Towards optimal decision making in personalized medicine
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Potential economic value of biomarkers in optimized patient care: an exemplary assessment study in heart failure disease management

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Working paper
ABSTRACT

Aim: To show how the potential economic value of adding biomarkers to a prognostic model with demographic and clinical covariates can be evaluated using a case study in heart failure (HF) disease management.

Methods: Patient-level 18-month mortality risks were predicted by both a prediction model which contains conventional risk predictors for HF-related outcomes and a model which contains three additional biomarkers: NT-proBNP, galectine, and troponin. A previously derived cut-off value of 0.16 was adopted to allocate an intensive form of disease management programs (DMP) to low-risk patients and a moderate form of DMP to intermediate to high-risk patients. The improved ability of risk classification after the incorporation of biomarkers was evaluated using the net reclassification improvement (NRI). Subsequently, a continuous-time semi-Markov model was developed to evaluate the potential economic value of the biomarkers through presenting the commercial headroom available, which is a price ceiling for which the intended clinical application of the new medical technology may be deemed cost-effective.

Results: A significantly ($P<0.001$) improved risk stratification was established with 0.1814 (95% confidence interval: 0.0926–0.2703) as the NRI estimate. Extending this finding for the base-case values of the decision model parameters, we found the commercial headroom available for the biomarkers to be €256 within a 5-year time horizon. This value was rather sensitive to the alteration of the risk thresholds to 0.1 and 0.2.

Conclusions: The estimates of the available commercial headroom in several scenario analyses indicate considerable economic potential of the biomarkers to support personalized disease management in HF.
7.1 INTRODUCTION
Prognostic models are developed to predict the clinical outcomes associated with a specific disease over a given time period\textsuperscript{1-5}, so that treatment selection decisions can be made in an informed manner. To ensure more unbiased prediction, such models are generally based on multiple demographic and clinical variables.\textsuperscript{6} However, given that prediction with simple and easy-to-use models has not been perfect, a considerable body of literature has appeared assessing the added prognostic value of including a single biomarker or a panel of biomarkers on top of the conventional risk factors.\textsuperscript{7-10} Such assessments generally assess the added value of those biomarkers in terms of improved risk prediction.\textsuperscript{11,12} However, because the need to take additional biomarker measurements results in a more expensive prognostic test, an assessment of model accuracy will not suffice to decide whether the newly added biomarkers have the potential to actually improve health outcomes at an affordable manner.\textsuperscript{13,14} This in fact suggests that cost-effectiveness analysis should be conducted to assess the economic value of biomarkers to enable more efficient allocation of the scarce health care resource.\textsuperscript{15}

The innovation of medical technology, i.e., a novel device for biomarker measurement, is often a costly and uncertain procedure\textsuperscript{14,16} in which early-stage assessment is important to conduct. Such assessment may aid in selecting out the favorable technology concepts for further development to reduce the chance of later-stage market failure and disinvestments.\textsuperscript{16} Early health economic modeling has recently been adopted to evaluate the potential economic value of innovative medical technologies.\textsuperscript{17-20} The main modeled outcome is a price ceiling for which the intended clinical application of the new medical technology may be deemed cost-effective.\textsuperscript{21,22} A recently developed approach\textsuperscript{20} provided a framework to illustrate how this upper cost bound, also known as the commercial headroom available, can be incorporated in assessing the potential economic value of a biomarker-based technology. Despite having been noticed as an important methodological extension to enable early-stage economic evaluations by two recently published systematic reviews\textsuperscript{16,23}, there is still no published work to illustrate a direct application of this framework. In this study, we therefore aim to present a first application to assess to what extent the inclusion of a panel of biomarkers in heart failure (HF) might improve risk stratification through allocating personalized care while remaining affordable.
Chapter 7

7.2 METHODS

7.2.1 Study cohort
The clinical evidence of this study was collected in a prospective observational cohort study included in TRanslational Initiative on Unique and novel strategies for Management of Patients with Heart failure (TRIUMPH). TRIUMPH was a program to identify novel biomarkers and molecular imaging modalities to innovate heart failure diagnosis, prognostication, and disease management by combining large-scale biological discovery with technologic advances. After the selection of a panel of novel biomarkers, which successfully passed the bioinformatics and early pre-clinical validation, this cohort study aimed to evaluate the clinical value of such biomarkers. All patients recruited were 18 years or older and had evidence of sustained systolic or diastolic left ventricular dysfunction as shown on echocardiography. Out of the 475 patients admitted to hospital with a diagnosis of acute HF, 454 were discharged alive and followed for a maximum of 400 days after having signed the informed consent. This latter group of patients forms the study population for this paper. The main endpoints of this study were time to the combined outcome death or hospital readmission because of HF, and time to each single endpoint.

7.2.2 Risk prediction and added prognostic value assessment
The 18-month mortality risk was predicted using a log-normal survival model with multiple risk factors that are commonly used for predicting HF-related outcomes. Age, gender, systolic blood pressure (SBP), body mass index (BMI), history of previous HF admission, history of ischemic HF, and comorbidity of diabetes were selected as the predictors to be included in the conventional clinical risk prediction model (referred to as conventional risk model hereafter). Baseline values of N-terminal prohormone brain natriuretic peptide (NT-proBNP), galectine and troponin were selected as the biomarkers potentially marking additional risk in the prediction model. SBP and BMI were measured at admission and biomarker values were included as the measurement conducted within 48 hours prior to or after hospital discharge. Most continuous variables were entered as linear terms, except for NT-proBNP and troponin, which were log transformed. Missing values on these predictor variables were dealt with using multiple imputation. Mortality risk was calculated by taking the average of the risk values predicted from each of the imputed datasets. A threshold value of 0.16 for 18-month mortality risk was adopted to stratify patients into low-risk and intermediate to high-risk subgroups for both the conventional risk model and the prediction model which includes biomarkers (referred to as biomarker risk model hereafter). This value was attained in a
previous study\textsuperscript{26} in which the allocation of an intensive form of HF disease management program (DMP) to low-risk patients and a moderate form of DMP to intermediate to high-risk patients was found to be more cost-effective than different one-size-fits-all strategies offered to the entire patient population. The improved risk stratification attained after incorporating biomarkers was assessed based on the incremental ability of an individual’s risk modification. This was achieved through calculating the net reclassification improvement (NRI) from the reclassification table with 0.16 as the cut-off value.

\textbf{Figure 1: Schematic representation of the structure of our decision model}

\textbf{7.2.3 Decision model structure, parameter estimation, and model validation}

To estimate the expected health effect and costs of assigning different interventions to different subgroups of patients, we developed a continuous-time homogeneous semi-Markov model (HSMM)\textsuperscript{27,28} with the following three health states (Figure 1): discharged alive (state 1), HF-related hospital readmission (state 2), and dead (state 3). The specification, parameter estimation and evaluation of this model was conducted using vertical modeling formulation\textsuperscript{29} based on a previously suggested framework.\textsuperscript{28} Weibull survival models were used to estimate the cumulative distribution functions of the sojourn time $u$ in both state 1 and state 2 ($F_i(u), i = 1, 2$). Conditional on time elapsed prior to making a transition, the probabilities of the next state visited, also referred to as the future state probabilities ($\pi_{ij}(u), i,j = 1,2,3; i \neq j$),
were estimated by fitting logistic regression models to the observed outcomes of out-of-hospital death and in-hospital death. Possible non-linear relationships between the sojourn time and these two probabilities were assessed based on fractional polynomials.\textsuperscript{30,31} The patient subgroup indicator $G$ was incorporated as the covariate in estimating $F_1(u), F_2(u)$, and $\pi_1(u), \pi_2(u)$ was assumed not to differ among patients as the observed in-hospital mortality was relatively low for the entire patient population. The specific subgroups corresponding to different values of $G$ were depicted as follows: $G=1$ when patients were classified as low-risk based on the two risk prediction models; $G=2$ when patients were classified as low-risk based on the clinical risk model and intermediate to high-risk based on the biomarker risk model; $G=3$ when patients were classified as intermediate to high-risk based on the clinical risk model and low-risk based on the biomarker risk model; $G=4$ when patients were classified as intermediate to high-risk based on the two risk prediction models. The content and structure of the two hypothetical interventions of this study were assumed to be the same as the two nurse-led DMPs (i.e., moderate form and intensive form) included in the previous study\textsuperscript{26} to derive the threshold risk value. The effect of the intervention was only incorporated in the Weibull survival function when estimating $F_1(u)$. Model performance regarding overall survival was internally validated by comparing the predicted (average across 100,000 simulation runs) to the observed empirical 400-day (Kaplan-Meier estimate) survival curves.

### 7.2.4 Headroom analysis

The commercial headroom available of the biomarkers can be estimated as

\[
h = \sum_{k=1}^{m} \sum_{j=1}^{n} f_{kl} \left[ \lambda \times (c_{kl}^{\text{t}_1} - c_{kl}^{\text{t}_2}) - (c_{kl}^{\text{t}_1} - c_{kl}^{\text{t}_2}) \right]
\]

where $\lambda$ denotes the willingness-to-pay (WTP) threshold and $f_{kl}$ denotes the proportion of the patients who were risk-reclassified (i.e., when their group indicators $G$ were shown to be either 2 or 3) out of the entire patient population. $c_{kl}^{\text{t}_1}$ and $c_{kl}^{\text{t}_2}$ denotes the average cost and health effect when assigning intervention $t_{kl}^{\text{t}_1}$ to the patients who were risk-reclassified. The indicator $i$ in $t_{kl}^{i}$ denotes whether the treatment needs to be assigned based on the 18-month mortality predicted using the clinical risk model ($i=1$) or the biomarker risk model ($i=2$). For patients remaining in the same risk groups (i.e., when their group indicators $G$ were shown to be either 1 or 4), the addition of biomarkers did not alter the recommended therapy.
7.2.4.1 Base-case scenario
A fixed out-of-hospital follow-up frequency for both interventions was assumed for our study. The resulting cost associated with the discharged alive state was equal to €1.56 per day for the moderate support DMP and €2.34 per day for the intensive support DMP.26 The cost associated with the HF-related hospital readmission state was set equal to €769 per day.32 Following the risk-stratified treatment recommendation33 developed previously, the moderate support needs to be assigned to intermediate to high-risk patients and the intensive support to low-risk patients within both reclassified risk groups. The hazard ratios between \( t_{\mu}^{2} \) and \( t_{\mu}^{1} \) were assumed to be 1.1 when \( G=2 \) and 0.9 when \( G=3 \) as base-case values to reflect the corresponding treatment allocations. The expected values of the health effects and costs were estimated by repeating the simulation process 100,000 times as suggested for our type of model28 with the discharged alive state as the starting state and survival time as the measure of health effect. The time horizon for this study was set at 5 years. Future costs and life years were discounted at an annual rate of 4% and 1.5% following the Dutch manual for costing.34 The WTP threshold was assumed to be €20,000.

7.2.4.2 Sensitivity analyses
Sensitivity analyses were preformed to investigate how the estimate of the commercial headroom available might be influenced by altering some of the model input parameters. Besides the risk threshold value of 0.16 for the base-case scenario, these values were assumed to be altered to 0.10 and 0.20. Also, different hazard ratios were assigned instead of the base-case assumption of the treatment effect.
7.3 RESULTS

7.3.1 Patient characteristics
During the follow-up period, 167 patients (37%) reached the combined endpoint of HF readmission or death, out of whom 123 patients (74%) were readmitted because of HF. A total number of 176 hospital readmissions were recorded with a median duration of 9 days (lower and upper quartile: 5–15 days) in hospital. There were 92 (20%) patients who died within the follow-up period of whom 15 (16%) in hospital. The observed incidence of in-hospital mortality was 9%.

Table 1 summarizes the baseline characteristics for the entire patient population and for the subgroups divided by whether they have reached the combined endpoint of HF readmission or death. Compared to patients with an event, the patients without an event were younger, more likely to be female, and were less likely to suffer from diabetes and to be previously admitted because of HF. In addition, their biomarker values were relatively low.

7.3.2 Added prognostic value of biomarkers
Table 2 depicts the subpopulations of the risk classifications when using the two risk prediction models. Most patients (60%) were classified as intermediate to high-risk based on the risk predicted using either model. Out of the entire population the proportions with the upward and downward risk reclassification when switching from the clinical risk model to the biomarker risk model comprised 6% and 15% respectively. Based on this table, the NRI was estimated as 0.1814 (95% confidence interval: 0.0926–0.2703). This indicates that addition of biomarkers significantly improved risk classification (P<0.001) for a net of 18% of individuals.

7.3.3 Model derivation and validation
The model parameter estimation results are presented in Table 3. The interaction terms between the group indicator $G$ and the sojourn time in both logistic regression models did not reach statistical significance (P≤0.05). A significant non-linear relationship was found between the out-of-hospital sojourn time and the log-odds of the out-of-hospital death. The relationship between the log-odds of the in-hospital mortality and the sojourn time in hospital was however found not to be significant. The latter probability was therefore assumed to be a constant with an estimated value of 0.09 for all patient subgroups. As is shown in Figure 2,
the predicted survival curves obtained from our decision model closely resembled the observed survival curves.

7.3.4 Headroom analysis

For the base-case values of the model parameters, we found the commercial headroom available of the biomarkers to be equal to €256. This indicates that the incorporation of different biomarkers may be deemed a potentially cost-effective improvement of risk stratification, i.e., the recommended therapy and downstream costs remain within the WTP range when the costs of the corresponding biomarkers remain less than this amount. As shown in Table 4, the amount of headroom decreases when there is no incremental health gain (i.e., hazard ratio=1) due to the increasing level of care. Higher headroom values were obtained with increasing treatment effects. In addition, the amount of headroom was prone to change across different risk thresholds. When the cut-off value increased to 0.20, the amount of headroom increased indicating more optimistic investment decisions. However, it might not be viable for further technology development if the cut-off value would decrease to 0.10.
Table 1: Patient baseline characteristics for the entire population and for the subgroups divided by whether they have reached the combined endpoint of HF readmission or death

<table>
<thead>
<tr>
<th>Variables*</th>
<th>Reached combined endpoint</th>
<th>Not reached combined endpoint</th>
<th>Overall sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>167</td>
<td>287</td>
<td>454</td>
</tr>
<tr>
<td>Age, years</td>
<td>72±12</td>
<td>70±13</td>
<td>71±13</td>
</tr>
<tr>
<td>Female sex</td>
<td>37%</td>
<td>38%</td>
<td>37%</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>126±26</td>
<td>135±30</td>
<td>131±29</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29±6</td>
<td>28±5</td>
<td>28±6</td>
</tr>
<tr>
<td>History of previous HF admission</td>
<td>32%</td>
<td>12%</td>
<td>20%</td>
</tr>
<tr>
<td>History of ischemic HF</td>
<td>55%</td>
<td>43%</td>
<td>48%</td>
</tr>
<tr>
<td>Comorbidity of diabetes</td>
<td>42%</td>
<td>33%</td>
<td>36%</td>
</tr>
<tr>
<td>NT-proBNP, pg/mL</td>
<td>4140 (7066)</td>
<td>1954 (2863)</td>
<td>2368 (4245)</td>
</tr>
<tr>
<td>Galectine, ng/mL</td>
<td>30±11</td>
<td>23±10</td>
<td>26±11</td>
</tr>
<tr>
<td>Troponin, ng/mL</td>
<td>45 (54)</td>
<td>30 (42)</td>
<td>33 (46)</td>
</tr>
</tbody>
</table>

*Continuous variables are presented as mean ± standard deviation or median (interquartile range) and categorical variables are presented as percentages.

Abbreviations: SBP, systolic blood pressure; BMI, body-mass index; HF, heart failure; NT-proBNP, N-terminal pro brain natriuretic peptide.

Table 2: Risk reclassification table when using both risk prediction models

<table>
<thead>
<tr>
<th>Predicted risk using biomarker risk model</th>
<th>Low risk</th>
<th>Intermediate to high risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predicted risk using conventional risk model</td>
<td>Low risk</td>
<td>89 (20%)</td>
</tr>
<tr>
<td></td>
<td>Intermediate to high risk</td>
<td>66 (15%)</td>
</tr>
<tr>
<td></td>
<td>high risk</td>
<td></td>
</tr>
</tbody>
</table>

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Table 3: The specification of the regression models and the results of the parameter estimation for our decision model

<table>
<thead>
<tr>
<th></th>
<th>Log((\rho))</th>
<th>Log((b))</th>
<th>(\alpha)</th>
<th>(\beta_{G})</th>
<th>(\beta_{u}^{-1}(100/u))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>coef. (s.e.)</td>
<td>coef. (s.e.)</td>
<td>coef. (s.e.)</td>
<td>coef. (s.e.)</td>
<td>coef. (s.e.)</td>
</tr>
<tr>
<td>(F_1(u))</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G=1</td>
<td>-0.55 (0.06)</td>
<td>8.98 (0.48)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G=2</td>
<td>-0.55 (0.06)</td>
<td>8.98 (0.48)</td>
<td>1.67 (0.35)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G=3</td>
<td>-0.55 (0.06)</td>
<td>8.98 (0.48)</td>
<td>0.57 (0.34)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G=4</td>
<td>-0.55 (0.06)</td>
<td>8.98 (0.48)</td>
<td>1.56 (0.27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(F_2(u))</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G=1</td>
<td>0.22 (0.05)</td>
<td>2.34 (0.23)</td>
<td>0</td>
<td>-0.23 (0.43)</td>
<td></td>
</tr>
<tr>
<td>G=2</td>
<td>0.22 (0.05)</td>
<td>2.34 (0.23)</td>
<td>0.09 (0.37)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G=3</td>
<td>0.22 (0.05)</td>
<td>2.34 (0.23)</td>
<td>0.09 (0.37)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G=4</td>
<td>0.22 (0.05)</td>
<td>2.34 (0.23)</td>
<td>-0.30 (0.30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\pi_{13}(u))</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G=1</td>
<td>-1.52 (0.65)</td>
<td></td>
<td>0.03 (0.01)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G=2</td>
<td>-1.52 (0.65)</td>
<td>1.05 (0.81)</td>
<td>0.03 (0.01)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G=3</td>
<td>-1.52 (0.65)</td>
<td>-1.55 (1.22)</td>
<td>0.03 (0.01)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G=4</td>
<td>-1.52 (0.65)</td>
<td>0.61 (0.67)</td>
<td>0.03 (0.01)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\pi_{23})</td>
<td>-2.37 (0.27)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Model parameterization

\[
\begin{align*}
F_1(u; \lambda, \rho) &= F_2(u; \lambda, \rho) = 1 - \exp(-\frac{u}{\lambda})^\rho \\
\lambda &= b \times \exp\left(\frac{-\beta_{G}G + \log(HR_p)}{\rho}\right) \\
\log\it{it}[\pi_{13}(u)] &= \alpha + \beta_{G}G + \beta_{u}^{-1}(100/u) \\
\log\it{it}[\pi_{23}] &= \alpha
\end{align*}
\]

\(HR_p\) : hazard ratio between interventions
Figure 2: Observed versus predicted survival curves for patients whose risks were not reclassified (left), and for patients whose risks were reclassified (right) when switching from the clinical risk model to the biomarker risk model. The grey area band widths reflect the 95% confidence intervals of the observed survival curves.

Table 4: Results of the headroom analysis

<table>
<thead>
<tr>
<th>Hazard ratios between interventions when risk groups were upward reclassified ($G=2$); All scenarios</th>
<th>1</th>
<th>1.1</th>
<th>1.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base-case (cut-off=0.16)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard ratios between interventions when risk groups were downward reclassified ($G=3$)</td>
<td>0.8</td>
<td>226</td>
<td>442</td>
</tr>
<tr>
<td></td>
<td>0.9</td>
<td>40</td>
<td>256</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>-153</td>
<td>63</td>
</tr>
<tr>
<td>Cut-off=0.20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard ratios between interventions when risk groups were downward reclassified ($G=3$)</td>
<td>0.8</td>
<td>346</td>
<td>627</td>
</tr>
<tr>
<td></td>
<td>0.9</td>
<td>104</td>
<td>385</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>-107</td>
<td>174</td>
</tr>
<tr>
<td>Cut-off=0.10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard ratios between interventions when risk groups were downward reclassified ($G=3$)</td>
<td>0.8</td>
<td>38</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>0.9</td>
<td>-62</td>
<td>-50</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>-138</td>
<td>-126</td>
</tr>
</tbody>
</table>
**7.4 DISCUSSION**

Currently, the interest in innovative medical technologies (i.e., medical devices, biotechnologies, information technologies) which enable more tailored patient care is raising sharply.\(^{35-37}\) High numbers of novel biomarkers have been identified, yet, their translational abilities, i.e., going from bench to bedside, have hardly been assessed in rigorous evaluation phases.\(^{13,38}\) Particularly, the investigation of the emerging role of biomarkers to improve personalized care at affordable cost largely remained in conceptual phase. This study presents a first application of a previously developed method\(^{20}\) to provide exemplary insight into early assessment opportunities using a case study in HF disease management.

A significantly improved risk stratification was detected when adding multiple biomarkers to the risk prediction model developed in this study. This improvement may contribute to the further development of a practical test procedure incorporating these biomarkers. The innovative medical technology foreseen may be economically and financially viable. This is because of the available commercial headroom estimated appeared to be considerable in several scenario analyses of this study. Note, however, that we have shown that the amounts of headroom were rather sensitive when altering the risk thresholds. The main results of our study should be interpreted cautiously. First, a generally accepted threshold to generate a risk-stratified treatment recommendation is still lacking for HF disease management. We therefore adopted the risk threshold and treatment recommendation derived in a previous study.\(^{26}\) As the threshold was developed in a different HF population, we performed sensitivity analyses to show how the estimates of commercial headroom available might be influenced by different threshold values when assuming the same risk-stratified treatment recommendation. Strictly speaking, the same graphical approach to develop a treatment recommendation that was previously adopted may be applied again to validate whether such recommendation can be generalized to a different population. However, the data required to enable such a development was not complete for the population considered in this study. Secondly, the clinical data in this study was obtained from an observational study with no interventions. We therefore implicitly assumed that the content and structure and effect of the interventions considered in this study would be similar to those of the two nurse-led DMPs considered in the study from which we derived the treatment recommendation. Such evidence scarcity from clinical data is a major complication when assessing the potential economic value of new medical technologies.\(^{16,19,39}\) Different scenario analyses were therefore conducted to assess how estimates of the commercial headroom available were influenced by altering the hazard ratios between interventions.
The innovation of medical technology is always costly and uncertain which requires proper methods applied at appropriate development stages to support timely investment and reimbursement decisions.\textsuperscript{18,40,41} The classical economic evaluation is conducted after synthesizing appropriate evidence from clinical trials. This serves reimbursement decision making on fully developed medical technologies in their targeted markets.\textsuperscript{17,20} The early-stage economic evaluation is of utmost importance to support prioritizing promising prototypes for further development of full products. Early health economic modeling is one of the evaluation methods that has been proposed when the potential application of a new medical technology is foreseen in its targeted clinical setting.\textsuperscript{19} For instance, the future clinical adoption considered in this study is a test-kit/molecular tool, which offers simultaneous measurement of a panel of biomarkers with the goal to ultimately improve HF disease management. One of the goals of such novel technology might be to accelerate the development of novel pharmaceutical interventions adding to personalized medicine. However, the use of early health economic modeling is not recommended at the very early stage of technology-driven innovations, when there are still many technical solution principles and/or target markets left to choose from.\textsuperscript{19,42} A recent study\textsuperscript{43} introduced multi-criteria decision analysis (MCDA) in support of very early-stage evaluation when the innovation is too uncertain to be assessed using more quantitative tools (i.e., early health economic modeling). Such very early-stage evidence can subsequently be incorporated into more quantitative evaluations\textsuperscript{18,21} to support later-stage investment decision making.

To conclude, this paper presents an approach to early assessment of the market potential biomarkers when applied in personalized treatment. Assessing and appraising the potential economic value of multiple biomarkers in personalized HF disease management offered an opportunity to apply and scrutinize new methods. The generalizability of our findings and our proposed method need to be validated in other studies. A practical limitation is that the biomarkers considered in this study were only measured at baseline. In future studies one might consider assessing the merits of serial biomarker measurements during follow-up, which might further improve risk stratification. Notably, a repeated measure implies additional costs which will have an effect on the commercial headroom available.
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7.6 REFERENCES

24. Study protocol TRIUMPH.