing number of PM interventions and applications, methods are needed for economic evaluation of PM that can handle the complexity of cascading decisions and patient-specific heterogeneity reflected in this myriad of testing and treatment pathways.

Traditional approaches (e.g. Markov models) have limitations and other modelling techniques may be required to overcome these challenges. Dynamic simulation models, such as discrete event simulation and agent-based models, are used to design and develop mathematical representations of complex systems and intervention scenarios to evaluate the consequence of interventions over time from a systems perspective.

Results

Some of the methodological challenges of modelling PM can be addressed using dynamic simulation models. For example, issues regarding companion diagnostics, combining and sequencing of tests, and diagnostic performance of tests can be addressed by capturing patient-specific pathways in the context of care delivery. Issues regarding patient heterogeneity can be addressed by using patient-level simulation models.

Conclusion

The economic evaluation of PM interventions poses unique methodological challenges that might require new solutions. Simulation models are well-suited for economic evaluation in PM

because they enable patient-level analyses and can capture the dynamics of interventions in complex systems specific to the context of health care service delivery.

HIGHLIGHTS

- Simulation modelling methods such as discrete event simulation may be better suited than traditional state-transition cohort models to address the complexity and specific challenges of economic evaluation of precision medicine interventions.

- Simulation models have the ability for patient-level analyses of care pathways and the ability to deal with system complexity of multiple tests, diagnostic performance, and testing and treatment sequences that present particular challenges for precision medicine.

Background

Economic evaluations are now commonly used by health technology assessment (HTA) organizations and payers to assess the value of new health care interventions (including medicines, pharmaceuticals, devices, and health care programs) and to inform decision-makers about the efficient allocation of health care resources.¹ Many countries have developed guidance on the key considerations in economic evaluations such as the target population, analytical perspective, choice of comparator, analytical methods, outcome measures, measures of utility, costs to be included, time horizon, discounting, and sensitivity analysis.² These economic evaluation guidelines commonly also consider the use of economic modelling.^{3,4} Traditional modelling approaches, such as decision trees or Markov cohort models, typically examine the value of one test compared to standard care where this test is conducted for a specific clinical reason, provides one result (e.g. diagnosis), and a single trajectory of costs and outcomes for cohorts of ‘average’ patients.^{5,6} However, the notion of the ‘average’ person is challenged in the evaluation of precision medicine (PM) interventions.⁷⁻⁹

From a broad perspective, personalized approaches in health applications can be defined as those using any type of patient-specific information (diagnostic tests, patient reported outcomes, risk estimates, functional performance) to inform therapy tailored to the patient.^{7,10} Ginsburg and Phillips differentiate between personalized and precision medicine with precision medicine going beyond genomics, preferences, beliefs, attitudes, knowledge, and social context.¹¹ They describe precision medicine as a model for health care delivery that relies on data, analytics, and information with the ability to guide health care decisions tailored to a specific patient. It is generally acknowledged that PM interventions have the ability to guide health care decisions

tailored to a specific patient, with the aim of improving the effectiveness and quality of care, reducing related adverse events and reducing the need for unnecessary testing and treatment.¹¹

While advanced diagnostic tests used to target treatments can drive improved outcomes, the result of using these tests is a complex and dynamic set of treatment pathways that varies for each individual and where the downstream consequences and outcomes are difficult to predict. In order to support decision making in PM, models need to reflect the dynamic treatment pathways, the underlying clinical evidence for improved outcomes as well as the uncertainties around the evidence.¹²

In the past decade, HTA organizations have considered a large and growing number of PM interventions for approval and reimbursement. For example, pembrolizumab was the first solid cancer therapy approved by the Food and Drug Administration in 2017 for use based on the presence of a specific biomarker rather than the location of a particular tumor.¹³ Methods are needed for economic evaluation of PM that can handle this complexity of cascading decisions that is reflected in this myriad of treatment pathways while simultaneously presenting results that provide meaningful information to support health policy decisions.

Given that many of the current health economic modeling approaches are not likely able to capture this complexity, the objective of this paper is to present dynamic simulation modeling as another modelling paradigm that can manage this complexity. The paper first describes the challenges of economic evaluation in PM and how simulation modelling methods can potentially address some of these challenges. Then we provide an overview of common simulation modelling methods in health. Finally, empirical examples are used to illustrate how simulation modelling methods could be and have been used to capture the individual care pathways as seen in PM.

Specific Technical Challenges of Economic Evaluation in Precision Medicine

The economic evaluation of PM interventions epitomises the need for methods that reflect a system view to health care that captures the upstream and downstream consequences of changes in health care with multiple decision points based on patient-level characteristics. PM typically involves multiple diagnostic tests and treatments over time, with the sequence of these tests and treatments differing between individual patients.¹¹ These pathways or clinical trajectories are complex, dynamic, and specific to the context of the delivery of health care services.⁸ Cohort and state-transition models have limited ability to deal with such pathways and typically report results for an ‘average’ patient.^{6,14}

The challenges of conducting economic evaluations of PM have been synthesized by Phillips *et al.*⁹ using next generation sequencing (NGS) as an example. NGS tests including targeted gene panels, whole-exome, and whole-genome sequencing, which simultaneously examine multiple genes and can contribute to making treatment recommendations. The top priority challenges include: 1) The requirement for a complex model structure that incorporates multiple pathways, results and testing uses, to reflect the fact that NGS tests evaluate multiple genes and consider interactive effects across multiple conditions; and, 2) The need to specify a time frame that captures both the upstream and downstream costs and outcomes specific to NGS and the need to capture downstream consequences for patients and families.

Additional conceptual and methodological challenges in PM relate to the valuation of outcomes including preferences for genomic information, multiple layers of uncertainty and risks.¹⁵ Patient heterogeneity is critically important in the context of economic evaluation in PM as individual care pathways and decisions about treatment and care need to be considered in the analysis. Although current guidelines for health economic modelling recognize the importance of

patient heterogeneity,^{3,16} there is little specific guidance on how to incorporate heterogeneity in cost-effectiveness models.

Nonetheless, in a systematic literature review of health economic models specifically in personalised and precision medicine (in general, and including patient stratification by other means than genetics) in all disease areas, Degeling *et al.*⁸ reported that decision tree models and Markov models remain the most frequently used approach (n=21 of 31 publications, 66%). When analysed over time, there was an observed increase in patient-level simulation modelling methods such as discrete event simulation since 2011. This review also provides a checklist of the 10 main challenges for health economic modelling in PM and these challenges are summarized in Table 2 along with a description of how these challenges can potentially be addressed by simulation modelling methods rather than traditional health economic modelling methods. Only a minority of these health economic models of PM addressed the 10 items in the checklist, or otherwise identified and reported the challenge. The most commonly addressed challenge was the diagnostic performance of the test (n=20 out of 31 studies, 65%) and the different combinations of test(s) and treatments(s) (n=22 out of 31 studies, 71%). Although 11 of the models (35%) included combinations of tests, all of them assumed a fixed sequence of tests. Only 6 of the models (19%) were defined on a patient level. These findings suggest that economic models of PM have not yet fully embraced these more advanced simulation modelling methods to address these challenges.

Overview of Simulation Modelling Methods in Health Economic Evaluation

Health economic evaluation models have commonly used cohort-based Markov or state-transition modelling to reflect the clinical evidence and estimate the cost-effectiveness of an

intervention compared with usual care in the form of an incremental cost-effectiveness ratio. For example, of 58 publications economic evaluations modelling therapies for rheumatoid arthritis identified between 1996 and 2012, 38 (66%) were decision trees (n=13) or Markov models (n=25).¹⁷ In these models, a limited number of health states represent the care pathway for a group of patients. These models typically aggregate the complexity in the real-world into a few distinct health states and therefore heavily rely on assumptions about how patients move from health state to another, how overall outcomes are synthesised and / or extrapolated, and importantly, they neglect the heterogeneity at the patient-level.

The use of cohort models has been partly driven by the use of economic evaluation in the context of health technology assessment (HTA) which has historically focussed on single interventions (often a new medicine).¹⁸ Further, many of these models are trial-based and thus they model the relatively straightforward head-to-head comparison of two interventions.

However, a different paradigm is needed as HTA increasingly breaks out of the ‘adoption addiction’ and moves towards health technology management (HTM) with a broader systems view of innovation, adoption and disinvestment throughout the technology life cycle to support health care decision making.^{18,19} Dynamic simulation modeling is a collection of methods developed primarily in the context of business operations that may be better suited than cohort-based models to reflect the dynamics of the health system and delivery of services.²⁰

Dynamic simulation models use mathematical representations of a complex systems with multiple intervention scenarios, and evaluate their consequences over time from a systems perspective.²⁰ Complex systems consist of tasks that are relationally dependent events with unpredictable outcomes.²¹ As a consequence, simulation models are generally nonlinear and described implicitly through rules or equations, whereas state-transition models are typically

linear and defined by transition matrices between health states that are indexed by time. The non-linearity in simulation models implies that individual must be simulated in context of the broader context of other individuals and the health care system across time such that emergent behaviour reflects the system rather than individuals.^{20,22}

The literature on the applications of simulation modelling in health care is growing rapidly but given its roots, most applications of these methods remain in the traditional areas of operations research including scheduling, transportation and allocation of resources. In this paper, we focus on two types of dynamic simulation models - discrete event simulation and agent-based models and discuss their potential for use in PM (see Box 1 and Table 1).^{5,23-28}

Discrete Event Simulation (DES)

DES is the most commonly used dynamic simulation modelling approach in the health care context.²⁵ In DES models, the behavior of a system is captured in an ordered sequence of defined events (e.g. a test is done, or a treatment is provided). Other events include points in time with respect to changes in health such as the detection or recurrence of a disease, or delivery of services such as admission to a health facility, receipt of medical or surgical treatment. DES has the flexibility to map care pathways that incorporate different testing strategies and services that may affect uptake of treatments and downstream patient outcomes.²⁰

There is a considerable body of literature on the application of DES in health to address a variety of health care issues.^{5,29,30} A recent systematic review by Zhang *et al.*³¹ identified 211 studies using DES as the main modelling technique in the context of health care delivery or public health scenarios (not specific to PM). The authors noticed a significant expansion of publications in this area especially after 2010. The studies were categorized in four main classes

of applications of DES - health and care systems operations, disease progression modelling, screening modelling, and health behavior modelling. Zhang *et al.* reported that most DES models (93%) belong to the first two categories (i.e. health and care systems operations and disease progression modelling) and aimed to evaluate the effects of operational changes, health economic evaluations, and patient scheduling.³¹

In comparison with state-transition models that do not capture dynamic interactions in the delivery of care, DES is more suited to modelling complex systems by reflecting patient flows through the system.²⁴ For instance, DES models can incorporate attributes of individuals that can affect or even determine responses to events, including age, sex, health status, illness history, duration of disease, and other demographics. These attributes can also vary over time.

Agent-based modelling (ABM)

ABM is another dynamic simulation method for modelling dynamic, adaptive, and autonomous systems where the agent (for example, the patient or doctor) serves as the entity of simulation.²⁸ The agents in an ABM model interact within an environment, based on a set of decision rules describing the agent's behaviour and operationalized using mathematical logic operators.²⁶ An agent's behaviour typically is non-linear and dependent on previous interactions. For instance, the likelihood of seeing a doctor increases after contamination with a virus resulting in a fever. Agents can also be programmed to change health states based on an interaction with the health system, which implies we can accumulate costs and outcomes attached to an agent's state as long as the simulation is running. ABM emphasizes agent-agent (for example, patient and care providers) and agent-environment (for example, patient and hospital clinic) interaction and is therefore well suited to examining patterns of health and

behavior of populations over time, for example, modelling infectious disease outbreaks.^{20,22}

In summary, simulation models such as DES and ABM modelling can enable decision makers to better understand the behavior of complex systems – characterized by these nonlinearities and spatial relationships among entities, multiple agents, feedback loops, and variables that evolve dynamically over time – and predict their response to changes with intended and unintended consequences.

Applications and Case Examples of Simulation Modelling for Precision Medicine

In this final section, we present several examples to illustrate how complex genomic testing affects clinical pathways that would be better addressed in dynamic simulation modelling. These case examples represent a range of applications of simulation models that address some of the 10 challenges identified in the checklist - including clinical risk stratification (which may not be based on genetics) at a patient level, diagnostic performance of the test, combinations of tests, and different testing and treatment sequences and study-specific outcome measures.

Molecular profiling to inform treatment decisions in patients with cancer

One of the most prominent changes in the treatment landscape in cancer is the availability of complex genomic tests in combination with targeted treatments and/or immunotherapy. However, the diagnostic component is usually not considered in health economic models.³² For instance, women with early-stage breast cancer (ESBC) are faced with challenging treatment decisions determined by stage of disease and the use of neo-adjuvant or adjuvant systemic therapy. Patients with overexpressed HER2 (HER2 positive) are eligible for anti-HER2 targeted therapies, such as trastuzumab.³³ Likewise testing for estrogen receptor will identify eligibility for hormone therapy. While these tests, either through immunohistochemistry or FISH, have

been available for quite some time, health economic models have rarely considered the diagnostic performance of the assays,³² despite the differences in test accuracy differs between methods to assess HER2 status reported in a recently published meta-analysis.³⁴ Likewise, clinical guidelines recommend determination of HER2, estrogen receptor and progesterone receptor expression status on tissue biopsy and excision material following surgery. Recent studies have shown discordance of up to 15% for progesterone receptor between both samples, which affects optimal treatment decisions.³⁵

While these examples only illustrate how a simple IHC or FISH test can change treatment pathways, it will soon become more complex in terms of the building the clinical and health economic evidence base. Several international studies have tested complex genomic profiling (NGS panels, whole exome sequencing and whole genome sequencing) in metastatic cancers to direct treatment. While earlier work on HER2 was only for one specific treatment, complex gene panels (140 genes) using in lung cancer can guide decisions for a dozen of targeted treatments, including ALK-TKI and EGFR-TKIs, and immunotherapy. The recently published PROFILER study presented the evidence for using complex genomic testing using two gene panels in nearly 2,600 patients in France, showing that 27% were recommended a molecularly based therapy (MBRT), while only 6% actually received a MBRT.³⁶ Modelling the health economic impact in this study is far more complex and may require more granularity than possible even through simulation modelling.

Several examples using DES in personalized oncology have been published, including comparisons to state-transition models in case of colorectal cancer.³⁷ While the previous study was a direct head-to-head economic evaluation of two treatment strategies based on a clinical trial, DES has also been used to model the health economic impact of using circulating tumor

cells to monitor progressive metastatic castration resistant prostate cancer (mCRPC). The model accounted for two lines of treatment where several biomarkers could be used to optimise treatment strategies.³⁸

Simulation modelling can also be useful in situations where there is decisional conflict such as when guidelines recommend adjuvant chemotherapy, but chances of recurrence are estimated to be low. In this scenario, personalized prediction tools such as gene expression profiling (GEP) (for example OncotypeDX or Mammaprint) can calculate the likelihood of cancer recurrence and can help to risk-stratify women who may not benefit from chemotherapy, sparing them from associated toxicity. Jahn *et al.*³⁹ developed a DES model to evaluate the cost-effectiveness of OncotypeDx used both with and without the Adjuvant! Online (AO) score, a web-based decision aid to guide decisions about the use of adjuvant chemotherapy. The combination of OncotypeDx and AO results resulted in 12 distinct risk groups of patients. A DES model was selected for this analysis for multiple reasons: a) individual patient pathways were influenced by multiple characteristics and test results; b) there were time-dependent functional relationships; c) OncotypeDx and AO could be modeled as companion tests; and, d) the desired to track and report individual patient pathways. In another publication using the same model, the authors moved even further towards personalized treatment strategies by evaluating the cost-effectiveness of adjuvant chemotherapy for women in specific risk-groups according to the joint results of GEP and AO. Using the DES model, the authors developed a flexible tool for the evaluation of several test-treatment strategies.⁴⁰

Precision Medicine Treatment Options in chronic obstructive pulmonary disease (COPD)

As noted earlier, state transition models have limited ability to deal with patient-specific pathways of diagnosis and treatment. The article by Hoogendorn *et al.*⁴¹ explores the suitability of models using more traditional approaches to evaluate PM treatment options for COPD. The authors assessed COPD models to determine which types of patient heterogeneity (risk stratification by patient characteristics) were included. The authors concluded that all of the currently available models are capable of running simulations for different age-and COPD severity classes and most models also have the ability to run analyses separately by sex and smoking status. However, the validity of subgroup analyses within the models was questioned because important input parameters were not specified by sex, age, or smoking status. Thus, the challenge for the evaluation of PM treatment options in COPD is that treatment is more likely to be personalized on the basis of clinical parameters rather than age, sex and smoking status, such that the existing models are likely of limited usefulness. Information on the effectiveness and cost-effectiveness of treatment options for these subgroups is needed to guide clinical guideline development and decisions for reimbursement. It was recommended that future models should include all clinical patient characteristics considered to influence disease severity, prognosis, and treatment response in COPD.⁴²

To address PM in COPD, where treatment is tailored to specific clinical phenotypes, such as patients with frequent exacerbations, Hoogendoorn *et al.*⁴² subsequently developed a patient-level DES simulation model for COPD that was able to estimate the incremental costs and effects of different treatments for many subgroups of patients. The model included 14 patient characteristics (e.g. current smoking status, the number of pack-years smoked, history of heart failure, presence of asthma, bronchodilator responsiveness, diabetes, history of depression), ten

intermediate outcomes (e.g. exacerbations, pneumonias, lung function), and three final outcomes (death, QALYs, and costs). This new model was unique because none of the previously published models had modeled time-to-events simultaneously with changes in clinical variables for individual patients.

Other considerations (Table 1)

Although there are some distinct advantages of simulation modeling over traditional state-transition models for the economic evaluation of PM, this approach can also present challenges for both the analysts who construct these models (e.g. data requirements, computational requirements, requirements for modelling skills, model reproducibility) and the decision-makers who use these models (e.g. additional expertise required by evidence review groups).

The additional complexity that can be captured using these modeling methods come at the cost of more complex structures and level of detail.²⁴ Consequently, analysts with specialized modeling and biostatistical skillsets are required to design, develop, program, and conduct analyses using simulation modelling software. These complex models require more data - both in terms of the number of parameters that need to be estimated and the volume of observations needed to inform these estimates. Simulation models require a great deal of data that may not be available in the detail required to populate the model, especially for early stage analyses of PM interventions.

This complexity can also present challenges for reviewers and users of these models. The complexity and transparency of cost-effectiveness modelling has been a longstanding concern, since decisions about the use of drugs and other therapeutic interventions were first influenced by economic analyses using modelling approaches.^{43,44} More recently, transparency in modelling

has been promoted through reporting standards, reference models, collaboration, model registration, peer review and open-source modelling.⁴⁵ With the additional complexity associated with dynamic simulation models, further challenges in communicating the structure, assumptions and outcomes from these models may be encountered. The uptake of such methods may therefore be lower than is optimal, and it may be more difficult to comprehend, assess the validity and interpret the findings from these models.

Summary

In this paper we discuss how simulation modelling methods such as discrete event simulation may be better suited than traditional Markov or state-transition cohort models to address the complexity and specific challenges of economic evaluation of PM interventions. Amongst the core advantages of simulation models are the ability for patient-level analyses of care pathways and the ability to deal with system complexity of multiple tests, diagnostic performance and testing and treatment sequences that present challenges for PM. Although the use of simulation modelling in health is growing in general, there remain few examples in PM to date.

Another modelling approach that we have not addressed in this paper and is potentially relevant for PM is constrained optimization. Constrained optimization is a mathematical approach to finding the best solution to a problem, subject to constraints.⁴⁶ Optimization methods may be useful for designing optimal treatment pathways that are relevant in the context of PM, where a specific treatment may be used in a specific subset of patients because of their genotypic or clinical phenotypic profile. Optimization modelling approaches are specifically suited to address constraints in the system (most commonly fixed budgets and time) which have resource

allocation implications for decision makers.^{46,47} An example of constrained optimization is the work by the Alliance for Paired Donation (APD) to make improved matches between kidney disease sufferers and potential kidney donors.⁴⁸ The Alliance developed and implemented an innovative technique called non simultaneous extended altruistic donor chains that permits better-optimized matching of potential donors to patients, greatly increasing the number of possible transplants.

Although there are benefits from applying dynamic simulation modelling methods for PM interventions, implementing these models to support policy decisions may be challenging. Dynamic simulation models are not a “one size fits all” solution, and continuing research, education and testing of these methods is required to understand when these methods should be applied. We offer three suggestions regarding the application of simulation modelling in economic evaluation of PM interventions:

- 1) Simulation modelling methods should be considered part of the ‘tool kit’ for economic evaluations in PM given the need to model a cascade of testing and treatment sequences.
- 2) Although simulation modelling may be an appropriate modelling approach for economic evaluation in PM, in general, models should aim to represent the decision problem and the decision context in which the results will be interpreted and applied in as simple a manner as possible.
- 3) Provide sufficient transparency to achieve understanding by decision makers and reflect the robustness of the model may be an even greater challenge for simulation modelling than other types of models. Modellers should explicitly document the

rationale for applying simulation modelling, the modelling assumptions, the strength of the data used to populate the model, and conduct an appropriate exploration of the uncertainty around the model.

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