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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

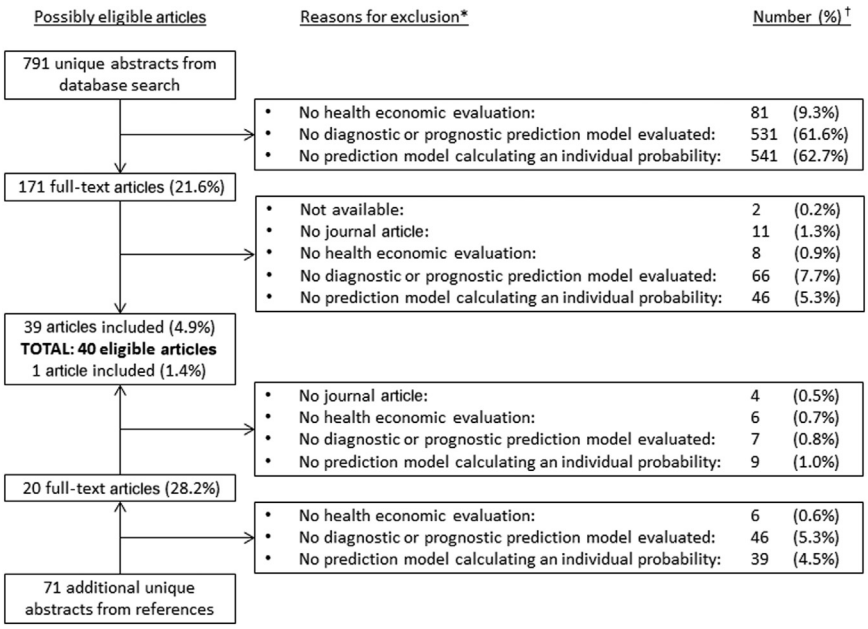

Fig. 1 – Flowchart of literature screening process. The selection of eligible articles from the database search (top-down) is shown. For each selection criterion, the number of articles not fulfilling this criterion (not mutually exclusive), along with the percentage of the total number of identified abstracts, is presented. References of the included HEEs from the initially included 39 articles followed the same screening process (bottom-up). *Reasons for exclusion are not mutually exclusive. †Percentage of all 862 identified article abstracts. HEE, health economic evaluation.

possibly describing an HEE of a PM strategy. One additional article was added to the 39 articles retrieved after following the same selection process. Details on the selection of eligible articles and reasons for exclusion can be found in Figure 1. A list of all included HEE articles can be found in Appendix Table 2 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.01.001.

General Characteristics

In the 40 HEE articles identified, 60 PMs were evaluated. Among these models, variations in the Framingham Risk Score (calculating the 10-year probability of a cardiovascular disease event) and FRAX (calculating the 10-year probability of an osteoporotic fracture) were evaluated 15 and 7 times, respectively. Most of the HEEs concerned the area of cardiology (n = 16; 40%), followed by orthopedics (n = 9; 23%) and oncology (n = 8; 20%). In the HEEs, implementation of a PM strategy was compared with 1) current practice (n = 32; 80%); 2) other ways of stratifying individuals for subsequent management (n = 19; 48%); 3) an updated or extended PM (n = 9; 23%); or 4) other PMs (n = 5; 13%). The 60 evaluated PMs were part of strategies in which they aided in decision making on preventive treatment (n = 42; 70%), further (diagnostic) testing (n = 18; 30%), or prioritization of treatment (n = 4; 7%). Additional general characteristics are presented in Table 1.

Table 1 – General characteristics of HEE of PMs.

Item	Categories	Number	Percentage
Disease area	Cardiology	16	40%
	Oncology	9	23%
	Orthopedics	8	20%
	Hematology	4	10%
	Infectious diseases	2	5%
	Diabetes	1	3%
Comparison type*	PM vs. current practice	32	80%
	PM vs. alternative individual selection	19	48%
	PM vs. updated/extended PM	9	23%
	PM vs. other PMs	5	13%
Decision type†	Preventive treatment	42	70%
	Further testing	18	30%
	Prioritization of treatment	4	7%

HEE, health economic evaluation; PM, prediction model.
* Within some of the HEEs multiple strategies were compared. Hence, these numbers do not sum up to the total of 40 HEEs.
† Within some HEEs a PM informed treatment in one strategy, whereas the same PM informed further testing (ultimately informing treatment) in another strategy. Hence, these numbers do not sum up to the total of 60 PMs.

Characteristics and Quality of the Health Economic Model

In 29 (73%) of the 40 HEEs, an Idem model was used that was developed specifically for the decision problem currently evaluated. A validated Idem model, such as the Archimedes model or the PopMod model [28,29], was used in 8 (21%) HEEs, whereas in 3 (8%) HEEs an Idem model that had been developed in a former HEE study was used. Individuals were represented as a cohort in 29 (73%) HEEs, as individual patients in 8 (20%) HEEs, whereas in 3 (8%) HEEs it was unclear how individuals were simulated. Of all 40 Idem models, 22 (55%) were state transition models, 11 (28%) decision tree models, and 4 (10%) consisted of both, whereas in 3 (8%) it was unclear what type of decision-analytic model was used. In 26 (65%) of the HEEs, time was handled in a discrete manner, in 9 (23%) continuously, and in 5 (13%) it was unclear.

Individuals in the HEEs were mostly simulated over their entire lifetime (n = 22; 55%), whereas 13 (33%) HEEs reported shorter "follow-up," and in 5 (13%) HEEs it was unclear. In 3 studies, the time horizon was varied in a scenario analysis. A health care perspective was most frequently used (n = 22; 55%). In 8 (20%) HEEs, a societal perspective was used. Other types of perspective, such as a payer perspective (including direct societal costs) or a governmental payer perspective, were reported in 4 (10%) HEEs, whereas in 6 (13%) HEEs it was not clear what perspective was taken.

Most of the 40 HEEs (n = 32; 80%) reported incremental costs per QALY gained as their health economic outcome, followed by costs per life-year saved (n = 7; 18%) and net monetary benefit (n = 5; 13%). In 5 (13%) HEEs, other outcomes, such as incremental cost per bleeding event averted [30] and cost per diagnosis of

Table 2 – Model characteristics and quality of HEEs of PMs.

Item	Categories	Number	Percentage
Was the economic model developed in this study?	Yes	29	73%
	No, in a former study	3	8%
	No, a validated model was used	8	20%
How were patients presented in the model?	Cohort level	29	73%
	Individual level	8	20%
	Not clear	3	8%
What type of decision-analytic model was used?	Decision tree	11	28%
	State transition	22	55%
	Both	4	10%
	Not clear	3	8%
How was time handled in the model?	Discretely	26	65%
	Continuously	9	23%
	Not clear	5	13%
What was the time horizon?	0 to ≤ 1 y	1	3%
	1 to ≤ 5 y	2	5%
	5 to ≤ 10 y	5	13%
	10 to ≤ 30 y	5	13%
	Lifetime	22	55%
	Not clear	5	13%
What was the perspective of the model?	Health care perspective	22	55%
	Societal perspective	8	20%
	Other	4	10%
	Not clear	6	15%
What were the model outcomes relating health effects to costs?*	ICUR—costs/QALY	32	80%
	ICER—costs/LY	3	8%
	Costs/DALY	2	5%
	Costs/LY saved	7	18%
	NMB—QALYs	5	13%
	Other	5	13%
Was probabilistic sensitivity analysis performed?	Including all parameters	14	35%
	Including some parameters	8	20%
	No	18	45%
Was (additional) sensitivity analysis performed?	One-way sensitivity analyses	32	80%
	Multiple-way sensitivity analyses	1	3%
	Both	5	13%
	Scenario analyses	1	3%
	No	1	3%
Were subgroup analyses performed?	Yes	20	50%
	No	20	50%
Was a VOI analysis included?	Yes	1	3%
	No	39	98%

DALY, disability-adjusted life-year; HEE, health economic evaluation; ICER, incremental cost-effectiveness ratio; ICUR, incremental cost-utility ratio; LY, life-year; NMB, net monetary benefit; PM, prediction model; QALY, quality-adjusted life-year; VOI, value of information.

* Because some HEEs presented multiple outcomes, combining health effects and costs, the numbers in this category do not sum up to the total of 40 HEEs.

Table 3 – Characteristics of PM strategies in HEEs.

PM characteristics	Categories	Number	Percentage
Was the PM fully reported?	Yes; model and coefficients	32	53%
	Yes; as a nomogram	4	7%
	Yes; as an online risk calculator	3	5%
	Other	3	5%
	No	18	30%
What type of PM was used?	Logistic	13	22%
	Survival, Cox	13	22%
	Survival, Weibull	9	15%
	Poisson	8	13%
	Other	9	15%
	Not clear	8	13%
What was reported to be the current state of the PM?*	No validation mentioned	14	23%
	Internally validated, bootstrapping	2	3%
	Internally validated, cross-validation	3	5%
	Externally validated	23	38%
	Internally and externally validated	18	30%
	Incorporated in clinical guidelines	19	32%
PM evaluation			
Were authors of PM article also authors of HEE article?	Yes	24	40%
	No	36	60%
What did the HEE refer to for the PM?	Original PM article	20	33%
	Article of PM application/validation	18	30%
	Article in which PM was extended/ updated	3	5%
	Online source	4	7%
	Guideline	3	5%
	PM is described in the HEE	6	10%
	Other	6	10%
Was IPD used for calculating risk prediction parameters in the HEE?	Yes	38	63%
	No	18	30%
	Not clear	4	7%
Were multiple thresholds evaluated?	Yes	20	33%
	No	36	60%
	Not appropriate	4	7%
What were thresholds based on?	Guideline	26	43%
	Optimized in HEE itself	7	12%
	Other	12	20%
	Not clear	11	18%
	Not appropriate	4	7%
Was the cost of performing risk prediction incorporated?	Yes	32	53%
	No, justified	5	8%
	No, not justified	23	38%
Prediction uncertainty			
Was any information to calculate the uncertainty around predictions given?	Covariance matrix of PM coefficients	3	5%
	Standard errors of PM coefficients	3	5%
	Confidence intervals of PM coefficients	20	33%
	No	34	57%
Was impact of the prediction uncertainty evaluated?	Yes; on cohort level	10	17%
	No	50	83%

HEE, health economic evaluation; IPD, individual patient data; PM, prediction model.
* Multiple outcomes can be reported per PM; hence, the numbers in this category do not sum up to the total of 60 PMs.

cardiovascular risk [31], were additionally reported. Assessment of the uncertainty in these outcomes was performed using probabilistic sensitivity analyses (PSA) in 22 (55%) of the HEEs. In 14 (35%) of these studies, nearly all parameters were included in the PSA, whereas in 8 (20%) only some parameters were varied. In 18 (45%) HEEs, PSA was not performed. Instead, other forms of sensitivity analysis, such as one-way (n = 37; 93%) and/or multiple-way (n = 6; 16%) sensitivity analyses, were applied. There were no HEEs that performed neither PSA or any other form of sensitivity analysis. Subgroup analyses were performed in 20 (50%) HEEs, mainly to assess heterogeneity in age groups or sex. Only 1 HEE included a value of information analysis. Additional information on characteristics of the HEEs is presented in Table 2.

Evaluating the Drummond checklist among all 40 HEEs, we found that general aspects, such as the selection of an appropriate time horizon, application of discounting, and choice of outcomes, were reported quite well. Nevertheless, there is still room for improvement on the completeness of reporting, mainly on items such as the perspective and quantities of resources as well as the performance of sensitivity analyses and the choice of parameters, values, and distributions included (see Appendix Table 1 in Supplemental Materials).

Characteristics of PM Strategies in HEEs

Of the 60 evaluated PMs, the development of 6 (10%) PMs was described in the HEE article. For 20 (33%) PMs, the HEE referred to the original article describing the development of the model, for 18 (30%) to an application or validation of the PM, for 3 (5%) to an article in which a PM is extended/updated, for 4 (7%) to an online risk prediction tool, for 3 (5%) to a guideline that mentions the PM, and for 6 (10%) the authors referred to other sources, such as a conference abstract or a health technology assesment (HTA) report. A list of the PM references that were evaluated for each HEE can be found in Appendix Table 2 in Supplemental Materials.

PM characteristics

In the sources the HEEs referred to for the 60 PMs, 32 (53%) PMs were fully reported, that is, in such a format the predicted risk for an individual could be calculated if the required predictor values were available. An online source for risk calculation was referred to for 3 (5%) of the models; 4 (7%) were represented as a nomogram, whereas for 18 (30%) PMs the risk could not be recalculated on the basis of the HEE or PM study reference. For most of the evaluated PMs, it was reported that they had been internally validated, externally validated, or both, whereas for 14 (23%) PMs no validation was mentioned. In either the HEE or the PM reference, for 19 (32%) PMs it was reported that they were already recommended in clinical guidelines.

In 9 (23%) of the HEEs, a PM was compared with an extended PM for which an imaging (n = 4), genetic (n = 2), or laboratory (n = 3) test was added. In 5 PM extensions a new PM was developed, whereas for 4 PM extensions the probability calculated by the original PM was multiplied by a relative risk of the added predictor or test to calculate the new individual probability.

PM evaluation

In 24 (40%) of the 40 HEEs, at least one of the authors was also author of the reference to the applied PM. It appeared that for 38 (63%) of the PM evaluations, individual patient data (IPD) were used in the HEE to calculate input parameters concerning the PM, such as the distribution of individuals over risk categories. For 4 (7%) PM evaluations it was unclear whether IPD were available, whereas for 18 (30%) HEEs, IPD were not available. Here, estimates of risk categorization from published data were used instead.

We found that for 36 (60%) PM strategies a single risk-based decision threshold was evaluated. Risk thresholds (single or multiple) selected for evaluation were mostly based on guidelines (n = 26; 43%), or the threshold was aimed to be optimized in the HEE itself (n = 7; 12%). Other explanations for the risk threshold choices were, for instance, that they were based on expert opinion [32], on literature [31,33], or were chosen in order not to exceed a prespecified disease or outcome prevalence [34,35]. Optimization of risk thresholds was commonly performed by evaluating a predefined number of thresholds and selecting the one with the highest desired outcome, such as optimal cost-effectiveness [36–38].

The costs of risk prediction, such as measurement of predictors, were taken into account for 32 (53%) of the PMs, whereas 5 (8%) mentioned the costs, but had arguments not to take them into account, such as unavailability of the price of a new predictor or test or the claim that risk prediction did not require additional resources because of assessment during routine visits [39,40]. Cost of risk prediction was not mentioned for 23 (38%) of the evaluated PMs.

Among the references from the HEEs informing on the PM, 26 (43%) reported some sort of information, allowing the calculation of uncertainty surrounding the predicted risks. In these cases, the covariance matrix (n = 3; 5%), standard errors (n = 3; 5%), or confidence intervals (n = 20; 33%) of the coefficient estimates of the PM were reported. Uncertainty around the predicted risk was incorporated (on a cohort level) in the uncertainty assessment of the HEE for 10 (17%) PMs.

Discussion

The aim of this comprehensive review was to provide an overview of HEEs of clinical risk PMs and their specific characteristics and challenges, given the increasing need for and relevance of such evaluations [17,18,41,42]. After searching four large databases up to January 2014 and subsequently screening 791 abstracts, 171 full texts, and checking references, 40 eligible HEEs were identified in which 60 PMs were evaluated. To systematically describe the current state of HEE of PMs, we compiled an extensive checklist to score items on characteristics, quality, and reporting of these evaluations. General aspects of HEEs have been modeled and reported quite well among the identified HEEs of PMs. Nevertheless, among aspects specifically concerning the HEE of PMs, we observed great variety in modeling choices and quality.

We chose a pragmatic search strategy with search terms focusing specifically on HEEs of (diagnostic or prognostic) risk PMs up to January 2014. Because only 40 articles were identified up to this date, of which only 1 article was additionally included after cross-checking the references of the 39 included articles, it is unlikely that we have missed any key articles. Moreover, because the article focused on methodological aspects of HEEs, it is unlikely to have affected our results. We included all journal articles of original research, hence excluding more extensive technical research reports, such as health technology assessment reports of the National Institute for Health Research. These reports commonly include more extensive (scenario and sensitivity) analyses and more extensive reporting, which is preferable, but thereby not comparable with HEEs reported in journal articles. Information on the PM under evaluation was obtained from the references in the HEE article (see Appendix Table 2 in Supplemental Materials). Hence, additional details regarding the PM that may have been available from other sources and references were not included in our analysis.

For conducting and reporting HEEs in general, several guidelines have been developed, such as the International Society for Pharmacoeconomics and Outcomes Research guidelines [21,22], the World Health Organization guidelines [23], and the Consolidated Health Economic Evaluation Reporting Standards statement [24]. We found that general aspects, such as the selection of an appropriate time horizon, application of discounting, and choice of HEE outcomes, were modeled and reported quite well among the 40 HEEs of PMs. Nevertheless, there is still room for improvement, mainly on items such as reporting of the perspective and of quantities of resources as well as the performance of sensitivity analyses and the choice of parameters, values, and distributions included in the model (see Appendix Table 1 in Supplemental Materials).

Table 4 – Recommendations to improve HEE of PMs.

Issue	Findings in present review	Recommendations for conducting/reporting HEEs of PMs
Comparators	Several different comparators were used in the HEEs of PM strategies, such as comparing different PM types and omitting current practice.	• Always (also) compare the PM strategy with current practice, which can be, for example, o no (preventive or curative) treatment o (preventive or curative) treatments according to current guidelines o alternative risk-based strategies, for example, recommended in current guidelines
PM-related parameters	Unclear referencing of sources informing application of the PM.	• Clearly report which (version of the) PM was used, for example, o data sources in which the PM was developed/specified such that risks can be recalculated o sources that report extensions or updates of the PM o guideline that specifies the use of the PM
Risk-based thresholds	• Single or multiple risk thresholds were evaluated on the basis of different (unclear) sources. • IPD, allowing evaluation of multiple risk thresholds, were not available for many (n = 18 of 60; 30%) PMs.	• Report applied thresholds for risk categorization and refer to source of information for these thresholds. • If the PM strategy is the usual care strategy, then use risk threshold(s) specified in the guideline. • If IPD are available, ideally the risk threshold may be optimized. Alternatively, sensitivity analysis on the threshold value may be performed. • If only one risk threshold is evaluated, motivate why the threshold is not varied and acknowledge HEE outcomes depend critically on the chosen threshold.
Cost of risk prediction	For many PMs (n = 28; 46%), costs of risk prediction were not incorporated in the HEE.	• If not specified in the original PM development and validation articles, clearly describe all costs involved in the use of the PM in the targets setting in the HEE, such as costs for consultation, physical examination, imaging, or biomarkers.
Uncertainty of risk predictions	• Impact of uncertainty surrounding risk predictions was rarely (n = 10; 17%) evaluated. • Information required to calculate this uncertainty was not available for many (n = 34; 57%) PMs.	• Articles describing the development or validation of PMs should more often report the confidence intervals, standard errors, or, preferably, the covariance matrix of PM coefficients to allow calculation of uncertainty in risk predictions. Alternatively, the IPD underlying the PM could be made publicly available.
PM development/ validation separate from impact evaluation	Most of the PM evaluations (n = 36; 60%) showed no signs of an integrated approach of PM development/validation and an HEE of the consequences of using the PM.	• An integrated approach combining developing, validating, and evaluating the cost-effectiveness of a PM strategy is the preferred option. • The resources required for the HEE of a PM strategy may prohibit its use up to the point at which the PM has at least been externally validated. Still, the HEE should be performed before implementing the PM, and ideally in collaboration with the original developers.

HEE, health economic evaluation; IPD, individual patient data; PM, prediction model.

For conducting and reporting HEEs of risk PMs, no specific guidance is available. In the literature, several frameworks are presented for evaluating the health economic impact of prognostic biomarkers and it has been proposed that professional societies and government bodies should consider cost-effectiveness in evaluating prognostic biomarker strategies using similar principles as they do for drugs, devices, and other technologies [14,17,18,42,43]. Possible consequences of the current lack of guidance in HEE of risk PMs are the wide variety in Health Economic modeling choices that were found, such as whether the costs of risk prediction were incorporated, whether uncertainty in risk prediction was assessed, and how risk thresholds for treatment or further testing were handled among the 40 HEEs we included (Table 3).

Several challenges with HEE of PM strategies were identified (Table 4). For instance, assessment of multiple risk thresholds within the HEE as well as assessment of the uncertainty surrounding predicted risks are examples of Health Economic modeling aspects that preferably use IPD. Appropriate IPD are often not (publicly) available, but would be available in case of an integrated approach comprising the development, validation, and evaluation of long-term health effects and costs of a PM strategy in one effort. Such an approach has previously been proposed to prevent making (unreliable) assumptions and extrapolations to, for instance, other populations or settings [32]. An integrated approach may, however, not always be feasible or necessary because few PMs are implemented in management strategies or used in clinical practice, relative to the large number of models published [1]. Hence, the resources required for the HEE of a PM strategy may prohibit its use up to the point at which the PM has at least been externally validated and is proposed to be implemented in guidelines.

If the development, validation, and HEE of a PM are not integrated and IPD are not available when conducting the HEE, the possible comprehensiveness of the HEE depends on the level of detail of the PM as retrievable from the PM development and validation studies. Hence, it depends on how much and how well evidence was reported in articles developing and validating the PM, for instance, whether the PM was fully reported. Several reviews have shown that across different disease areas and different journals the level of reporting on PM studies is generally poor [1,44]. Although reporting guidelines for PMs are currently available [45], they typically do not include aspects valuable for conducting HEEs of PM strategies, such as information necessary to calculate the uncertainty surrounding predicted risks. These and other challenges with HEEs of PM strategies that were identified are further presented in Table 4, which can be a starting point for specific guidance on this topic.

We found that despite the overwhelming number of risk PMs in the medical literature, health economic impact evaluations of PMs remain rare. If done, there is also great variety in the quality and methodology of such HEEs. This variation may complicate the interpretation of HEE results and thereby the implementation of PM strategies in practice. Guidelines on HEE of risk PM strategies, as well as additional reporting items for (impact) evaluation of risk PMs, could help to standardize and enhance methodological quality, which may improve adequate implementation of such strategies and thereby gain health effects and/or save costs.

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Supplemental Materials

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