


11-2015

## Tools for Economic Analysis of Patient Management Interventions in Heart Failure Cost-Effectiveness Model: A Web-based program designed to evaluate the cost-effectiveness of disease management programs in heart failure.

Shelby D. Reed  
*Duke University, School of Medicine*

Matthew P. Neilson  
*University of Glasgow*

Matthew Gardner  
*Duke University, School of Medicine*  
Follow this and additional works at: <https://jdc.jefferson.edu/medfp>

 Yanhong Li  
Part of the [Cardiology Commons](#)  
*Duke University, School of Medicine*

[Let us know how access to this document benefits you](#)

Andrew H. Briggs  
*University of Glasgow*  
**Recommended Citation**

Reed, Shelby D.; Neilson, Matthew P.; Gardner, Matthew; Li, Yanhong; Briggs, Andrew H.; Polsky, Daniel E. E.; Graham, Felicia L.; Bowers, Margaret T.; Paul, Sara C.; Granger, Bradi B.; Schulman, Kevin A.; Whellan, David J.; Riegel, Barbara; and Levy, Wayne C., "Tools for Economic Analysis of Patient Management Interventions in Heart Failure Cost-Effectiveness Model: A Web-based program designed to evaluate the cost-effectiveness of disease management programs in heart failure." (2015). *Department of Medicine Faculty Papers*. Paper 177.  
<https://jdc.jefferson.edu/medfp/177>

This Article is brought to you for free and open access by the Jefferson Digital Commons. The Jefferson Digital Commons is a service of Thomas Jefferson University's [Center for Teaching and Learning \(CTL\)](#). The Commons is a showcase for Jefferson books and journals, peer-reviewed scholarly publications, unique historical collections from the University archives, and teaching tools. The Jefferson Digital Commons allows researchers and interested readers anywhere in the world to learn about and keep up to date with Jefferson scholarship. This article has been accepted for inclusion in Department of Medicine Faculty Papers by an authorized administrator of the Jefferson Digital Commons. For more information, please contact: [JeffersonDigitalCommons@jefferson.edu](mailto:JeffersonDigitalCommons@jefferson.edu).

---

**Authors**

Shelby D. Reed, Matthew P. Neilson, Matthew Gardner, Yanhong Li, Andrew H. Briggs, Daniel E E. Polsky, Felicia L. Graham, Margaret T. Bowers, Sara C. Paul, Bradi B. Granger, Kevin A. Schulman, David J. Whellan, Barbara Riegel, and Wayne C. Levy



Published in final edited form as:

*Am Heart J.* 2015 November ; 170(5): 951–960. doi:10.1016/j.ahj.2015.08.015.

## TEAM-HF Cost-Effectiveness Model: A Web-Based Program Designed to Evaluate the Cost-Effectiveness of Disease Management Programs in Heart Failure

Shelby D. Reed, PhD<sup>a,b</sup>, Matthew P. Neilson, PhD<sup>d</sup>, Matthew Gardner, BS<sup>a</sup>, Yanhong Li, MD<sup>a</sup>, Andrew H. Briggs, DPhil<sup>d</sup>, Daniel E. Polsky, PhD<sup>e</sup>, Felicia L. Graham, MBA<sup>a</sup>, Margaret T. Bowers, RN, MSN<sup>c</sup>, Sara C. Paul, RN, DNP, FNP<sup>g</sup>, Bradi B. Granger, RN, PhD<sup>c</sup>, Kevin A. Schulman, MD<sup>a,b</sup>, David J. Whellan, MD<sup>h</sup>, Barbara Riegel, DNSc<sup>f</sup>, and Wayne C. Levy, MD<sup>i</sup>

<sup>a</sup>Duke Clinical Research Institute, Durham, North Carolina

<sup>b</sup>Department of Medicine, Duke University School of Medicine, Durham, North Carolina

<sup>c</sup>Duke University School of Nursing, Durham, North Carolina

<sup>d</sup>Institute of Health and Wellbeing, University of Glasgow, Glasgow, United Kingdom

<sup>e</sup>Division of General Internal Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

<sup>f</sup>University of Pennsylvania School of Nursing, Philadelphia, Pennsylvania

<sup>g</sup>Catawba Valley Cardiology, Conover, North Carolina

<sup>h</sup>Department of Medicine, Jefferson Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania

<sup>i</sup>University of Washington, Seattle, Washington

### Abstract

**Background**—Heart failure disease management programs can influence medical resource use and quality-adjusted survival. Because projecting long-term costs and survival is challenging, a consistent and valid approach to extrapolating short-term outcomes would be valuable.

**Methods**—We developed the Tools for Economic Analysis of Patient Management Interventions in Heart Failure (TEAM-HF) Cost-Effectiveness Model, a Web-based simulation tool designed to integrate data on demographic, clinical, and laboratory characteristics, use of evidence-based medications, and costs to generate predicted outcomes. Survival projections are based on a

---

Address for correspondence: Shelby D. Reed, PhD, PO Box 17969, Durham, NC 27715; telephone: 919-668-8101; shelby.reed@duke.edu.

**Disclosures:** The University of Washington Center for Commercialization holds the copyright to the Seattle Heart Failure Model. Drs Schulman and Reed have made available online detailed listings of financial disclosures ([www.dcri.duke.edu/research/coi.jsp](http://www.dcri.duke.edu/research/coi.jsp)).

**Additional Contributions:** Damon M. Seils, MA, Duke University, assisted with manuscript preparation.

**Publisher's Disclaimer:** This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

modified Seattle Heart Failure Model (SHFM). Projections of resource use and quality of life are modeled using relationships with time-varying SHFM scores. The model can be used to evaluate parallel-group and single-cohort designs and hypothetical programs. Simulations consist of 10,000 pairs of virtual cohorts used to generate estimates of resource use, costs, survival, and incremental cost-effectiveness ratios from user inputs.

**Results**—The model demonstrated acceptable internal and external validity in replicating resource use, costs, and survival estimates from 3 clinical trials. Simulations to evaluate the cost-effectiveness of heart failure disease management programs across 3 scenarios demonstrate how the model can be used to design a program in which short-term improvements in functioning and use of evidence-based treatments are sufficient to demonstrate good long-term value to the health care system.

**Conclusion**—The TEAM-HF Cost-Effectiveness Model provides researchers and providers with a tool for conducting long-term cost-effectiveness analyses of disease management programs in heart failure.

---

## Introduction

Although economic evaluations of heart failure disease management programs are plentiful, a recent review identified only 2 formal cost-effectiveness analyses that extrapolated beyond a trial's follow-up period.<sup>1</sup> Without extrapolation, the value of a disease management program may be underestimated. For example, an analysis of the South Texas Congestive Heart Failure Disease Management Project reported an incremental cost-effectiveness ratio greater than \$100,000 per quality-adjusted life-year (QALY) within the trial's 18-month follow-up period.<sup>2</sup> However, extension of the time horizon with a Markov model structured using New York Heart Association (NYHA) classification reduced the incremental cost-effectiveness ratio to less than \$50,000 per QALY.<sup>3</sup> This example demonstrates the importance of accounting for all downstream costs and health benefits attributable to an intervention to provide a fair assessment of its cost-effectiveness.

With support from the National Institute of Nursing Research, we developed user-friendly tools to facilitate high-quality economic evaluations of patient-focused interventions. In our project, Tools for Economic Analysis of Patient Management Interventions in Heart Failure (TEAM-HF), we developed a costing tool<sup>4</sup> and a cost-effectiveness model. In this paper, we describe the TEAM-HF Cost-Effectiveness Model, a generalizable, Web-based tool designed to assist researchers, administrators, and providers in estimating short-term or long-term estimates of resource use, costs, and cost-effectiveness of disease management programs or other care strategies in heart failure. We then compare predicted estimates of resource use and costs from the model to estimates from 3 studies to evaluate the internal and external validity of the model. We also evaluate the potential cost-effectiveness of 3 disease management scenarios to demonstrate how the model can be used to design more cost-effective interventions.

## Methods

### Web-Based Application

To maximize accessibility, we developed a freely available Web-based tool that allows users to select modeling options and specify inputs in an integrated simulation model. The tool takes the form of a series of input pages (Table 1). It includes 3 study design options: hypothetical scenario; parallel groups; and single cohort (Supplemental Figure A).

The hypothetical scenario design option allows the user to generate simulated outcomes for 2 patient groups with different clinical and treatment characteristics. The parallel groups design option is appropriate for randomized trials or other studies with 2 comparator groups. The user prescribes observed counts of resource use and deaths for the observed follow-up period. After the observation period, simulated outcomes are generated over the time period specified by the user. The single cohort design option allows users to evaluate a program that has already been implemented. The user prescribes clinical and treatment characteristics for the patients before and after their participation in the program.

Additional input pages correspond to patients' demographic and clinical characteristics, laboratory test results, use of diuretics, and use of evidence-based medications and devices that represent parameters in the prognostic model integrated with the tool. The user can also prescribe unit costs for medications, hospitalizations, emergency department visits, and outpatient visits.

A cost-effectiveness analysis requires users to account for the costs associated with a disease management program. Therefore, the user must specify the duration and monthly cost of the program. If the program includes an "intense" phase and a less intense "maintenance" phase, the user can specify the duration and monthly cost for each phase. The user can also extend the monthly costs of the program indefinitely (ie, until death). The final inputs relate to the time horizon for the simulations, discount rates, and options for reporting.

### Model Structure

We selected the Seattle Heart Failure Model (SHFM) as the underlying prognostic model, because its external validity has been tested in 14 clinical cohorts, more than any other model for heart failure.<sup>5,6</sup> Also, its inclusion of multiple clinical and laboratory variables and the integration of treatment effects for evidence-based therapies allows our model to account for the effects of disparate disease management programs or treatment care strategies. For example, the same model could be used to evaluate a program to improve physical functioning or a program to increase the use of  $\beta$ -blockers.

### Modifications to the SHFM

In the original SHFM publication, an exponential hazard function was suggested to generate long-term survival estimates.<sup>5</sup> An exponential hazard function assumes a constant mortality rate, which can lead to overestimation of survival. Therefore, we replaced the exponential function with a calibrated competing risks regression model in which the baseline hazard for each mode of death was assumed to follow a Gompertz distribution, under the proportional

hazards assumption, using data representing 7151 patients from 4 clinical trials and prospective observational cohorts.<sup>6</sup> The shape parameters for heart failure death and non-heart failure death were positive (0.281 and 0.204, respectively), indicating increasing risk over time, whereas the parameter for sudden death was approximately equal to zero ( $< .001$ ), indicating constant risk. The fitted survival model enables us to calculate expected survival time for any SHFM score. Figure 1 shows the overall survival curves for integer SHFM scores; the corresponding table displays the mean survival estimates. See the Online-Only Supplement for details.

We also modified the treatment effects of several medication classes in the SHFM. First, we removed the effect of statins on mortality risk to reflect findings from 2 clinical trials.<sup>7,8</sup> Second, although meta-analyses support the benefits of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) in heart failure, clinical trials have not demonstrated additive treatment effects of ARBs with ACE inhibitors.<sup>9–11</sup> Therefore, we modified the SHFM to apply a hazard ratio of 0.77 for patients treated with an ACE inhibitor and/or ARB.<sup>12</sup> Third, we reduced the treatment benefit of aldosterone antagonists by replacing the hazard ratio of 0.70 from the Randomized Aldactone Evaluation Study (RALES) with a hazard ratio of 0.76 from the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF),<sup>13</sup> an effect consistent with an earlier meta-analysis.<sup>14</sup>

### Mode of Death

Resource use, associated medical costs, and health-related quality of life in the year before death differ markedly between patients who die from sudden death versus other causes.<sup>15</sup> To account for these differences, we used mathematical relationships derived from data from the 4 cohorts described above to estimate the conditional probability of dying from heart failure, sudden death, or another cause as a function of time and a patient's baseline SHFM score (Figure 2). We incorporated these probabilities into the model such that the assigned cause of death for each virtual patient was conditional on the patient's initial SHFM score and simulated time of death.

### Modeling Medical Resource Use and Health Utilities

In addition to estimating survival and assigning a mode of death for each virtual patient, the model assigns rates of medical resource use and health utility (ie, quality of life) weights across time. We used data from Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) to estimate relationships between SHFM scores and rates of medical resource use<sup>16</sup> and health utilities.<sup>17</sup> As expected, patients with higher SHFM scores had significantly higher rates of hospitalization, emergency department or urgent care visits, and nonurgent outpatient visits in the following year.<sup>16</sup> We assigned cause-specific hospitalizations according to distributions observed in HF-ACTION. Similarly, higher SHFM scores predicted lower health utilities at baseline, and their mean utilities decreased at a faster rate relative to lower SHFM scores.<sup>17</sup>

## Modeling Change in SHFM Scores

To relate the natural progression of heart failure with corresponding SHFM scores, we used mathematical relationships to determine the rate at which SHFM scores would have to increase to maintain consistency with the time-varying global hazard function (Online-Only Supplement). By quantifying the relationships between initial SHFM scores and SHFM scores across time, the model updates each virtual patient's SHFM score each year. This approach allows the model to assign higher rates of resource use and lower health utilities over time.

## Model Simulations

Simulations consist of 10,000 Monte Carlo iterations. Each iteration represents a single realization of the 2 user-defined virtual patient cohorts with sample sizes specified by the user. For each virtual patient within a cohort, demographic, laboratory, and clinical characteristics are sampled from a multivariate mixed distribution based on user-prescribed inputs. The default values and associated correlation matrix were derived from the 4-cohort sample of 7151 patients described above (Supplemental Tables B1 and B2).<sup>5</sup>

For each virtual patient, the simulated time of death is sampled from the corresponding SHFM score-specific survival function (Supplemental Figure 3.1). The cause of death is then assigned using the cumulative probabilities of death (for heart failure, sudden cardiac death, and other cause), conditional on the initial SHFM score and the simulated time of death (Figure 2). The SHFM score for each virtual patient is then updated for each subsequent year.

Annual counts of medical resources are generated for each virtual patient using negative binomial regression models, in which the predicted SHFM score at the beginning of each year is the explanatory variable. When less than 1 year of survival remains, the explanatory variables in the regression models include the patient's predicted SHFM score at the beginning of that year, the simulated cause of death, and the number of days alive in the final year of life (Supplemental Table 5.1). For each simulated year across the 10,000 Monte Carlo iterations, unit cost estimates are multiplied by the corresponding counts for each type of medical resource for each patient in each cohort. Costs in each year are then discounted and summed to calculate cumulative costs for each cohort.

Utility weights are assigned to account for differences in quality of life across patients. Each virtual patient's utility weight is a linear function of the patient's corresponding time-adjusted SHFM score. When the user opts to allow utilities to vary (ie, "stochastic" option), each virtual patient's initial utility score is sampled from a normal distribution and then decays in a linear fashion until the time of death. In cases for which the sampled utility weight exceeds 1, the value is capped at 1.

## Variability

The model incorporates stochastic uncertainty, which represents differences in outcomes that can occur between 2 realizations of the same patient. For example, a patient with an SHFM score of 1.0 may have an estimated life expectancy of 5.14 years, but the sampled

life expectancy for 2 simulated patients with the same SHFM score could be 3 months or 8 years, representing stochastic uncertainty.

The user has the option to select “deterministic” or “stochastic” for SHFM coefficients, time of death, resource use, and utility weights. With the deterministic option, expected values for resource use, health utilities, and survival are assigned to virtual patients in each of the 10,000 iterations. With the “stochastic” option, outcomes for each patient are sampled from their corresponding parametric distributions in each iteration, resulting in 10,000 estimates for resource use, cost, and survival. Corresponding 95% CIs are calculated by sorting the 10,000 estimates in ascending order and taking the 250th and 9750th ranked values.

### **Validation**

We applied the TEAM-HF Cost-Effectiveness Model to 3 heart failure trials to compare simulated and observed estimates and to demonstrate how the model can be used to reverse-engineer a cost-effective disease management program. The inputs specified in each of the 3 validation tests are reported in Supplemental Table D.1. We performed the simulations using both the stochastic and deterministic options to demonstrate the impacts of these choices.

### **CHIME**

The Medication Adherence in Chronic Illness: Medications, Meaning and Me (CHIME) pilot study tested an intervention to improve medication adherence in 86 high-risk patients with heart failure.<sup>18</sup> The intervention included quarterly phone calls to the patient from a nurse. At 1 year, medical resource use and costs were similar across both groups. To increase the sample size for validation testing, we combined patients from both groups.

To demonstrate how the model could be used to evaluate the cost-effectiveness of a disease management program, we included the 86 patients from CHIME in the standard care group. Then, we modeled 3 hypothetical scenarios representing programs that could increase proportions of patients in NYHA class II and increase use of evidenced-based medications. For program costs in scenario A, we computed the cost per patient per month in CHIME using the TEAM-HF Costing Tool.<sup>4</sup>

### **Internal Validation in HF-ACTION**

Several statistical associations embedded in the TEAM-HF model were derived from HF-ACTION.<sup>19</sup> Thus, comparisons between estimates from the model with estimates from HF-ACTION represent an internal validation test. Because observed resource use and outcomes were similar between groups in the trial, baseline characteristics were pooled across study groups and modeled over 2 years.

### **SCD-HeFT**

The economic evaluation of the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) provides an opportunity to compare estimates over a longer time horizon (20). SCD-HeFT was a randomized trial of 2521 patients with symptomatic heart failure that found a statistically significant reduction in all-cause mortality among patients who received a



single-lead implantable cardioverter-defibrillator (ICD), compared with patients who received medical therapy or placebo. Median follow-up was 45.5 months.

### **Funding/Support**

Development of the TEAM-HF Cost-Effectiveness Model was supported by grant 5R01NR011873-02 from the National Institute of Nursing Research. The development and content of the TEAM-HF economic tools are solely the responsibility of the authors and do not necessarily represent the official views of the National Institute of Nursing Research or the National Institutes of Health. The trials used for validation purposes were supported separately.

## **Results**

### **CHIME**

In CHIME, patients were hospitalized an average of 1.3 times, had 0.5 emergency department visits, and had 3.1 outpatient visits (Table 2). By comparison, our model estimated 1.1 hospitalizations, 1.0 emergency department visits, and 13.9 outpatient visits. Mean total costs estimated using patient-level data from CHIME were similar to mean total costs estimated with the TEAM-HF model (\$23,861 vs \$23,621) when all levels of uncertainty were varied stochastically. When parameter estimates were modeled deterministically, the point estimate was \$19,622.

To evaluate potential disease management programs, we assumed that the intervention in scenario A increased the proportion of patients with NYHA class II by 10 percentage points and the use of evidence-based medications increased by 5 percentage points. Intervention costs in scenario A included initiation costs of \$70 and maintenance costs of \$59 per patient per month for 1 year. Compared with standard care, mean total costs in scenario A increased by \$1393 and QALYs increased by 0.2, corresponding to an incremental cost-effectiveness ratio of \$6128 per QALY (Table 3). Scenarios B and C represent a higher-cost program with \$2000 initiation costs plus ongoing costs of \$200 per patient per month. With the same level of effectiveness as scenario A, the incremental cost-effectiveness ratio increased to \$64,865 per QALY in scenario B. However, with greater effectiveness in scenario C, the higher cost of the program is offset by greater gains in QALYs (0.4), resulting in an incremental cost-effectiveness ratio of \$29,701 per QALY.

### **HF-ACTION**

Observed estimates of medical resource use in HF-ACTION and estimates from our model were similar (Table 4). In HF-ACTION, patients were hospitalized an average of 2.0 times, visited the emergency department or urgent care clinic 1.6 times, and had 30.6 outpatient visits. Based on the TEAM-HF model, patients would have been expected to have an average of 2.1 hospitalizations, 1.9 emergency department or urgent care visits, and 26.3 outpatient visits. Total costs were also similar between estimates based on empirical data (\$46,361) and modeled estimates (\$48,098). Observed survival at 2 years was 83.4% in HF-ACTION compared to a modeled estimate of 79.6%.

## SCD-HeFT

Five-year estimates of resource use and total costs generated with the TEAM-HF model were higher than reported for SCD-HeFT (20) in the ICD and placebo groups (Table 5). However, the estimated differences in mean costs at 5 years were similar: \$23,472 with the TEAM-HF model and \$27,141 in SCD-HeFT. Five-year survival predicted with the model was 3 to 4 percentage-points lower than reported for SCD-HeFT. Nevertheless, 5-year survival gains and incremental cost-effectiveness ratios were similar for ICDs compared with standard care.

## Discussion

The TEAM-HF Cost-Effectiveness Model provides a flexible tool for the research and clinical communities to evaluate the long-term cost-effectiveness of disease management programs in heart failure. In addition to facilitating formal cost-effectiveness analyses, the model can be used for budget planning, projecting hospitalization rates, and quantifying life expectancy for a cohort of patients over a time period specified by the user. For example, the model could be used by health systems to predict cost offsets with a given program or to demonstrate expected longer-term cost-savings for a payer for a program that increases costs in the short-term. The model's flexibility also offers users the opportunity to represent different perspectives by specifying direct medical costs to represent the health care system perspective or payments to represent the payer perspective.

We believe ours to be the first generalizable simulation model developed to evaluate clinical and economic outcomes of patient-centered programs in heart failure. Previous models were developed to evaluate specific interventions and were structured using NYHA class<sup>3,21</sup> or hospitalization counts as health states.<sup>22</sup> Such models are not publicly available and cannot account for a broader range of factors that disease management programs may affect. Furthermore, variations in methods and reporting hinders the ability to make valid comparisons across studies.<sup>1,23</sup> With repeated use of a common model by different investigators, a collection of studies could develop to provide a body of evidence on which types of interventions targeting specific patient groups consistently provide better or worse value. In addition, individual stakeholders could apply the model to support local decision making by modifying unit costs, patient characteristics, changes in prognostic variables affected by an intervention, and the time horizon of interest.

## Model Validity

It is not possible to simply declare a model as "valid."<sup>24</sup> There are several types of validity, including face validity, internal validity, cross validity (between models), external validity, and predictive validity, with the latter 2 types being the strongest. Demonstration of an economic model's external and predictive validity, particularly for resource use and costs, is limited by variations in practice patterns and unit costs across settings.<sup>24</sup> Furthermore, for a model like TEAM-HF that can have multiple applications, numerous validation exercises across a range of interventions across various patient populations, outcomes, and time horizons may be necessary. In fields such as diabetes, where multi-application simulation

models were initially developed more than a decade ago, the relative strengths and limitations of these models are only now becoming understood.<sup>25</sup>

In our examination of the model's internal validity, we found that modeled estimates of resource use and mortality were consistent with empirical estimates from HF-ACTION. The findings of the 2 external validation tests were also promising. Our modeled estimates of hospitalizations were similar to CHIME, but modeled estimates of emergency department and outpatient visits were higher. The discrepancy can be attributed to differences in the scope of emergency department and outpatient visits included in the analysis. In CHIME, patients reported emergency department visits and outpatient physician visits associated with heart failure, whereas the TEAM-HF model includes all-cause visits to all health care providers (as collected in HF-ACTION). Compared with claims-based analyses in which all outpatient visits are considered (approximately 14 to 20 per year for patients with type 2 diabetes<sup>26</sup>; approximately 18 to 22 per year for patients with atrial fibrillation<sup>27</sup>), the TEAM-HF model produces counts of similar magnitude.

SCD-HeFT provided an opportunity to examine the model's external validity over a longer time horizon. Cost data were not available in SCD-HeFT over a 5-year time frame for all patients, and partitioned estimators were used to adjust cost estimates to account for censoring. Because this approach did not account for higher rates of medical resource use that occurs with disease progression, one could expect costs from SCD-HeFT to be lower than costs from the model. Although reported 5-year costs in SCD-HeFT were lower than predicted with the TEAM-HF model, the CIs from the TEAM-HF model included the point estimates from SCD-HeFT, and the estimated differences in 5-year survival were similar between analyses. We believe the 3 sets of validation tests indicate that the resource use, cost, and survival estimates generated with the TEAM-HF model demonstrate respectable internal and external validity.

### Variability

Across the simulations, we generally observed higher point estimates for costs and resource use when simulations were varied stochastically. This occurs because high counts (ie, outliers) of resource use are sometimes generated with stochastic sampling, which better represents empirical distributions of resource use. Thus, we expect that stochastic sampling will better represent variability that can be expected in real-world situations. In addition, recognition that costs and survival may substantially vary in cohorts with small sample sizes is important. The literature includes many small studies of disease management programs that reported cost savings over a short time period. Such findings could be attributable to one or more high-cost outliers in the comparison group and would not likely be replicated if the study was repeated. The TEAM-HF model could be used to evaluate whether observed differences in resource use, costs, and survival could be expected, given the impact of the disease management program on the prognostic factors represented in SHFM scores.

### Limitations

Although we believe this model could prove to be a valuable resource, its users should be aware of its limitations. First, because HF-ACTION largely enrolled patients with NYHA

class II and III heart failure, the statistical relationships between SHFM scores and resource use and health utilities that are embedded in the model will be less precise for individuals with more advanced disease. Nevertheless, by integrating end-of-life costs incurred by 339 HF-ACTION participants who died,<sup>15</sup> our model incorporates high rates of resource use incurred during this period. In addition, resource use patterns in HF-ACTION may not be representative of other settings. Nevertheless, clinical sites in HF-ACTION included both academic and nonacademic institutions. Users should also recognize that the treatment effects for medications and devices embedded in the SHFM are based on randomized clinical trials. Therefore, when proportions of patients treated with evidence-based medications are modeled, those proportions should represent individuals who adhere to their treatments at a level similar to what would be observed in a clinical trial, not the proportions of patients prescribed specific medications. Lastly, although the SHFM offers several advantages, it does not include some variables found to be predictive of mortality in other prognostic models, such as B-type natriuretic peptide level.<sup>28</sup>

We plan to expand the model to incorporate other prognostic models to allow users to perform sensitivity analyses or choose the prognostic model that includes variables that best capture the intermediate effects of a given disease management program. In the near term, we hope that the model proves useful to researchers and health care managers in evaluating the costs and outcomes associated with disease management programs in heart failure.

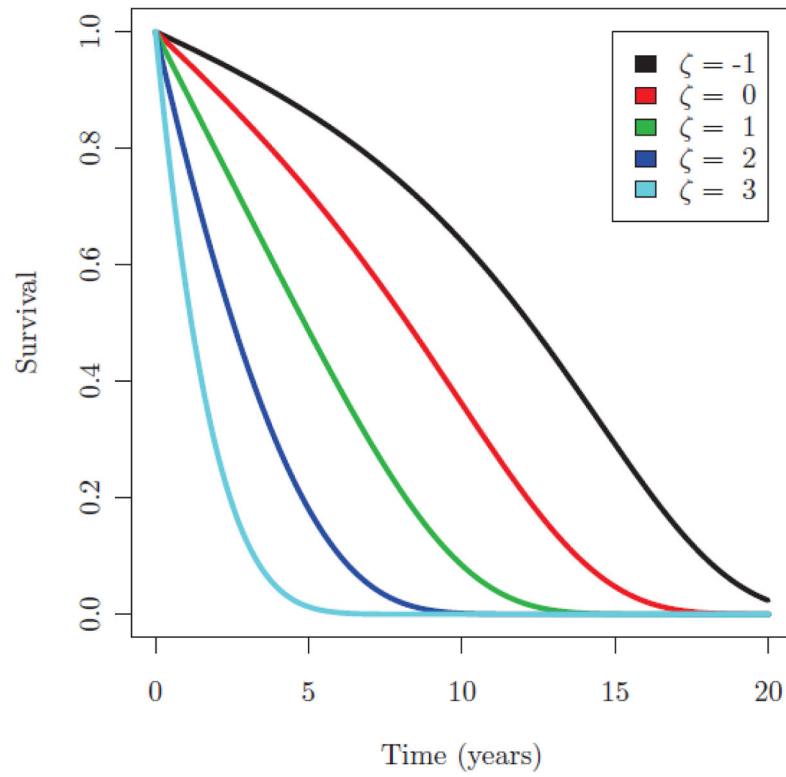
## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## References

1. Maru S, Byrnes J, Whitty JA, et al. Systematic review of model-based analyses reporting the cost-effectiveness and cost-utility of cardiovascular disease management programs. *Eur J Cardiovasc Nurs.* 2015; 14:26–33. [PubMed: 24836972]
2. Smith B, Hughes-Cromwick PF, Forkner E, et al. Cost-effectiveness of telephonic disease management in heart failure. *Am J Manag Care.* 2008; 14:106–15. [PubMed: 18269306]
3. Miller G, Randolph S, Forkner E, et al. Long-term cost-effectiveness of disease management in systolic heart failure. *Med Decis Making.* 2009; 29:325–33. [PubMed: 19147835]
4. Reed SD, Li Y, Kamble S, et al. Introduction of the TEAM-HF Costing Tool: a user-friendly spreadsheet program to estimate costs of providing patient-centered interventions. *Circ Cardiovasc Qual Outcomes.* 2012; 5:113–9. [PubMed: 22147884]
5. Levy WC, Mozaffarian D, Linker DT, et al. The Seattle Heart Failure Model: prediction of survival in heart failure. *Circulation.* 2006; 113:1424–33. [PubMed: 16534009]
6. Alba AC, Agoritsas T, Jankowski M, et al. Risk prediction models for mortality in ambulatory patients with heart failure: a systematic review. *Circ Heart Fail.* 2013; 6:881–9. [PubMed: 23888045]
7. Tavazzi L, Maggioni AP, et al. GISSI-HF Investigators. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet.* 2008; 372:1231–9. [PubMed: 18757089]
8. Kjekshus J, Apetrei E, Barrios V, et al. Rosuvastatin in older patients with systolic heart failure. *N Engl J Med.* 2007; 357:2248–61. [PubMed: 17984166]
9. Lee VC, Rhew DC, Dylan M, et al. Meta-analysis: angiotensin-receptor blockers in chronic heart failure and high-risk acute myocardial infarction. *Ann Intern Med.* 2004; 141:693–704. [PubMed: 15520426]

10. Kuenzli A, Bucher HC, Anand I, et al. Meta-analysis of combined therapy with angiotensin receptor antagonists versus ACE inhibitors alone in patients with heart failure. *PLoS One*. 2010; 5:e9946. [PubMed: 20376345]
11. Shibata MC, Tsuyuki RT, Wiebe N. The effects of angiotensin-receptor blockers on mortality and morbidity in heart failure: a systematic review. *Int J Clin Pract*. 2008; 62:1397–402. [PubMed: 18793376]
12. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. *JAMA*. 1995; 273:1450–6. [PubMed: 7654275]
13. Zannad F, McMurray JJ, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med*. 2011; 364:11–21. [PubMed: 21073363]
14. Ezekowitz JA, McAlister FA. Aldosterone blockade and left ventricular dysfunction: a systematic review of randomized clinical trials. *Eur Heart J*. 2009; 30:469–77. [PubMed: 19066207]
15. Reed SD, Li Y, Dunlap ME, et al. Inpatient resource use and medical costs in the last year of life by mode of death in HF-ACTION. *Am J Cardiol*. 2012; 110:1150–5. [PubMed: 22762718]
16. Reed, SD.; Li, Y.; Ellis, S.J., et al. Seattle Heart Failure Model scores significantly predict medical resource use and costs in HF-ACTION. Presented at: 15th Annual Scientific Meeting of the Heart Failure Society of America; September 2011; Boston, Massachusetts.
17. Li Y, Neilson M, Whellan DJ, et al. Associations between Seattle Heart Failure Model scores and health utilities: findings from HF-ACTION. *J Card Fail*. 2013; 19:311–6. [PubMed: 23663813]
18. Granger, B.; Bosworth, H.; Hernandez, A., et al. Results of the Chronic Heart Failure Intervention To Improve Medication Adherence (CHIME) Study: a randomized self-management intervention in high risk non-adherent patients. Presented at: American Heart Association Scientific Sessions; November 8, 2013; Dallas, Texas.
19. O'Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA*. 2009; 301:1439–50. [PubMed: 19351941]
20. Mark DB, Nelson CL, Anstrom KJ, et al. Cost-effectiveness of defibrillator therapy or amiodarone in chronic stable heart failure: results from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). *Circulation*. 2006; 114:135–42. [PubMed: 16818817]
21. Cowper PA, DeLong ER, Whellan DJ, et al. Economic effects of beta-blocker therapy in patients with heart failure. *Am J Med*. 2004; 116:104–11. [PubMed: 14715324]
22. Chan DC, Heidenreich PA, Weinstein MC, et al. Heart failure disease management programs: a cost-effectiveness analysis. *Am Heart J*. 2008; 155:332–8. [PubMed: 18215605]
23. Maru S, Byrnes J, Carrington MJ, Stewart S, Scuffham PA. Economic implications of cardiovascular disease management programs: moving beyond one-off experiments. *Expert Rev Pharmacoecon Outcomes Res*. 2015; 15:657–666. [PubMed: 25974038]
24. Eddy DM, Hollingworth W, Caro JJ, et al. Model transparency and validation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--7. *Value Health*. 2012; 15:843–50. [PubMed: 22999134]
25. Palmer AJ, Clarke P, et al. Mount Hood 5 Modeling Group. Computer modeling of diabetes and its complications: a report on the fifth Mount Hood Challenge Meeting. *Value Health*. 2013; 16:670–85. [PubMed: 23796302]
26. Pelletier EM, Shim B, Ben-Joseph R, et al. Economic outcomes associated with microvascular complications of type 2 diabetes mellitus: results from a US claims data analysis. *Pharmacoeconomics*. 2009; 27:479–90. [PubMed: 19640011]
27. Ladapo JA, David G, Gunnarsson CL, et al. Healthcare utilization and expenditures in patients with atrial fibrillation treated with catheter ablation. *J Cardiovasc Electrophysiol*. 2012; 23:1–8. [PubMed: 21777324]
28. Chyu J, Fonarow GC, Tseng CH, et al. Four-variable risk model in men and women with heart failure. *Circ Heart Fail*. 2014; 7:88–95. [PubMed: 24281135]



**Figure 1.** Survival Curves and Mean Survival Estimates for Integer Seattle Heart Failure Model Scores

|                      | SHFM Score ( $\zeta$ ) |             |             |             |             |
|----------------------|------------------------|-------------|-------------|-------------|-------------|
|                      | -1                     | 0           | 1           | 2           | 3           |
| Expected survival, y | 11.53                  | 8.07        | 5.14        | 2.93        | 1.48        |
| 95% CI               |                        |             |             |             |             |
| N = 100              | (10.51–12.55)          | (7.22–8.92) | (4.50–5.78) | (2.51–3.35) | (1.24–1.72) |
| N = 1000             | (11.21–11.85)          | (7.80–8.34) | (4.94–5.34) | (2.80–3.06) | (1.40–1.56) |

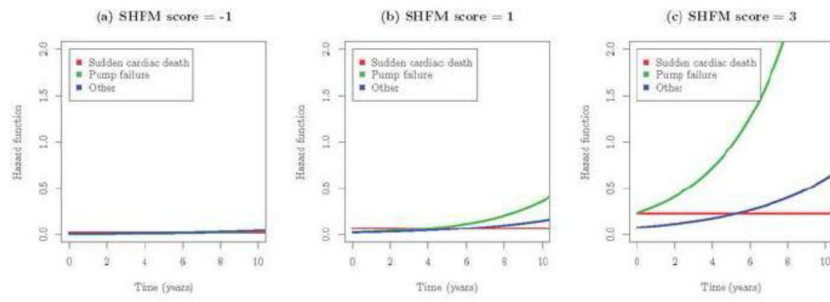


Figure 2a

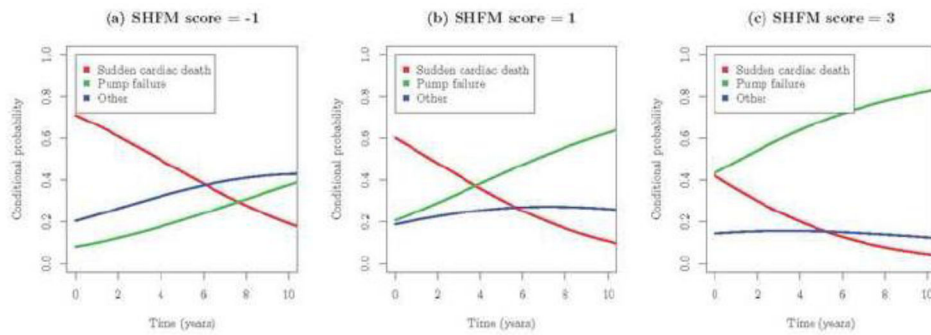


Figure 2b

**Figure 2.** Cause-Specific Hazard for Death (Upper Panel) and Cause-Specific Probability of Death (Conditional on Having Died at the Time Indicated by the Time Axis) as a Function of an Initial Seattle Heart Failure Model Score (Lower Panel)



**Table 1**

## User-Defined Inputs for the TEAM-HF Cost-Effectiveness Model

| Input Page                                    | Parameters (Options)  |
|---|---|
| General information                           | Scenario name   |
|   | Scenario comments   |
|   | Study design (parallel groups, single cohort, hypothetical)   |
|   | Group name*   |
|   | Group sample size*  |
|   | Length of observation <sup>†</sup>  |
| Observed resource use and death* <sup>†</sup> | Counts of cardiovascular procedure-related hospitalizations; medically treated heart failure hospitalizations; non-heart failure hospitalizations; emergency department visits; outpatient visits     |
|   | Number of patients who died   |
| Clinical characteristics* <sup>†</sup>        | Age   |
|   | Sex   |
|   | Weight  |
|   | New York Heart Association class  |
|   | Systolic blood pressure   |
|   | Ejection fraction   |
| Laboratory measurements* <sup>†</sup>         | Percent lymphocytes   |
|   | Serum sodium  |
|   | Total cholesterol   |
|   | Hemoglobin  |
|   | Uric acid   |
| Diuretics* <sup>†</sup>                       | Proportion of patients receiving diuretics, and daily doses for each of the following medications: furosemide, bumetanide, torsemide, metolazone, hydrochlorothiazide                                 |
| Medications and devices* <sup>†</sup>         | Proportions of patients treated with $\beta$ -blocker, aldosterone antagonist or potassium-sparing diuretic, ARB, ACE inhibitor, biventricular pacemaker, ICD, biventricular ICD                      |
| Unit costs                                    | Cost per month for $\beta$ -blocker, aldosterone antagonist or potassium-sparing diuretic, ARB, ACE inhibitor, diuretic   |
|   | Cost per event for cardiovascular procedure-related hospitalization, medically treated heart failure hospitalization, non-heart failure hospitalization, emergency department visit, outpatient visit |
| Disease management program characteristics    | Time period for intense and maintenance phases of the program   |
|   | Program cost per patient upon initiation  |
|   | Program cost per patient per month during intense and maintenance phases of program   |
| Simulation options                            | Time horizon  |
|   | Discount rates  |
|   | Select output for resource use counts, costs, survival, and incremental cost-effectiveness ratios   |

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; ICD, implantable cardioverter-defibrillator.

\* Inputs for both the intervention and comparison groups.



<sup>†</sup> Applies to parallel group design only.

<sup>‡</sup> Variables included in computation of Seattle Heart Failure Model scores.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

**Table 2** One-Year Estimates of Resource Use and Costs from CHIME and the TEAM-HF Cost-Effectiveness Model

| Outcome   | CHIME                  | TEAM-HF Cost-Effectiveness Model |                            |
|---|------------------------|----------------------------------|----------------------------|
|   |                        | Stochastic*                      | Deterministic <sup>†</sup> |
| Resource use, total count (95% CI) <sup>‡</sup> |                        |                                  |                            |
| Hospitalizations                                | 109 (84–140)           | 98 (30–252)                      | 79 (73–88)                 |
| Emergency department or urgent care visits      | 45 (30–63)             | 87 (43–155)                      | 82 (79–87)                 |
| Outpatient visits                               | 269 (249–291)          | 1198 (733–1770)                  | 1231 (1179–1288)           |
| Resource use, mean (95% CI) <sup>‡</sup>        |                        |                                  |                            |
| All-cause hospitalizations                      | 1.3 (1.0–1.6)          | 1.1 (0.3–2.9)                    | 0.9 (0.8–1.0)              |
| Emergency department or urgent care visits      | 0.5 (0.4–0.7)          | 1.0 (0.5–1.8)                    | 1.0 (0.9–1.0)              |
| Outpatient visits                               | 3.1 (2.9–3.4)          | 13.9 (8.5–20.6)                  | 14.3 (13.7–15.0)           |
| Costs, mean (95% CI), \$ <sup>‡</sup>           |                        |                                  |                            |
| All-cause hospitalizations                      | 21,676 (16,139–28,493) | 20,751 (6345–53,302)             | 16,774 (15,358–18,548)     |
| Heart failure hospitalizations                  | 9104 (6503–13,006)     | 4324 (1322–11,108)               | 3496 (3201–3865)           |
| Non-heart failure hospitalizations              | 5379 (3631–7800)       | 7431 (2272–19,089)               | 6007 (5500–6642)           |
| Cardiovascular procedures                       | 7192 (3320–11,619)     | 8995 (2750–23,105)               | 7271 (6658–8040)           |
| Medications                                     | 199 (181–216)          | 140 (120–153)                    | 148 (140–157)              |
| Emergency department or urgent care visits      | 660 (440–924)          | 1282 (631–2274)                  | 1210 (1154–1274)           |
| Outpatient visits                               | 325 (3014–351)         | 1449 (886–2140)                  | 1488 (1426–1557)           |
| Total   | 22,861 (17,357–29,750) | 23,621 (8,237–57,555)            | 19,622 (18,093–21,516)     |

\* All levels of uncertainty modeled as stochastic except unit costs.

<sup>†</sup> All levels of uncertainty modeled as deterministic except patient profiles.

<sup>‡</sup> Confidence intervals for CHIME were estimated using the bias-corrected nonparametric bootstrap method.

**Table 3**

**Estimated Cost-Effectiveness of Hypothetical Disease Management Programs**

| Variable                              | Standard Care                | Inputs  |  |                               |
|---------------------------------------|------------------------------|---|--|-------------------------------|
|                                       |                              | Scenario A*   | Scenario B*  | Scenario C*                   |
| Program costs                         | —                            | \$70 initiation plus \$59 per patient per month for 12 months | \$2000 initiation plus ongoing cost of \$200 per patient per month |                               |
| NYHA class, %                         |                              |   |  |                               |
| I                                     | 0                            | Increase 0 percentage points                                  |  | Increase 0 percentage points  |
| II                                    | 51                           | Increase 10 percentage points                                 |  | Increase 20 percentage points |
| III                                   | 38                           | Decrease 5 percentage points                                  |  | Decrease 10 percentage points |
| IV                                    | 11                           | Decrease 5 percentage points                                  |  | Decrease 10 percentage points |
| Evidence-based medications, %         |                              |   |  |                               |
| Beta-blockers                         | 80                           | Increase 5 percentage points                                  |  | Increase 15 percentage points |
| Aldosterone antagonists               | 41                           | Increase 5 percentage points                                  |  | Increase 15 percentage points |
| Angiotensin receptor blockers         | 15                           | Increase 5 percentage points                                  |  | Increase 15 percentage points |
| ACE inhibitors                        | 48                           | Increase 5 percentage points                                  |  | Increase 15 percentage points |
| Results <sup>†</sup>                  |                              |   |  |                               |
| Lifetime costs                        | 170,279 (139,843 to 201,468) | 171,672 (141,593 to 203,576)                                  | 185,021 (139,843 to 201,468)                                       | 185,890 (152,506 to 219,375)  |
| Difference in costs <sup>‡</sup>      | —                            | 1393 (−42,048 to 46,083)                                      | 14,742 (−31,180 to 60,044)   | 15,464 (−29,534 to 59,514)    |
| Life-years                            | 5.8 (2.5 to 9.9)             | 6.0 (2.7 to 9.9)  |  | 6.3 (2.9 to 10.2)             |
| Difference in life-years <sup>‡</sup> | —                            | 0.2 (−0.9 to 1.3)   |  | 0.5 (−0.6 to 1.6)             |
| QALYs                                 | 4.6 (1.9 to 8.1)             | 4.8 (2.0 to 8.2)  |  | 5.0 (2.2 to 8.4)              |
| Difference in QALYs <sup>‡</sup>      | —                            | 0.2 (−0.7 to 1.1)   |  | 0.4 (−0.5 to 1.4)             |
| ICER, \$ per QALY <sup>§</sup>        | —                            | \$6128  | \$64,865   | \$29,701                      |

Abbreviations: ICER, incremental cost-effectiveness ratio; NYHA, New York Heart Association; QALY, quality-adjusted life-year.

\* All levels of uncertainty modeled as stochastic except unit costs. Dominant = less costly, more QALYs; dominated = more costly, fewer QALYs.

<sup>†</sup> Discounted estimates reported.

<sup>‡</sup> Hypothetical program – standard care.

<sup>§</sup> Dominant – dominated.

**Table 4**  
Resource Use, Costs, and Survival from HF-ACTION and the TEAM-HF Cost-Effectiveness Model

| Outcome   | HF-ACTION              | TEAM-HF Cost-Effectiveness Model |                            |
|---|------------------------|----------------------------------|----------------------------|
|   |                        | Stochastic*                      | Deterministic <sup>†</sup> |
| Resource use, mean (95% CI) <sup>‡</sup>          |                        |                                  |                            |
| Hospitalizations                                  | 2.0 (1.9–2.1)          | 2.1 (0.8–4.3)                    | 1.9 (1.8–1.9)              |
| Emergency department or urgent care visits        | 1.6 (1.5–1.8)          | 1.9 (1.2–2.7)                    | 1.9 (1.9–2.0)              |
| Outpatient visits                                 | 30.6 (29.3–32.0)       | 26.3 (18.0–32.9)                 | 28.9 (28.7–29.2)           |
| Medical costs, mean (95% CI), \$ <sup>§</sup> §// |                        |                                  |                            |
| Hospitalizations and physician fees               | 41,947 (38,210–46,354) | 42,552 (16,291–45,072)           | 38,982 (38,332–39,664)     |
| Emergency department or urgent care visits        | 1763 (1607–1957)       | 2731 (1698–3854)                 | 2796 (2772–2821)           |
| Outpatient visits                                 | 2651 (2536–2776)       | 2815 (1931–3523)                 | 3097 (3073–3121)           |
| Total   | 46,361 (42,536–50,856) | 48,098 (19,979–95,799)           | 44,874 (44,180–45,604)     |
| Survival, % (95% CI)                              | 83.4 (81.9 – 84.9)     | 79.6 (51.3 – 94.5)               | 99.9 <sup>¶</sup>          |

\* All levels of uncertainty were modeled stochastically.  
<sup>†</sup> All levels of uncertainty were modeled as deterministic except patient profiles.  
<sup>‡</sup> CIs for HF-ACTION were estimated using the bias-corrected nonparametric bootstrap method.  
<sup>§</sup> Costs updated to 2013 US dollars using the Consumer Price Index for Medical Care and a discount rate of 0%.  
<sup>//</sup> Medication costs were excluded due to costing based on branded medications in HF-ACTION.  
<sup>¶</sup> When survival time is modeled deterministically, only 0.1% of patient profiles corresponded to an expected period of survival less than 5 years.

**Table 5**  
Five-Year Estimates From SCD-HeFT and the TEAM-HF Cost-Effectiveness Model

| Outcome   | SCD-HeFT Economic Evaluation |         |            | TEAM-HF Cost-Effectiveness Model* |                         |                        |
|---|------------------------------|---------|------------|-----------------------------------|-------------------------|------------------------|
|   | ICD                          | Placebo | Difference | ICD                               | Placebo                 | Difference             |
| Resource use, mean                                  |                              |         |            |                                   |                         |                        |
| Hospitalizations                                    | 2.8                          | 2.7     | 0.1        | 4.0                               | 4.4                     | -0.4                   |
| Emergency department visits                         | 1.2                          | 1.4     | -0.1       | 3.9                               | 4.1                     | -0.2                   |
| Outpatient visits                                   | 18.9                         | 19.7    | 0.8        | 56.7                              | 55.5                    | -1.2                   |
| Total medical costs, mean (95% CI), \$ <sup>†</sup> | 88,630                       | 61,489  | 27,141     | 122,624 (76,827–179,007)          | 99,152 (50,278–156,255) | 23,472 (13,964–31,959) |
| 5-year survival, proportion                         | 0.65                         | 0.59    | 0.06       | 0.61                              | 0.56                    | 0.05                   |
| 5-year ICER (95% CI), \$/life-year saved            | 182,460 <sup>‡</sup>         |         |            | 166,571 (65,284–3,653,130)        |                         |                        |

Abbreviation: ICER, incremental cost-effectiveness ratio.

\* All levels of uncertainty modeled as stochastic.

<sup>†</sup> Costs reported in Mark et al. (20) updated to \$2013 using the Consumer Price Index for Medical Care.

<sup>‡</sup> Re-estimated by applying life-years saved (0.149) derived from the 5-year incremental cost-effectiveness ratio reported in Mark et al. (20).