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CURRENT OPINION

Four Aspects Affecting Health Economic Decision Models and Their Validation

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Abstract

Health care decision makers in many jurisdictions use cost-effectiveness analysis based on health economic decision models for policy decisions regarding coverage and price negotiation for medicines and medical devices. While validation of health economic decision models has always been considered important, many reviews of model-based cost-effectiveness studies report limitations regarding their validation. The current opinion paper discusses four aspects of current health economic decision modeling with relevance for future directions in model validation: increased use of complex models, international cooperation, open-source modeling, and stakeholder involvement. First, new, more complex clinical study designs and treatment strategies may require relatively complex model structures and/or input data analyses. Simultaneously, more widespread technical knowledge along with wider data availability have led to a broader range of model types. This puts extra requirements on model validation and transparency. Second, increased international cooperation of policy makers and, in particular, health technology assessment (HTA) authorities in performing model assessments is discussed in relation to the repeated use of health economic models (multi-use disease models). We argue such coordinated efforts may benefit model validity. Third, open-source modeling is discussed as one possible answer to increased transparency requirements. Finally, involvement of all relevant stakeholders throughout the whole decision process is an ongoing development that necessarily also includes health economic modeling. We argue this implies that model validity should be considered in a broader perspective, with more focus on conceptual modeling, model transparency, accuracy requirements, and choice of relevant model outcomes than previously.

Key Points for Decision Makers

This paper highlights four aspects of health economic decision modeling, namely use of complex models, international cooperation, open-source modeling, and stakeholder involvement in the modeling process.

These aspects underline the need for proper model validation and/or enhance the opportunities for extensive validation, including model transparency, insights from a broader perspective, and increased efficiency in validation efforts.

More standardization in model validation terminology and clear-cut overviews of validation techniques, together with operational guidance, would benefit health economic modelers and decision makers.

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1 Introduction

In health economics (HE), ever since their use, decision models have been challenged regarding balancing their credibility (validity), salience (the relevance of the model), and legitimacy (the representation of stakes and viewpoints) [1–3]. A complicating factor regarding legitimacy (and, related to this, credibility) is that many models are built for the account of parties (sponsors) with clear stakes in the model outcomes. Examples of such conflicts of interest involve not only reimbursement dossiers but also models built for the account of parties interested in advocating a healthy lifestyle, or models of infectious disease spread commissioned by parties working in these areas. Several authors and reviews in various disease areas point this out [4–7].

Broad consensus exists that the validation of HE decision models is important [8, 9]. Validation is then defined as "the act of evaluating whether a model is a proper and sufficient representation of the system it is intended to represent" [10]. The notion of the importance of validating models is almost as old as when the use of simulation models started to become more widespread. In 1967, Naylor et al. discussed the relevance of validating computer simulation models used in industrial systems and issues surrounding this validation [11]. Without proper validation, it cannot be assessed whether the outcomes produced by a model make any sense in view of what these outcomes are intended to be used for. Many errors may occur in model development and application. For instance, a study of the quality of models used in Australian health care policy making reported flaws in 203 of the 247 reviewed models in 2008 [12], while a similar recent UK study reported errors in 39 of 41 studies investigated [13]. A pilot study performed on 77 cost-effectiveness analyses submitted to the French National Authority for Health (HAS) between 2013 and 2017 identified major issues with validation of decision models in two-thirds of the models [14]. Validation helps to minimize these errors and their effects on model outcomes, and also serves to establish the boundaries of the applicability of an HE model, provided it is performed with clear applications in mind.

Gaps occur between what is desired in terms of validation and what is practically feasible. In particular, the validation of endpoints such as lifetime quality-adjusted life-years (QALYs) or life expectancy is problematic because long-term data are typically missing, which is the very reason why HE decision models are built in the first place: to extrapolate beyond the domain of the data, for instance towards a longer time horizon. Instead, most HE decision models will, for pragmatic reasons, be validated on relevant short- to medium-term clinical outcomes that feed into the final endpoints (QALYs, life-years gained, and total costs), like numbers of events, annual costs, and mortality [15]. Thus, it is more workable to consider model validity as a relative rather than an absolute judgment; that is, we talk about the 'validation status' of a model based on the efforts that have been made to validate the model and how these affect the confidence in the model.

Terminology is a clear issue in the field of validation [9, 16]. Hence, it is practical to point out at this stage that we have chosen below to use the categories and terminology as distinguished in the operations research simulation field: conceptual model validation, input data validation, computerized model validation (also called code verification), and operational model validation [17]. Within each category, several validation tests can be distinguished. Examples of such validation tests are face validity testing, sensitivity analyses, or comparison with external data [16, 17]. Comparison of (intermediate) model outcomes with external data is often called external or independent validation when performed as part of operational model validation.

In this opinion paper, we consider four contemporary aspects of health economic modeling with relevance to model validation. These aspects are increased use of complex models, international cooperation, open-source modeling, and stakeholder involvement. We argue why validation still requires more structured attention and give some suggestions on how model validation efforts can be increased and improved in light of the above aspects.

2 Description of Four Aspects of Health Economic Decision Modeling with Impacts on Model Validation

2.1 Complex Models and Multiple Use of Models for Different Evaluations Call for Additional Validation Efforts

New treatment strategies, like precision medicine, and, closely connected, new diagnostics, e.g. next-generation sequencing tests, as well as new vaccine and immunization treatments, tend to be more complex than previous treatments. This increased complexity in turn requires HE decision models to be more complex than the typical cohort-based state transition models, either in terms of model structure or input data analysis, or both [18–20]. In general, these more complex models arise as a result of the need to deal with patient heterogeneity and various sequential treatment decisions.

This is reflected in an increasing variety in model structures being employed with discrete event simulations and agent-based models as examples [21, 22]. In addition, software environments accepted by reimbursement authorities

start to go beyond spreadsheets and a limited set of dedicated software. Simultaneously, more widespread technical knowledge along with wider data availability have led to a broader range of model types being in use and to more complex statistical analyses being deployed for parameter estimation. Next to requirements for modeling structures and software used, this increased model complexity is accompanied by increased demands for validation, and specifically the reporting of validation tests performed.

Except for model outcomes, all other components of the modeling cycle (conceptual model, input data analysis and computer code) are harder to check or review at face value when the model is more complex and hence require more explicit validation efforts. Validation of model outcomes will require attention regardless of the complexity of the model involved.

Moreover, many HE models in the past were only used for supporting a single decision problem. For more complex models, which require a lot of time and effort to build, it is attractive to reuse them for new analyses, not only in new settings but also for the evaluation of new interventions. This supports development of multi-use disease models, also called whole disease models [23], or reference models [24], at the cost of tailored 'single use' models. Examples are found in several chronic disorders.

Multiple uses of models, in the sense of repeated use for different decision problems over time, imply that the investment in model development as well as validation is more worthwhile for the model developers since they can use their model several times. It hence increases the importance of model validation since only models with a generally accepted 'track record' will be attractive for reuse. The reuse of models still has to come with an assessment of fitness for purpose. Reapplication of an existing model to a new intervention will thus require renewed validation.

In sum, we conclude that current clinical developments in terms of treatment options and data availability increase the use of more complex HE decision models, reinforcing the need for proper model validation.

2.2 International Cooperation Offers New Possibilities for Validation

Further international cooperation among policy makers and model reviewers may benefit model validation by concentrating the different efforts for this and increasing the number of users and stakeholders involved. Many HE models are commissioned for the purpose of reimbursement dossiers by international headquarters of pharmaceutical companies. Therefore, models developed for the purpose of reimbursement are often developed for a specific setting (e.g. the UK) and then partially adapted to other local settings and requirements. This implies that reimbursement authorities may benefit from international coordination of efforts to enhance model validity since they are basically repeatedly assessing the same model, with often small local adaptations.

The European Network for Health Technology Assessment (EUnetHTA) aims to enhance European coordination and cooperation regarding reimbursement decision making and health technology assessment (HTA). As part of this, the EUnetHTA has presented the HTA Core Model for supporting such cooperation, which has culminated in a legislative proposal from the European Commission [25]. However, as of yet, cooperation is limited to the evidence regarding the Core Model's clinical domains only; modeling and cost information are left to national institutions (see, for example, https://www.eunethta.eu/hta-core-model/). As regards modeling, we perceive this as a missed opportunity. If, for example, Irish authorities have spent elaborate resources in validating an HE model, and a locally adjusted variant of the same model is subsequently presented as part of an application to, for instance, Dutch authorities, it is clear that international collaboration is worthwhile. Within Beneluxa, this is currently piloted by Austria, Belgium, Ireland, The Netherlands, and Luxembourg (https://beneluxa.org/), who cooperatively review coverage submissions. While many obstacles exist for cooperation in price negotiations and policy making, added value of cooperation exists in the assessment, including the HE model assessment [26].

Next to joint efforts in model reviewing, another example of international collaboration relates to facilitating access to national cohorts and claims databases. Of course, this only works when settings are sufficiently comparable with respect to treatments available and patient population. An example of this is an ongoing project about the French model of rheumatoid arthritis (RA) [27]. The potential use of European registries (e.g., British Society of Rheumatology Biologics Register for Rheumatoid Arthritis) should improve the external validity of the model with independent real-world data. In this example, the management of the disease is quite comparable and relates to similar clinical indications and target populations. Model developers for industry might be encouraged to also use external sources from various countries to operationally validate their models and better test model transferability to different local settings.

In conclusion, closer international collaboration of model users and, in particular, reimbursement authorities support efficient use of model assessment efforts, while international access to relevant data sources widens the options for input data and external validation.

2.3 Code Sharing and Open-Source Software Models

Performing model validation usually requires sufficient insight into the model, which is improved by having access

to the code or to a spreadsheet executable along with any code attached to this, such as Visual Basic for Applications macros. Therefore, most validation guidelines and tools aim at model developers or the model assessment groups that may have full access to this. HE modeling has been lagging behind compared with other simulation modeling fields regarding open-source software and code sharing [28]. Code-sharing initiatives and other efforts for enhancing model transparency may increase model validity since they widen the group of potential assessors, as already mentioned in the first US panel book [29].

Open-source codes such as *hesim* and *heemod* can now be found on *github* [30, 31], while other R packages for several modeling steps are also available [32] and templates to use for spreadsheet-based models can be found (for instance, https://www.herc.ox.ac.uk/downloads/decision-modelling-for-health-economic-evaluation); however, these open-source codes or spreadsheet macros are for general model structures and do still require elaborate modeling work to result in complete HE decision models. Actual complete open-source HE decision models are still scarce [33–36].

Even when the full code is made available, this does not guarantee transparency. Without well-structured documentation, many models might be perceived as black boxes by external users. This is not an exclusive issue for open-source code, but for open-source code the problem is especially clear since it is intended to be used by others than the model developers. Transparency, in the sense of sufficient insight into the model structure, input data, and methods, is a prerequisite for validation [16]. Several guidelines stress the need for proper documentation and transparency [9, 37, 38]. The models referenced above [33–36] show how open-source offers several ways to address this issue by using available documentation structures, such as *github*.

Another option to improve transparency, as well as flexibility, is to develop standard modules for health conditions that can be extensively validated individually and (re-)used as building bricks in HE models [14]. With model elements being more frequently used, it is more worth the investment to elaborately validate them. Examples are the input data building blocks on the Cancer Intervention and Surveillance Modeling Network (CISNET) site for cancer [39], or the UK Prospective Diabetes study (UKPDS) risk engine for diabetes [40]. During use, such building blocks could either increase in validation status or be discarded for better alternatives. Currently, the validation status is not explicitly reported for model building blocks and it is up to those applying them to determine how valid they are.

Ownership and liability and, related, funding for open-source models is an open question. This is probably one of the reasons why, up to now, open-source code is the exception not the rule in HE modeling. Commercial ownership of HE models by consultancy companies, and/or confidentiality of part of the input data, seem to reduce the possibilities for open-source code. Possible solutions might be found in drawing a parallel to scientific publications, and the ongoing developments to enhance open access publication and recognize the efforts of authors and reviewers. Journals now enable different types of open access, as well as access 'upon request', which could serve as an inspiration for a variety of 'open-source options', leaving model developers more control over who has what type of access to their model code.

In sum, while transparency requirements are increasing, as in other scientific fields, open-source modeling is still not very widespread in HE decision models. Possible reasons for this include several unsolved issues regarding finances, accountability, and ownership. Ideally, open-source offers more extensive validation options by a wider group of assessors. The number of good practice examples in HE modeling is increasing.

2.4 Enhanced Stakeholder Involvement May Improve Model Validity

Model development and validation may generally benefit from the involvement of stakeholders through an iterative process, in which the modeler's understanding of what is to be modeled or validated may improve from stakeholder participation, while stakeholders may also learn from model outputs and provide new input for model improvement and validation [41]. This has become common practice in, for instance, environmental impact modeling, and different approaches to stakeholder-participated modeling ('participatory modeling') have been developed [42].

Stakeholder involvement, next to validation, may improve the transparency of HE modeling and the acceptance of the modeling work, as well as policy decisions based on modeling work by these stakeholders [43]. Stakeholder involvement will require a presentation of material in such a way that stakeholders can grasp the meaning and provide comments. This in turn benefits model validation efforts [43, 44].

A major group of stakeholders that has the potential of making real contributions to the process of HE model development and validation consists of patients. Patient involvement may include discussing the validity of the conceptual model and, for instance, treatment adherence, perception of remission, good treatment response, and quality-of-life dimensions not captured by existing health-related quality of life (HRQoL) measures. Patients may discuss the origin and appropriateness of modeling assumptions and approaches, data sources, and model outcomes [45]. Involving patients as stakeholders in the modeling process may increase their understanding of the modelers' work, suppress 'not invented here' perceptions, and instead increase the societal acceptance of the modeling work.

There is an increased recognition of public and patient involvement (PPI) as stakeholders in health research [46]; yet, thus far, the engagement of, in particular, patients has not been prominent in HE modeling [47], partly because, as primary stakeholders they (as the name suggests) have a stake in the results and can easily appear biased, and also most likely since simulation models are considered by model developers as being 'too technical' for patients to be successfully involved. We argue that the latter reasoning is not valid, supported by habits in other modeling fields and by recent developments in HE decision modeling. Rather than rejecting the idea of involving patients in the modeling process, it could be considered how best to involve these stakeholders to 'have the good without the bad' [48]. Several recent examples underline this [49–51]. One group used workshops in which stakeholders, including patients, developed a conceptual HE model by describing causal relationships [49]. In another model development project, a 20-member advisory board including five patients was involved to guide the modeling, by commenting on objectives, comparators, inputs, and outputs [51].

Questions may arise regarding the required education of stakeholders and the presentation of material in such a way that stakeholders can grasp the meaning and provide comments. The development of user-friendly software interfaces that allow for easy model demonstrations will likely improve the access of non-technical stakeholders to simulation models. Having a model version that is easy to work with via an interface allows the user to see the effect of changing relevant input variables or scenarios. This will help stakeholders to understand the purpose of an HE decision model better than any presentation or report would be able to do [52].

In sum, best practice for patient involvement in the HE research process has been suggested [48], while recent examples [49–51] could pave the way for an earlier and more complete involvement of all relevant stakeholders in model development and validation.

3 Discussion

When economic evaluation is required in reimbursement decisions and pricing negotiations, and cost-effectiveness analyses are model based, HE decision models considerably affect healthcare decisions and therefore their validity is crucial. Although model validation has always been considered important, there is a pressing need to again address this topic. Guidelines and tools for HE model validation, especially those including detailed guidance that goes beyond the idea that all models should be fully validated, are still scant [9, 12, 16, 53, 54]. At the same time, current developments around more complex models, open-source coding, and new types of HE models suggest that there are additional demands for model validation to be addressed.

Above, we identified new opportunities and challenges around HE model validation. More complex technologies require more complex models, while international reuse of centrally developed models requires collaboration of model users and reviewers. At the same time, such international collaborations, as well as code sharing and patient involvement in modeling, not only present opportunities to improve the validation status of models but also risks if this is not done in a sensible way.

We therefore recommend focusing research efforts towards how to systematically involve patients in model development in a useful way and how to work with open-source code so that it indeed enhances validation status. Different flavors of open-source access might be helpful to further support this. Both patient engagement and open-source coding may require more resources than traditional models for initial model development, but could greatly increase transparency and support the acceptance of policy decisions based on model outcomes.

Increasing international cooperation regarding model assessment is very relevant, especially so for multi-use disease models, that is models intended for repeated use in different decision problems. More research is needed to investigate whether complete whole disease models, a very extensive form of multi-use disease models that cover the entire disease trajectory from healthy population to palliative care [23], are the solution, or models that only cover part of the disease process, or even modules that can serve as building blocks in an HE model, are more fruitful [55].

We furthermore suggest that the undertaking and discussion of validation efforts should become a default component in economic evaluation literature, and, as a prerequisite for this, sufficient model transparency is also required. By making the reporting of validation efforts a requirement for publication in peer-reviewed journals, not only would the perceived importance of validation most likely increase but other modelers would also be inspired to report validation and would be able to pick up new ideas for performing and reporting validation. With the current availability of online resources, the 'lack of space' argument is hardly valid anymore. What remains is a need for uniformity since lengthy appendices may shift the resource constraint to the reader of the article, unless they are very well organized. Here, good practice guidelines, critical reviews, and examples, both within the field and from similar initiatives in other simulation modeling fields, may be helpful. Model validation should hence become more structured and standardized, as well as more transparent. This would serve to increase the quality of health economic modeling and help us set the step from considering model validation as an art to it being a science with clear and established quality requirements.

4 Conclusion

Increased use of more complex HE decision models reinforces the need for extensive model validation. Simultaneously, closer international collaboration of model users, and especially reimbursement authorities, support efficient use of model assessment efforts and might enhance more extensive validation.

Transparency could be considered a prerequisite for validation. Distinguishing grades of open-source code access similar to those found in current open access of scientific publications might be a way forward here, while more extensive involvement of stakeholders also enhances transparency. Recent examples of patient involvement will hopefully pave the way for an earlier and more complete involvement of all relevant stakeholders in model development and validation.

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