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Systematic Review of Health Economic Impact Evaluations of Risk Prediction Models: Stop Developing, Start Evaluating

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ABSTRACT

Background: Although health economic evaluations (HEEs) are increasingly common for therapeutic interventions, they appear to be rare for the use of risk prediction models (PMs). **Objectives:** To evaluate the current state of HEEs of PMs by performing a comprehensive systematic review. **Methods:** Four databases were searched for HEEs of PM-based strategies. Two reviewers independently selected eligible articles. A checklist was compiled to score items focusing on general characteristics of HEEs of PMs, model characteristics and quality of HEEs, evidence on PMs typically used in the HEEs, and the specific challenges in performing HEEs of PMs. **Results:** After screening 791 abstracts, 171 full texts, and reference checking, 40 eligible HEEs evaluating 60 PMs were identified. In these HEEs, PM strategies were compared with current practice (n = 32; 80%), to other stratification methods for patient management (n = 19; 48%), to an extended PM (n = 9; 23%), or to alternative PMs (n = 5; 13%). The PMs guided decisions on treatment (n = 42; 70%), further testing (n = 18; 30%), or treatment prioritization (n = 4; 7%). For 36 (60%) PMs, only a single decision threshold was evaluated. Costs of risk prediction were ignored for 28 (46%) PMs. Uncertainty in outcomes was assessed using probabilistic sensitivity analyses in 22 (55%) HEEs. **Conclusions:** Despite the huge number of PMs in the medical literature, HEE of PMs remains rare. In addition, we observed great variety in their quality and methodology, which may complicate interpretation of HEE results and implementation of PMs in practice. Guidance on HEE of PMs could encourage and standardize their application and enhance methodological quality, thereby improving adequate use of PM strategies.

Keywords: diagnostic model, health economic evaluation, impact, prognostic model, risk prediction model, systematic review.

Introduction

In the past decades, thousands of clinical risk prediction models (PMs) have been developed, updated, and validated with the purpose to aid in medical decision making [1–3]. Such PMs include both diagnostic models, predicting the presence of health outcomes, and prognostic models, predicting the future occurrence of health outcomes [4]. In both the diagnostic and prognostic settings, predictions are commonly multivariable because doctors naturally integrate several patient characteristics and symptoms (predictors and test results) to make a prediction [5,6]. Hence, PMs (also commonly called "risk scores" or "prediction rules" [1]) are tools that combine multiple predictors by assigning relative weights to each predictor to obtain a probability of a present or future outcome [7,8]. Well-known PMs include the Framingham Risk Score [9], the Ottawa Ankle Rules [10], EuroScore [11], and the Nottingham Prognostic Index [12].

Generally, PMs are internally and externally validated before implementation and use in practice. Such evaluations, however, often appear to be limited to assessment of statistical performance. When applied in clinical practice, these clinical PMs are commonly accompanied by patient management decision strategies, such as the decision to initiate preventive or curative treatment or to refer for further diagnostic testing. The application of a PM, in particular one including new, innovative, and costly diagnostic or prognostic tests or markers, may thus be regarded as a medical intervention—though by itself not therapeutic only via the subsequent actions such models direct. Although ideally PMs and accompanying patient management

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strategies directed by the predicted risks should properly be evaluated with regard to their impact on (long-term) health outcomes (and costs), doing so in randomized model-treatment trials is often infeasible [13,14]. A suitable and adequate alternative to trials for assessment of the (long-term) costs and effects of implementing or updating a PM could be the use of model-based health economic evaluation (HEE) [15–18]. Nevertheless, such evaluations, which are increasingly common for therapeutic interventions, seem to remain rare. For instance, in the field of cardiology, a recent review identified the development of 363 different risk PMs [19], whereas several reviews have shown that studies of the effects of PMs on health outcomes and cost-effectiveness of care are scarce [1].

HEEs are usually performed after a developed risk PM itself has been validated and also after the effects of its subsequent therapeutic or preventive management strategies (including, e.g., specification of risk thresholds for subsequent management) have been established [3,20]. Hence, if HEEs of PMs are performed, this is often done separately from the process of PM development and/or validation. Indeed, conducting HEEs of PMs requires health economic expertise rather than merely statistical, clinical, or epidemiological expertise, which is obviously needed for PM development and validation.

As for all HEEs, when performing an HEE of a risk PM with its subsequent risk-based management decisions and pathways, many choices and assumptions have to be made. Although guidance is available for conducting and reporting HEEs in general [21–24], there is currently no guidance available specifically for the HEE of PMs. This may result in a wide variety of choices, for example, with regard to the parameters included and uncertainty analyses performed. We therefore performed a comprehensive systematic review to evaluate the current state of HEEs of clinical risk PMs, including modeling choices and quality as well as reporting aspects, and considering all types of HEEs and PMs across all disease areas.

Methods

Literature Search

We focused on HEEs, often referred to as cost-effectiveness analyses, of both diagnostic and prognostic PMs and associated patient management strategies and used corresponding keywords. The range of sources searched included Embase, MEDLINE, EconLit, and the National Health Service Economic Evaluations Database up to January 2014. Finally, we searched the references of the identified articles for additional eligible articles. Full details of the search strategy are provided in Appendix 1 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.01.001.

Inclusion Criteria

The following restrictions were applied:

1. The HEEs were required to evaluate at least one strategy including the use of any clinical risk PM. The application of the PM, along with associated further clinical pathways and consequences, such as subsequent testing or treatment, could be a strategy in itself or the PM could be embedded in a strategy, for instance, combined with other tests. Hence, we excluded HEEs in which the PM was used only to select individuals (e.g., high-risk individuals), in which subsequently different treatment strategies were evaluated.
2. The HEEs were required to result in impact outcomes that enable comparison across disease areas, such as incremental costs per life-year, deaths avoided, or quality-adjusted life-years (QALYs) gained, as opposed to providing only disease-specific health outcomes, as for instance complications or recurrent diseases averted.
3. PMs, diagnostic or prognostic, were required to represent a model of a combination of predictors to yield risks or probabilities of outcome presence (diagnostic model) or future outcome occurrence (prognostic PM) in individuals. PMs could be presented, for instance, by a regression formula, a simple score, or a nomogram.
4. Journal articles of original research were included. Technical research report, editorials, letters, and conference proceedings were excluded.

We have not made any restrictions on language nor on medical area or PM or HEE model type. On the basis of these inclusion criteria, two reviewers first independently examined titles and abstracts to identify eligible studies. If both reviewers agreed on exclusion, the article was excluded. For articles of which the exclusion was not unanimous, as well as the remaining articles, full texts were obtained and the same criteria were applied to assess their eligibility. In case of doubt, a third or fourth reader was involved, resulting in the final list of included studies.

Scoring Quality, Modeling, and Reporting Items

We compiled a comprehensive checklist to score items focusing on

1. general characteristics of HEEs of PMs (Table 1);
2. model characteristics and quality of the HEEs (Table 2);
3. evidence on PMs that was typically available and used in the HEEs (Table 3);
4. specific challenges in performing HEEs of PMs (Table 3).

To cover these four topics, the Drummond checklist (extensive 36-item version) was included for quality appraisal of the included HEEs (see Appendix Table 1 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.01.001) [25]. On the basis of existing methodological recommendations for conducting and reporting HEEs, further items describing and evaluating the HEEs were included [22,24–27]. Finally, on the basis of extensive discussions among coauthors, items were added that focus on describing general characteristics of the included HEEs, such as disease area and type of clinical decision problem studied, and identifying specific issues relating to the HEE of PMs, such as whether the PM had already been validated and how the PM was applied in the HEE, for example, with what kind of subsequent management.

Often, details of the PMs under evaluation were not discussed in the HEE articles. Therefore, we consulted the source article for (development and validation of) the PM to assess details of the PMs studied on their Health Economic impact. The final checklist was scored by two reviewers and adjustments were made, if necessary. Items were mostly scored as present, absent, not applicable, or unclear. If an item concerned a descriptive answer, we extracted these answers and, if possible, translated these into categories. One reviewer extracted the data and in case of doubt, items were discussed with a second reviewer.

Results

On searching MEDLINE, Embase, EconLit, and the National Health Service Economic Evaluations Database, we identified 791 unique abstracts (Fig. 1). In the phase of abstract screening, 620 (78.4%) articles were excluded. Subsequently, 171 (21.6%) full-text articles were screened, of which 39 (4.9%) were eligible. These included articles were each checked for references of additional articles