Alberta Heritage Foundation for Medical Research

Cost Estimation of Point of Care B-Type Natriuretic Peptide for the Diagnosis of Heart Failure in the Emergency Department: Application to Alberta

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May 2005

Information Paper #25

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CONFLICT OF INTEREST

Conflict of interest is considered to be financial interest, either direct or indirect, that would be affected by the research contained in this report, or creation of a situation where an author's judgement could be unduly influenced by a secondary interest such as personal advancement.

Based on the statement above, no conflict of interest exists with the authors of this report.

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25 YEARS OF EXCELLENCE

AHFMR
ALBERTA HERITAGE FOUNDATION
FOR MEDICAL RESEARCH

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- Mr Brian Roskewich, Point of Care Specialist, Somagen Diagnostics Inc., Edmonton

PREFACE

This report represents the collaborative efforts of the Alberta Heritage Foundation for Medical Research Health Technology Assessment Unit and the Public Health Sciences Department at the University of Alberta. The AHFMR and U of A are committed to building the capacity for creating and applying high quality evidence to inform questions facing policy and decision makers in Alberta's health care system. The Health Technology Assessment and Economics streams at the University of Alberta and the HTA unit at AHFMR have been collaborating for several years in building capacity and capability in health technology assessment in Alberta. Graduate students are encouraged and invited to undertake projects which are relevant and timely through the participation and leadership of their supervisors. We would appreciate hearing from you if you found this report useful or have ideas for other projects that might be brought to the attention of the HTA unit and future graduate students. Please forward your comments to Nicola.Cherry@ualberta.ca or Don.Juzwishin@ahfmr.ab.ca

The publication is also available on the web at:
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ABBREVIATIONS

AMI = Acute myocardial infarction

BNP = B-type natriuretic peptide

CHF = Congestive heart failure

CLL = Council of Laboratory Leaders

CMA = Cost minimization analysis

ED = Emergency department

ECG = Electrocardiogram

ECHO = Echocardiography

FN = False negative

FP = False positive

LVA = Left ventricular assessment

LVD = Left ventricular dysfunction

LVF = Left ventricular function

POC = Point of care

QALY = Quality adjusted life year

RD = Renal dysfunction

TN = True negative

TP = True positive

UA = Unstable angina

EXECUTIVE SUMMARY

Background

Congestive heart failure (CHF) is a condition where the heart cannot supply enough blood to satisfy the metabolic requirements of the body. Indications are characterized by symptoms of acute dyspnea (shortness of breath). Patients with symptoms of acute dyspnea often present at emergency departments (ED) where the diagnosis of CHF is primarily based on medical history, physical examination, electrocardiogram (ECG) and chest X-ray.

Nevertheless, differentiating CHF from other causes of dyspnea remains a clinical challenge and clinicians are left with diagnostic uncertainty that can result in misdiagnosis. B-Type Natriuretic Peptide (BNP) is a 32-amino-acid polypeptide that is secreted by the cardiac ventricles in response to ventricular volume expansion, filling pressure and thickened arteries. Accordingly, testing for BNP blood concentration can be used as a diagnostic tool to rule out CHF from other pulmonary conditions for patients with symptoms of acute dyspnea.

Objectives

The aim of this report is to provide a cost estimate, over a one year time period from a payer's perspective, of Biosite Triage Point-of-Care (POC) BNP assay used to rule out CHF from other pulmonary conditions for patients presenting in Alberta EDs with acute dyspnea, but who do not have acute myocardial infarction (AMI), renal dysfunction (RD) or unstable angina (UA). The scope of this report is limited to the use of BNP for diagnosis and does not address prognosis, management or patient monitoring.

Methods

To estimate the cost of BNP testing, several hypothetical cost models were developed and designed to compare potential BNP scenarios with standard clinical diagnostic protocols in Alberta. In urban settings the use of BNP could reduce the number of patients referred for echocardiography (ECHO) and hospitalization days or reduce the number of hospitalization days alone, or have no impact (add-on cost). In rural settings, BNP could either reduce the number of patients referred to an urban centre for ECHO or have no impact.

Costs of resources were estimated and valued based on provincial data and existing available literature. Cost minimization analysis (CMA) was used to compare the costs for potential scenarios of BNP use.

Results

In a given year there are an estimated 5000 patients in urban settings and 1600 patients in rural settings presenting at EDs in Alberta with symptoms of acute dyspnea (who do not have AMI, RD or UA). In urban settings the total cost of standard diagnostic protocols was $4,507,639 per annum. The total savings achieved by reducing the number of ECHOs and hospitalization days was $990,543 per annum. The total savings achieved by reducing the number of hospitalization days alone was $207,771. The total add-on cost of BNP testing was $99,998.

In rural settings the total cost of standard diagnostic protocols was $1,245,136 per annum. The total savings achieved if BNP testing reduces the number of ECHOs conducted at an urban centre was $65,442. The total add-on cost of BNP testing was $1646.

Conclusions and Considerations

The results indicate that compared to standard diagnostic protocols, BNP testing in one year could significantly reduce total costs with greater cost implications in urban settings and in older populations with a higher prevalence of CHF. The economic utility of BNP testing however is highly dependent on the reduction of the number of ECHOs. Thus, strict diagnostic protocols must be followed with clear diagnostic guidelines for physicians such that BNP is properly used. It may be worth pursuing a pilot study of BNP testing to produce the information necessary for more definitive conclusions that reflect actual use in Alberta.

Moreover, results should be interpreted cautiously in light of a number of inherent limitations:

- First, the analysis was conducted from a payer's perspective and applies specifically to diagnosing CHF. Consequently, the analysis does not capture other potential cost implications associated with patients as they progress through their disease and the health care system.
- Second, while the analysis did account for age and sex, the results reflect use of BNP in patients who were assumed to have no other comorbid conditions including AMI, RD and UA. However, the number of comorbid conditions increases in older populations and persons with CHF.
- Third, cost models are limited by the type and availability of cost data in Alberta. There are, therefore, other cost implications associated with BNP testing that have not been accounted for.

- Fourth, and the most important limitation to the present analysis, was that health outcomes for patients who receive BNP testing were not captured. Economic considerations are secondary to health outcomes. Justification for BNP testing must be predicated on improving clinical care at reduced costs. As a result, this analysis is only the first step in elucidating the potential cost implications of BNP testing in EDs within Alberta.

Further study will be required using a framework that not only includes treatment management and patient monitoring but also long-term health outcomes and quality of life taken from a broader societal perspective.

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STUDY OBJECTIVE AND CONTEXT

This report has been prepared following interest from the Council of Laboratory Leaders (CLL) to provide economic information about the use of B-Type Natriuretic Peptide (BNP) testing as an added diagnostic protocol in the process of diagnosing congestive heart failure (CHF). Specifically, the relevant question addressed was the economic impact of BNP used as a laboratory blood test to differentiate CHF from other pulmonary conditions (diagnosis) for patients presenting to the emergency department (ED) in the province of Alberta. The research question is further limited to patients older than 19 years of age who do not have acute myocardial infarction (AMI), renal dysfunction (RD) or unstable angina (UA).

The aim of this report is to provide a cost estimate, over a one year time frame, from a payer's perspective, of Biosite Triage Point-of-Care (POC) BNP assay for use in Alberta EDs. A POC assay was chosen as it can be utilized in both urban and rural settings. Costs of resources are estimated and valued based on provincial data and existing available literature. This report utilizes cost minimization analysis (CMA) to compare the costs for potential scenarios of BNP use for urban and rural settings in Alberta. This report does not evaluate the costs of using BNP for prognosis, patient management, or monitoring.

BACKGROUND

Congestive heart failure (CHF) is characterized by the inability of the heart to supply a sufficient amount of blood to meet the metabolic requirements of the body's tissues [1]. Consequently, there is no objective definition of CHF because there is no physiological cut-off value and indications of CHF are characterized by specific symptoms such as acute dyspnea and fatigue.

While the first management task in the care of the dyspneic patient is correct diagnosis, CHF is one of the most difficult conditions to diagnose [2]. Patients with symptoms of acute dyspnea often present at EDs and the diagnosis of CHF is primarily based on medical history, physical examination, electrocardiogram (ECG) and chest X-ray. Still, differentiating CHF from other causes of acute dyspnea remains a clinical challenge and clinicians are left with great diagnostic uncertainty resulting in misdiagnosis and delays in the initiation of appropriate therapy [3, 4].

Doppler Echocardiography (ECHO) is a device that can assess heart wall dimensions, cardiac motion and cardiac ejection fraction measurements. ECHO has become a widely accepted diagnostic tool for assessing potential CHF and other cardiac pathologies. However, ECHO in the urgent care setting however is not without its own limitations.

ECHO can be expensive and is not always readily available [4, 5]. Depending on the time of day and the availability of the ultrasound machine, even in urban centres it can take several hours before echocardiographic results are complete (personal communication, Dr K. Dong). Furthermore, the interpretation of the echocardiogram requires a thorough understanding of the ultrasound device in relation to the cardiovascular system but ED physicians have limited training with ECHO. ECHO in the ED therefore requires well trained sonographers, echocardiographers, or cardiologists (trained in ECHO) who can respond to clinical needs at any moment. However, this is often not possible [6]. Another limitation associated with ECHO is that it may not always reveal the underlying cause of acute CHF.

THE TECHNOLOGY

Although ECHO is the gold standard in diagnosing CHF, the limitation of this technique in the urgent care setting suggest the need for other objective measures [7]. B-Type Natriuretic Peptide (BNP) is a 32-amino-acid polypeptide with blood concentrations that correlate well with the clinical severity of CHF and has prognostic potential regarding adverse clinical events [8]. BNP is secreted by the cardiac ventricles in response to ventricular volume expansion, filling pressure and thickened arteries [8-10].

Some studies have suggested that when used in conjunction with other clinical information, BNP testing may be useful in establishing or ruling out the diagnosis of CHF in patients with acute dyspnea [3-5, 11, 12] particularly in the urgent care setting [5, 13].

Currently, there are three primary types of BNP assays available.

1. The Biosite Triage POC BNP assay (Triage® BNP test, Biosite Inc., San Diego, CA) is a rapid fluorescence immunoassay where a sample of blood can be analyzed immediately at the location of the patient. This assay can determine the BNP concentration level within 5 minutes. This assay requires a portable hand held device, a cartridge for collecting blood samples and a nurse or other personnel to conduct the test.
2. The Bayer BNP assay (Advia Centaur® System, Bayer Diagnostics, Tarrytown, NY) is a high-throughput (240 tests per hour) automated assay. It requires that blood samples be taken to an external centralized laboratory where a highly sophisticated and expensive immunodiagnostic machine analyzes the samples. The immunodiagnostic machine requires minimal supervision and can determine BNP blood concentrations within approximately 30 minutes.
3. The Roche NT-proBNP assay (Elecsys® proBNP, Roche Diagnostics Corp., Indianapolis, IN) measures a derivative of BNP called N-terminal inactive BNP. Blood samples from patients are taken to an external laboratory where they are analyzed on a bench top analyzer. This fully automated assay can be adapted for use in either medium or high volume laboratories (can analyze approximately 85 tests per hour). The bench top analyzer requires minimal supervision and can determine BNP blood concentrations within approximately 30 minutes.

EVIDENCE ON EFFECTIVENESS AND EFFICIENCY

Diagnostic Effectiveness

In general, while BNP testing does accurately reflect physiological conditions, the level of clinical evidence surrounding its ability to differentiate between CHF from other pulmonary conditions is limited by the lack of randomized controlled trials [14]. In a recent health technology assessment of the clinical evidence [15], the highest level of evidence came from a large multi-centre prospective trial involving 1568 patients from seven centres in three countries. The assessment concluded that BNP assays appear to provide additional diagnostic value to clinical judgement, especially for ruling out CHF in patients without AMI, RD and UA in emergency departments where ECHO is not available. The BNP assay is not a stand alone test and does not replace any elements of the CHF diagnostic protocol.

A major issue of contention however, is that there is no consensus on the appropriate BNP cut-off value that should be used to rule out CHF from other pulmonary conditions for patients with acute dyspnea. According to Redfield and colleagues [16], the use of discriminatory BNP concentrations need to be corrected for age and sex because levels of BNP increase with age [17] and are higher in women than in men [11, 18]. BNP blood concentrations levels can also be elevated in patients with other co-morbidities such as AMI, RD and UA [19]. Nevertheless, most studies of BNP have not accounted for this biological variability [15].

Overall, the report by Guo and Harstall [15] concluded that there was currently insufficient evidence to determine whether BNP assays (BNP and NT-proBNP) were useful in identifying CHF in persons with acute dyspnea. However, the report did suggest that BNP testing may provide additional diagnostic value to clinical judgement when it is used to rule out CHF in patients with acute dyspnea.

Efficiency

A comprehensive search was conducted for evidence that describes the potential cost impact of BNP when used in the ED to differentiate CHF from other pulmonary conditions in the ED (see Appendix A for search strategy, selection criteria and search results). Three articles were identified as being relevant and were retrieved for review. Assessment of the quality of the selected studies was based on criteria adapted from Drummond and colleagues [20] (see Appendix B for summary and review).

Mueller and colleagues [21] conducted a randomized controlled trial that compared the standard diagnostic protocol for patients presenting with acute dyspnea with a diagnostic strategy guided by BNP. The control group was comprised of 227

patients with a mean age of 70.3 years who underwent standard clinical assessment that included history, physical examination, ECG, pulse oximetry, blood test, chest radiography, and ECHO. In the BNP group, in addition to receiving standard clinical protocols, 225 patients with a mean age of 70.8 years were also assessed with Biosite Triage POC BNP assay (the diagnostic cut-off value for CHF was 100pg/ml). Demographic characteristics such as age, sex, and medical history were well matched between study groups. Outcomes measured were the time to discharge and the total cost of treatment based on hospital charges for patients over a one year period. Time to discharge was defined as the interval from presentation at the ED to discharge while time to treatment was defined as the interval from presentation at the ED to the initiation of appropriate treatment. All end points were assessed with blinded protocols by physicians who were not involved in patient care.

Results of the study revealed that the BNP group, compared to the control group, had a reduced median time to the initiation of treatment (63 minutes compared to 90 minutes, $p = 0.03$), time to discharge (8 days compared to 11 days, $p = 0.001$) and total cost ($5410 compared to $7264, $p = 0.006$). Based on their findings, the authors concluded that BNP used in conjunction with other clinical information reduced the time to the initiation of the most appropriate treatment, the need for hospitalization, time to discharge, and total cost of treatment.

Weaknesses of the study stemmed from the fact that the authors did not specify whether the reported costs of BNP included labour and equipment. Also, they did not conduct a sensitivity analysis to account for areas of uncertainty; in particular, the cost of hospital charges given that the study used this measure as an estimate of true costs.

Sim and colleagues [22] conducted an observational study that compared open access ECHO with a strategy of using BNP as a precursor test for ECHO. Specifically, the cost strategy utilized was to compare the costs associated with all patients receiving ECHO (standard diagnostic protocol) with the cost associated with all patients receiving BNP testing to determine the need for ECHO. BNP levels were measured with the Bayer BNP assay using a diagnostic cut-off value of 19 pg/ml and 20 pg/ml. The study sample consisted of 83 patients with dyspnea, ages ranged between 37 and 87 years (mean of 72 years) and 48% were male. Outcomes were the cost of BNP (including labour, equipment and supplies) and ECHO (including labour, equipment and supplies) for patients over a one year period.

Results of the study indicated that at a threshold of 19 pg/ml and 20 pg/ml, the total cost of using BNP as a precursor test for ECHO saved £964.20 and £1288.20 respectively. However, a cut-off value of 20 pg/ml did produce one false negative test. Based on these findings, the authors concluded that using BNP to pre-select patients who require ECHO is cost effective.

The primary weakness of the study was that the relevant costs identified were simply the cost of the BNP test and ECHO. Yet, the diagnostic precision of BNP and ECHO directly influence the etiology of patients and determine the number of patients who are potentially hospitalized for CHF. Hospitalization does have a significant impact on associated costs and should be included in the analysis.

Craig and colleagues [23] conducted a health technology assessment evaluating the cost-effectiveness of a diagnostic strategy guided by BNP. Their cost analysis was a replication of the study conducted by Mueller and colleagues [21] modified for the Scottish ED setting. A cohort of 100 patients receiving BNP guided diagnostic protocols was compared to 100 patients receiving standard diagnostic protocols only.

Total treatment costs were £156,000 for the BNP guided cohort and £199,400 for the cohort receiving standard protocols. This provided a potential cost saving of £43,400 and a savings per patient of £434.

Due to the uncertainty of whether cost-effective evidence observed by Mueller and colleagues [21] would generalize to the Scottish setting, the authors concluded that the cost analysis did not provide convincing evidence. The authors recommend that pilot studies be conducted to validate potential cost savings with Scottish protocols, diagnostic and discharge procedures.

Based on these studies there is some evidence to indicate that BNP could potentially reduce costs by minimizing the number of patients who receive ECHO. However, it is important to note that these studies did not take account the biological variability of BNP. Furthermore, valuations of costs were derived from various sources that limit the extent to which their results can be generalized to Alberta. Further limiting the generalizability of these results is that it is not known whether the patient populations in these studies are similar to that of Alberta or whether clinical practice patterns are comparable. Consequently, these studies offer limited guidance on what conditions and for what populations BNP testing should be made available and what it would potentially cost the Alberta health care system.

COST MINIMIZATION ANALYSIS

The analytical approach used to estimate the cost of BNP testing in Alberta's EDs was based on several hypothetical cost models that were designed to compare potential BNP scenarios with standard clinical diagnostic protocols. It was imperative that the cost analysis not only determine the estimated cost of BNP testing but also accurately reflect the context within which it is used and applied. Providing an accurate and realistic cost estimation required that the analysis account for the biological variability of BNP and its potential cost impact within both urban and rural contexts. Therefore, cost models were further stratified by setting (urban versus rural), age, and gender.

BNP Assay

In an urgent care setting it is essential to interpret cardiac marker data such as BNP at the same time as clinical symptoms and signs [24]. Appropriate patient risk stratification and timely delivery of appropriate treatment requires that diagnostic information be available immediately. Therefore, availability of biochemical test results within the time frame when clinicians are providing care of the individual patient in the ED is a critical advantage of POC assays.

BNP assays that require sample to be taken to external laboratories (e.g. Bayer BNP and Roche NT-proBNP assays) for assessment essentially provide limited diagnostic benefit in providing timely care to patients in the ED. Laboratory accessibility during non-office hours and the waiting time between requesting the test and receiving the results all serve to delay the delivery of treatment.

The underlying principle for POC testing is that quick biochemical test results performed near the patients will result in better patient and cost outcomes [24]. Biosite Triage POC testing is robust, reproducible, potentially saves physician time, allows high-risk patients to be treated more rapidly, allows low-risk patients to be released in a more timely fashion and potentially reduces overall costs [24, 25]. The Biosite Triage BNP assay satisfies the analytical requirements for clinical validation while also allowing for widespread clinical use in contrast to competing BNP assays with longer turn around times [25]. In a rural setting, the Biosite Triage POC assay may have greater practical utility because highly sophisticated technologies such as ECHO are less readily available. Conducting the POC test and interpreting its results does not require highly trained personnel nor is it as costly as other BNP alternatives.

Therefore, the BNP assay chosen for the present cost estimation was the Biosite Triage POC assay. The Canadian distributor for the Biosite Triage POC assay is

Somagen Diagnostics Inc., located in Edmonton, Alberta. There are two service contracts available depending on patient volume: volumes equal or greater than 300 annual tests fall under a reagent rental plan while volumes less than 300 annual tests fall under a capital purchase plan.

Under the reagent rental plan, the portable BNP analyzer is provided at no charge and is fully guaranteed for the duration of a contract (i.e. as long as cartridge kits are provided by Somagen). Under this plan, cartridges cost approximately $35 each and come in a kit of 25 assays ($875 per kit).

Under the capital purchase plan, the portable BNP analyzer is purchased (at a cost of $5500) and fully guaranteed for the duration of a contract. Under this plan, cartridges cost approximately $30 each and come in a kit of 25 assays ($750 per kit).

Quality control is required every 30 days at a cost of $155. Calibration verification controls are also required every six months at a cost of $125. The total cost of the Biosite Triage POC assay was estimated at approximately $40 per test (personal communication, Dr D. Isaac).

Source of Model Probabilities and Cost Valuation

Table 1 shows the model inputs and their sources of valuation. Model probabilities were obtained from available literature while costs of resources and population characteristics were estimated and valued based on provincial data. Cost factors for which there was limited information available were estimated through consultation with experts and from available data.

Population and Model Cohorts

The study population included in the analysis were men and women older than 19 years of age who presented to an ED with symptoms of acute dyspnea and who did not have RD, AMI or UA. Age categories for model cohorts were persons aged 20-49 years, 50-64 years, 65-74 years, and older than 75 years.

The total sample sizes for each model cohort (Table 1) were estimated based on provincial population data [26], expert opinion and discharge diagnosis data from the University of Alberta Hospital in Edmonton and Foothills Hospital in Calgary. In a given year, it is estimated that approximately 10,000 patients present to the ED with symptoms of acture dyspnea in urban settings and 3200 patients in rural settings.

Standard Clinical Diagnostic Protocols

The Canadian Cardiovascular Society consensus guidelines [27] update for the diagnosis and management of heart failure recommended that patients who present with acute dyspnea with unclear but suspected cardiac etiologies may be considered to have venous blood withdrawn for the measurement of BNP concentration to

assist with the diagnostic decision. BNP assays however, are currently unavailable in EDs throughout Alberta and are only available in limited capacity at the Foothills Hospital's Cardiac Transplant and Heart Function Clinics in Calgary.

In general, standard clinical diagnostic protocols for patients presenting with acute dyspnea at the ED are as follows:

Urban Setting

ED physician takes the patient's history and conducts a physical examination, ECG and a chest x-ray. If there is a possible cardiac pathology the patient is referred for ECHO (personal communication, Dr D. Isaac, Dr M. Bullard and Dr K. Dong).

Rural Setting

ED physician takes the patient's history, conducts a physical examination, ECG and a chest x-ray. If there is a threatening cardiac pathology the patient is referred for ECHO and is transported by ambulance to an urban centre (personal communication, Dr D. Isaac and Dr R. Wedel).

Cost Outcomes and Model Scenarios

There were five model scenarios developed. Each was designed to compare potential BNP cost scenarios with standard clinical diagnostic protocols in both urban and rural settings for each sex within each age cohort (56 total model comparisons). Appendix C and D illustrate the general framework from which all models were derived.

There are two primary cost outcomes of BNP testing identified in the literature and from various experts. First, BNP testing can potentially reduce costs by minimizing the number of ECHOs that are performed for patients who are assessed for potential CHF. Second, BNP testing may shorten the number of hospitalization days due to rapid diagnosis and expeditious treatment. The number of hospitalization days however is not assumed to decrease in rural settings given that patients are transported to an urban centre for ECHO.

The cost comparators for urban and rural settings are as follows:

- *Urban*

  Scenario A: BNP testing effectively reduces the number of ECHOs and the number of hospitalization days.

  Scenario B: BNP testing does not effectively reduce the number of ECHOs but does reduce the number of hospitalization days.

  Scenario C: BNP testing does not effectively reduce the number of ECHOs nor does it reduce the number of hospitalization days (i.e. add-on cost of BNP testing).

- *Rural*

  Scenario D: BNP testing effectively reduces the number of ECHOs at an urban centre.

  Scenario E: BNP testing does not effectively reduce the number of ECHOs at an urban centre (i.e. add-on cost of BNP testing).

Cost outcomes are listed in Table 1 and for each model scenario could include the following:

1. History, physical, ECG and chest x-ray.
2. BNP assay (includes labour, equipment and supplies).
3. ECHO (includes labour, equipment and supplies).
4. Hospitalization (note that percent change was used to estimate the reduction in hospitalization days and was calculated from results provided by Mueller and colleagues [21]).
5. Ambulatory care.
6. Ambulance (rural context only).

Given that the basic economic premise of BNP testing is that it can potentially avert unneeded ECHOs or reduce the number of hospitalization days, cost models were specifically designed to attribute any changes in costs associated with BNP testing to those patients who are referred to ECHO for suspected CHF (refer to section describing model assumptions for further details). That is, the resulting cost savings or cost additions observed in each model scenario are attributable to the proportion of patients who are referred to ECHO for suspected CHF. As previously mentioned, while all dyspneic patients eventually receive ECHO in urban settings, at least 50% are referred for suspected CHF. In rural settings due to the unavailability of ECHO, it was estimated that only 5% of dyspneic patients are referred to an urban centre for ECHO and of these 50% are referred for suspected CHF.

Table 1: Model inputs and source of valuation

Cost Input	Value (Range for Sensitivity Analysis) [a]				Source /Ref	Comments
	Ages 20-49	Ages 50-64	Ages 65-74	Ages ≥ 75		
Cohort Size (Urban / Rural)	1000/200	2500/500	3000/1000	3500/1500	*	Based on expert opinion and available data.
Probabilities						
Presenting at ED						
Men	0.503	0.504	0.484	0.388	26	Used population estimates by health region.
Women	0.497	0.496	0.516	0.612	26	
Does not have AMI, RD or UA	0.50	0.50	0.50	0.50	*	Based on expert opinion and available info.
Prevalence of CHF						
Men (per thousand)	1 (0.8-1.2) [a]	2 (1.6-2.4) [a]	8 (6.4-9.6) [a]	33 (26-40) [a]	28	Based on data collected from April 1, 1994 to March 31, 2000 in Alberta
Women (per thousand)	1 (0.8-1.2) [a]	2 (1.6-2.4) [a]	8 (6.4-9.6) [a]	33 (26-40) [a]	28	
BNP						
Men – Concentration Level	24 pg/ml	43 pg/ml	75 pg/ml	356 pg/ml	16	Population was >44 years of age. Values were optimal values based on ROC curve.
Men – Sensitivity	0.75 (0.60-0.90) [a]	1.00 (0.80-1.00) [a]	0.82 (0.66-0.98) [a]	0.78 (0.62-0.94) [a]	16	
Men – Specificity	0.86 (0.69-1.00) [a]	0.82 (0.66-0.98) [a]	0.81 (0.65-0.97) [a]	0.90 (0.72-1.00) [a]	16	
Women – Concentration Level	43 pg/ml	109 pg/ml	98 pg/ml	219 pg/ml	16	Used 43 pg/ml male values because none was provided for women aged 44-49 in the study.
Women – Sensitivity	1.00 (0.80-1.00) [a]	1.00 (0.80-1.00) [a]	1.00 (0.80-1.00) [a]	0.75 (0.60-0.90) [a]	16	
Women – Specificity	0.82 (0.66-0.98) [a]	0.95 (0.76-1.00) [a]	0.86 (0.69-1.00) [a]	0.86 (0.69-1.00) [a]	16	
ECHO						
Sensitivity	0.92 (0.90-1.00)	0.92 (0.90-1.00)	0.92 (0.90-1.00)	0.92 (0.90-1.00)	29	Assumed nuclear angiography was the gold standard.
Specificity	0.96 (0.90-1.00)	0.96 (0.90-1.00)	0.96 (0.90-1.00)	0.96 (0.90-1.00)	29	
History, Physical, ECG & chest X-Ray						
Sensitivity	0.36 (0.29-0.43)	0.36 (0.29-0.43)	0.36 (0.29-0.43)	0.36 (0.29-0.43)	30	
Specificity	0.89 (0.71-1.00)	0.89 (0.71-1.00)	0.89 (0.71-1.00)	0.89 (0.71-1.00)	30	
Hospitalization	0.35 (0.28-0.42)	0.35 (0.28-0.42)	0.35 (0.28-0.42)	0.35 (0.28-0.42)	31	
ECHO (referred to assess potential CHF)	0.50 (0.40-0.60) [a]	0.50 (0.40-0.60) [a]	0.50 (0.40-0.60) [a]	0.50 (0.40-0.60) [a]	§	Dr. D. Isaac

Cost Input	Value (Range for Sensitivity Analysis) [a]				Source / Ref.	Comments
	Ages 20-49	Ages 50-64	Ages 65-74	Ages ≥ 75		
Referred to ECHO from a rural centre	0.05 (0.04-0.06) [a]	0.05 (0.04-0.06) [a]	0.05 (0.04-0.06) [a]	0.05 (0.04-0.06) [a]	§	Dr. D. Isaac
Costs						
History & Physical	$92 (74-110)	$92 (74-110)	$92 (74-110)	$92 (74-110)	32	Used ED physician fee.
ECG	$22 (17.6-26.4) [a]	$22 (17.6-26.4) [a]	$22 (17.6-26.4) [a]	$22 (17.6-26.4) [a]	33	From British Columbia.
Chest X-Ray	$87 (70-104.4) [a]	$87 (70-104.4) [a]	$87 (70-104.4) [a]	$87 (70-104.4) [a]	32	Used ED physician fee.
BNP (labour & supplies)	$40 (32-48) [a]	$40 (32-48) [a]	$40 (32-48) [a]	$40 (32-48) [a]	§	B. Roskewich, Dr. D. Isaac
ECHO (test, labour & equipment)	$236 (189-283) [a]	$236 (189-283) [a]	$236 (189-283) [a]	$236 (189-283) [a]	34	
Hospitalization for CHF (per hospital day) [b]	$1,339 (1,252-1,427)	$1,080 (1,034-1,127)	$954 (922- 987)	$820 (743-888)	28	From Alberta Centre for Health Service Utilization.
Average Hospitalization Days (no BNP)	7.8 (6.4-9.2)	8.2 (7.5-9.0)	8.5 (8.0-9.0)	11 (9.5-12.6)	28	
Average Hospitalization Days (BNP) [c]	5.7 (4.5-6.9) [a]	6.0 (5.5-6.6) [a]	6.2 (5.8-6.6) [a]	8.0 (7.0-9.2) [a]	21	Used Percent Change from study
Ambulatory Care (i.e. treat & discharge)	$126 (101-151) [a]	$126 (101-151) [a]	$126 (101-151) [a]	$126 (101-151) [a]	34	
Ambulance from rural to urban centre	$1,700 (1,360-2,040) [a]	$1,700 (1,360-2,040) [a]	$1,700 (1,360-2,040) [a]	$1,700 (1,360-2,040) [a]	35	Based on cost from Cold Lake to Edmonton.

CHF – Congestive Heart Failure BNP – B-Type Natriuretic Peptide ECHO – Echocardiography ECG – Electrocardiogram LVF – Left Ventricular Systolic Function

[a.] Took ± 20% for parameters with no reported range or confidence interval.

[b.] Reported cost are decreasing with age because older patients were: 1) less often admitted to special care units; 2) seen by specialists or designated most responsible physician; 3) given cardiac catheterizations; 4) prescribed beta blockers, angiotensin converting enzyme inhibitors, and receptor blockers on discharge.

[c.] Applies only to urban context.

§ Personal Communication

* Direct Estimate

Model Assumptions

The assumptions inherent in every cost analysis can vary considerably across settings. It is therefore necessary that economic investigations develop economic frameworks that are contextually relevant [11]. The estimated cost of BNP testing in Alberta depend on the relative cost of the diagnostic tests/devices available, the diagnostic accuracy of available tests for specific populations, the prevalence of CHF in the population, and the contextual standard diagnostic protocol for CHF diagnosis in the ED.

A summary of the primary assumptions are as follows:

Diagnostic Properties

- The cost analysis is based specifically on the premise that BNP testing rules out CHF. This assumption is based on a previous HTA report [15] and the available economic literature [1, 36].

Setting and Population

- It is estimated that 50% of patients presenting with acute dyspnea at the ED do not have RD, AMI or UA.
- In urban settings, of the 50% who do not have RD, AMI, or UA, it is estimated that at least 50% are referred to ECHO for suspected CHF.
- In rural settings, of the 50% who do not have RD, AMI, or UA, it is estimated that 5% are referred to an urban centre for ECHO and of these 50% are referred for suspected CHF.

Cost Attribution

- To provide a more conservative estimate of the cost implications attributable to BNP testing and to better reflect the variability in the use and request of ECHO, BNP testing is not conducted on all patients presenting to the ED with symptoms of acute dyspnea but rather on those referred to ECHO for suspected heart failure. This assumption is based on two underlying principles.
    - First, BNP testing is NOT required for patients where causes of acute dyspnea and presence of CHF are clear. Potential application of BNP should be reserved for dyspneic patients where presence of CHF is uncertain (personal communication, Drs M. Bullard and C. Harley). ECHO is commonly performed in these "more diagnostically complex" patients.

  - Second, in addition to CHF, ECHO is also used to determine pericarditis, cardiomyopathy, leaky valves (personal communication, Dr M. Bullard), cardiac ischemia (heart attack), hemodynamic instability, cardiac tamponade, myocarditis, and pulmonary embolus (personal communication, Dr K. Dong). Therefore, not all patients referred to ECHO are referred for suspected CHF.
- In the ED, patients receive a diagnostic procedure only once during their triage and assessment.
- Hospitalization days are reduced in urban settings only.
- ECHO is unavailable in rural EDs and patients who require ECHO are transported to urban centres by ground ambulance.

RESULTS

Urban Context: Base Case Results

Table 2 shows the estimated costs of BNP testing for urban settings. For 5000 dyspneic patients older than 19 years of age and who did not have AMI, RD or UA, the total cost of standard diagnostic protocols per year was $4,507,639. Of 5000 dyspneic patients, 2500 were referred to ECHO for suspected CHF and were eligible to receive BNP testing.

In Scenario A, the total savings attained by reducing the number of ECHOs and hospitalization days was $990,543. In Scenario B, the total savings achieved by reducing the number of hospitalization days alone was $207,771. In Scenario C, the total add-on cost of BNP testing, if it neither minimizes the number of ECHOs nor the number of hospitalization days, was $99,998.

Furthermore, the cost impact of BNP testing differed by age cohort. Reducing the number of ECHOs and the number of hospitalization days saved $548,167 for persons older than 74 years of age and $442,379 for persons younger than 75 years of age. Reducing the number of hospitalization days alone saved $213,915 for persons older than 74 years of age, but added $6142 for persons younger than 75 years of age.

Rural Context: Base Case Results

Table 3 shows the estimated costs of BNP testing for rural settings. For 1600 dyspneic patients older than 19 years of age who did not have AMI, RD, or UA, the total cost of standard diagnostic protocols per year was $1,245,136. Of 1600 dyspneic patients, 41 patients were referred to ECHO at an urban centre for suspected CHF and were eligible to receive BNP testing.

If BNP testing reduces the number of ECHOs the total costs saved was $65,442. If BNP testing does not effectively reduce the number of ECHOs the total add-on cost was $1646. Similar to the results in urban settings, greater cost savings were associated with older age cohorts.

Table 2: Cost estimation for urban context

Scenario	Cohort Size [a]	Incremental Cost ($) Comparison with Standard [b]		
		Scenario A	Scenario B	Scenario C
Men				
20–49 years of age				
Standard [b]	251	148,401	148,401	148,401
Comparator		111,582	148,372	153,431
		-36,819	-29	+5030
50–64 years of age				
Standard [b]	630	359,188	359,188	359,188
Comparator		277,633	360,849	371,788
		-81,555	+1661	+12,600
65–74 years of age				
Standard [b]	726	417,188	417,188	417,188
Comparator		325,593	418,595	431,708
		-91,595	+1407	+14,520
≥ 75 years of age				
Standard [b]	679	1,023,533	1,023,533	1,023,533
Comparator		813,794	940,534	1,037,113
		-209,739	-82,999	+13,580
Sub-Total	**2286**	**-419,708**	**-79,960**	**+45,730**
Women				
20–49 years of age				
Standard [b]	249	146,633	146,633	146,633
Comparator		112,251	146,602	151,601
		-34,379	-31	+4968
50–64 years of age				
Standard [b]	620	353,486	353,486	353,486
Comparator		258,646	355,121	365,886
		-94,840	+1634	+12,400
65–74 years of age				
Standard [b]	774	444,771	444,771	444,771
Comparator		341,583	446,270	460,251
		-103,188	+1500	+15,480
≥ 75 years of age				
Standard [b]	1071	1,614,439	1,614,439	1,614,439
Comparator		1,276,011	1,483,523	1,635,859
		-338,428	-130,916	+21,420
Sub-Total	**2,714**	**-570,835**	**- 127,813**	**+54,268**
Grand Total	**5,000**	**-990,543**	**-207,773**	**+99,998**

Note. Standard scenario reflects the standard clinical diagnostic protocol. **Scenario A** reflects the cost of BNP minimizing both the number of ECHOs referred for suspected CHF and the number of hospitalization days. **Scenario B** reflects the cost of BNP minimizing the number of hospitalization days only. **Scenario C** reflects the cost of BNP having minimized neither the number of ECHOs nor the number of hospitalization days (i.e. add-on cost of BNP test).

[a.] There were an estimated total 10,000 patients presenting with symptoms of acute dyspnea at urban EDs in Alberta of which 50% were assumed to not have AMI, RD or UA.

[b.] Referent Category. Incremental costs represent comparisons with the Standard Scenario. Costs added +/ Costs saved -.

Table 3: Cost estimation for rural context

Scenario	Cohort Size [a]	Incremental Cost ($) Comparison with Standard [b]	
		Scenario D	Scenario E
Men			
20–49 years of age			
Standard [b]	50	35,067	35,067
Comparator		32,863	35,118
		-2204	+51
50–64 years of age			
Standard [b]	126	80,476	80,476
Comparator		75,284	80,647
		-5192	+171
65–74 years of age			
Standard [b]	242	148,985	148,985
Comparator		139,208	149,227
		-9777	+242
≥ 75 years of age			
Standard [b]	291	274,675	274,675
Comparator		263,308	274,966
		-11,367	+291
Sub-Total	**709**	**-28,540**	**+755**
Women			
20–49 years of age			
Standard [b]	50	34,649	34,649
Comparator		32,576	34,699
		-2073	+50
50–64 years of age			
Standard [b]	124	79,199	79,199
Comparator		73,259	79,323
		-5940	+124
65–74 years of age			
Standard [b]	258	158,835	158,835
Comparator		147,798	159,093
		-11,037	+258
≥ 75 years of age			
Standard [b]	459	433,250	433,250
Comparator		415,398	433,709
		-17,852	+459
Sub-Total	**891**	**-36,902**	**+891**
Grand Total	**1600**	**-65,442**	**+1646**

Note. Standard scenario reflects the standard clinical diagnostic protocol. **Scenario D** reflects the cost of BNP minimizing the number of ECHOs referred for suspected CHF at an urban centre. **Scenario E** reflects the cost of BNP having not minimized the number of ECHOs referred for suspected CHF at an urban centre.

[a.] There was an estimated total of 3200 patients presenting with symptoms of acute dyspnea at rural EDs in Alberta of which 50% were assumed to not have AMI, RD, or UA.

[b.] Referent Category. Incremental costs represent comparisons with the Standard Scenario. Costs added +/ Costs saved -.

Sensitivity Analyses

A one-way sensitivity analysis was conducted to account for the uncertainty surrounding cost and model probabilities. Probabilities and costs were varied through the ranges listed in Table 1. Specifically, eight separate sensitivity analyses were conducted for each age cohort within both urban and rural settings and are as follows:

1. Increase prevalence by 20%
2. Decrease prevalence by 20%
3. Increase proportion referred to ECHO for suspected CHF by 20%
4. Decrease proportion referred to ECHO for suspected CHF by 20%
5. Highest diagnostic accuracy with minimum costs
6. Highest diagnostic accuracy with maximum costs
7. Lowest diagnostic accuracy with minimum costs
8. Lowest diagnostic accuracy with maximum costs.

Tables 4 and 5 show results from the sensitivity analysis for urban and rural contexts respectively. Model scenarios were considered to be sensitive to a cost parameter if it had a change of greater than 25% compared to the base case results.

For rural contexts (Table 5), the cost estimation for each scenario was insensitive to the prevalence of CHF, the proportion referred to ECHO, diagnostic accuracy (of BNP and ECHO) and costs. That is, compared to the base case costs, the cost estimates for each scenario remained relatively steady at varied inputs within the model.

However, it is noteworthy that for the proportion referred to ECHO at an urban centre (Table 4), diagnostic accuracy and cost were associated with a greater variability in costs compared to other inputs for both Scenarios D and E. Although, the cost estimation was not considered sensitive to the proportion referred to ECHO, diagnostic accuracy, and cost, the associated changes in costs did approximate the 25% minimum criteria used to identify sensitivity to a cost parameter.

In Scenario D (base case = $65,442), the total costs saved by reducing the number of ECHOs ranged between $52, 355 and $78,119 when varying the proportion referred to ECHO at an urban centre, and ranged between $50,272 and $79,047 when varying diagnostic accuracy and costs. In Scenario E (base case = $1646), the total add-on cost if BNP testing is completely ineffective ranged between $1288 and $1920 when varying the proportion referred to ECHO at an urban centre or the diagnostic accuracy and costs.

For urban contexts, the cost estimation was insensitive to CHF prevalence but was sensitive to the proportion referred to ECHO, diagnostic accuracy and costs for Scenarios A and B. In Scenario A (base case = $990,543), the total costs saved for reducing both the number of ECHOs and hospitalization days ranged between $792,410 and $1,188,615 when varying the proportion referred to ECHO for suspected CHF, and ranged between $576,210 and $1,491,462 when varying diagnostic accuracy and costs.

In Scenario B (base case = $204,773), the total costs saved by reducing the number of hospitalization days alone ranged between $165,853 and $249,326 when varying the proportion referred to ECHO for suspected CHF, and ranged between $113,074 and $374,306 when varying the diagnostic accuracy and costs.

Table 4: One-way sensitivity analysis for urban context

Scenario	Total Incremental Cost ($) Comparison with Standard [b]		
	Scenario A	Scenario B	Scenario C
Men (for all age cohorts)			
Base [a]	-419,708	-79,960	+45,730
Increase Prevalence by 20%	-443,921	-98,474	+45,730
Decrease Prevalence by 20%	-395,432	-61,448	+45,730
Increase Proportion Referred 20%	-503,612	-95,953	+54,876
Decrease Proportion Referred 20%	-335,741	-63,604	+36,584
Highest Diagnostic Accuracy			
Minimum Cost	-243,738	-38,864	+36,584
Maximum Cost	-533,571	-66,675	+54,876
Lowest Diagnostic Accuracy			
Minimum Cost	-429,835	-103,784	+36,584
Maximum Cost	-636,836	-153,858	+54,876
Women (for all age cohorts)			
Base [a]	-570,835	-127,813	+54,268
Increase Prevalence by 20%	-611,773	-156,743	+54,268
Decrease Prevalence by 20%	-529,898	-98,879	+54,268
Increase Proportion Referred 20%	-685,003	-153,373	+65,124
Decrease Proportion Referred 20%	-456,669	-102,249	+43,416
Highest Diagnostic Accuracy			
Minimum Cost	-332,472	-74,210	+43,416
Maximum Cost	-514,587	-124,923	+65,124
Lowest Diagnostic Accuracy			
Minimum Cost	-571,475	-144,667	+43,416
Maximum Cost	-854,626	-220,448	+65,124
Men & Women (for all age cohorts)			
Base [a]	-990,543	-207,773	+99,998
Increase Prevalence by 20%	-1,055,694	-255,217	+99,998
Decrease Prevalence by 20%	-925,330	-160,327	+99,998
Increase Proportion Referred 20%	-1,188,615	-249,326	+120,000
Decrease Proportion Referred 20%	-792,410	-165,853	+80,000
Highest Diagnostic Accuracy			
Minimum Cost	-576,210	-113,074	+ 80,000
Maximum Cost	-1,048,158	-191,598	+120,000
Lowest Diagnostic Accuracy			
Minimum Cost	-1,001,310	-248,451	+80,000
Maximum Cost	-1,491,462	-374,306	+120,000

Note. Standard scenario reflects the standard clinical diagnostic protocol. **Scenario A** reflects the cost of BNP minimizing both the number of ECHOs referred for suspected CHF and the number of hospitalization days. **Scenario B** reflects the cost of BNP minimizing the number of hospitalization days only. **Scenario C** reflects the cost of BNP having minimized neither the number of ECHOs nor the number of hospitalization days (i.e. add-on cost of BNP test).

[a.] Refers to base case results (Table 2).

[b.] Referent Category. Incremental costs represent comparisons with the Standard Scenario. Costs added + / Costs saved -.

Table 5: One-way sensitivity analysis for rural context

Scenario	Total Incremental Cost ($) Comparison with Standard [b]	
	Scenario D	Scenario E
Men (for all age cohorts)		
Base [a]	-28,540	+709
Increase Prevalence by 20%	-28,135	+709
Decrease Prevalence by 20%	-28,948	+709
Increase Proportion Referred 20%	-34,250	+863
Decrease Proportion Referred 20%	-22,833	+567
Highest Diagnostic Accuracy		
Minimum Cost	-23,409	+567
Maximum Cost	-35,512	+863
Lowest Diagnostic Accuracy		
Minimum Cost	-21,774	+567
Maximum Cost	-32,543	+863
Women (for all age cohorts)		
Base [a]	-36,902	+891
Increase Prevalence by 20%	-36,422	+891
Decrease Prevalence by 20%	-37,364	+891
Increase Proportion Referred 20%	-43,869	+1,057
Decrease Proportion Referred 20%	-29,522	+713
Highest Diagnostic Accuracy		
Minimum Cost	-29,232	+713
Maximum Cost	-43,535	+1,057
Lowest Diagnostic Accuracy		
Minimum Cost	-28,498	+713
Maximum Cost	-42,727	+1,057
Men & Women (for all age cohorts)		
Base [a]	-65,442	+1,646
Increase Prevalence by 20%	-64,557	+1,646
Decrease Prevalence by 20%	-66,312	+1,646
Increase Proportion Referred 20%	-78,119	+1,920
Decrease Proportion Referred 20%	-52,355	+1,280
Highest Diagnostic Accuracy		
Minimum Cost	-52,641	+1,280
Maximum Cost	-79,047	+1,920
Lowest Diagnostic Accuracy		
Minimum Cost	-50,272	+1,280
Maximum Cost	-75,270	+1,920

Note. Standard scenario reflects the standard clinical diagnostic protocol. **Scenario D** reflects the cost of BNP minimizing the number of ECHOs referred for suspected CHF at an urban centre. **Scenario E** reflects the cost of BNP not having minimized the number of ECHOs referred for suspected CHF at an urban centre.

a. Refers to base case results (Table 3).

b. Referent Category. Incremental costs represent comparisons with the Standard Scenario. Costs added + / Costs saved -.

LIMITATIONS

Several aspects in the analysis serve to construct a more accurate and contextually relevant cost estimation of BNP testing for Alberta. The cost estimation did attempt to account for the biological variability associated with age and gender. Several cost models were developed to compare potential BNP scenarios with standard clinical diagnostic protocols with each designed to reflect the clinical diagnostic protocols of urban and rural settings. Furthermore, valuation of resources was based on provincial data (with the exception of ECG). However, there were also a number of inherent limitations.

Perspective and Context

- The analysis was conducted from a payer's perspective. Therefore, results reflect costs from the perspective of who pays for the service and not from society as a whole or the individual patient.
- The cost estimation applies specifically to diagnosis and does not include prognosis, management, or patient monitoring. Consequently, the analysis does not capture other potential cost implications associated with patients as they progress through their disease and the health care system.

  For instance misdiagnosis of CHF has significant health and cost implications. If BNP testing reduces the number of misdiagnoses leading to more timely initiation of appropriate treatment and reduced number of ED readmissions, the magnitude of the costs saved or added has yet to be identified.
- Training costs of ED physicians to use BNP may be important but is not captured in the present analysis.
- The cost estimation applies specifically to the ED and therefore utilizes the Biosite Triage POC assay in the cost analysis. As a result, the economics of utilizing other BNP assays in other applications and settings is not addressed in this report.

Potential Confounders

- While the analysis did account for age and sex, the results reflect patients who were assumed to have no other comorbid conditions including AMI, RD and UA. However, the number of co-morbid conditions increase in older populations and persons with CHF [37-39].

Nonetheless, the extant literature on BNP provided no further insight to inform the proper BNP cut-off value that not only accounts for age and sex but also other confounders that affect BNP blood concentration levels.

Modelling Constraints

- Cost models are limited by the type and availability of cost data in Alberta. While BNP testing may have other cost implications, the models developed in the present analysis reflect data that were available at the time of the analysis.

  Time to treatment is an important cost factor with significant implications associated with BNP testing. Furthermore, there are other technologies that are potentially averted with BNP testing such as those associated in identifying pulmonary pathologies. However, due to time constraints and the unavailability of data, the cost implications of BNP testing when including these other cost factors remain to be determined.

- The inputs used in the models are heavily dependent on existing literature despite the uncertainty surrounding the degree to which the studies could be generalized to the Alberta scene. Accordingly, the sensitivity analysis indicated that there was some variation in the magnitude of costs saved or added at varied inputs.

- No economic model can reflect reality perfectly [40] and the models required a certain level of simplicity for straightforward interpretation of results. This however sacrifices the level of detail that can be incorporated into the models.

DISCUSSION

General

The present analysis provides economic information on the potential cost impact of BNP testing for patients presenting with symptoms of acute dyspnea in EDs within Alberta. To elucidate various cost implications, several cost models were developed each designed to compare potential BNP scenarios with standard clinical diagnostic protocols in both rural and urban settings.

Overall the results indicate that compared to standard diagnostic protocols, BNP testing in one year could considerably reduce total costs. Specifically, BNP testing was observed to have a much greater cost impact in urban settings compared to rural settings which is not unexpected in light of the greater cost minimization potential in urban EDs. Urban EDs not only receive a greater volume of dyspneic patients but also offer highly sophisticated and expensive diagnostic technologies.

Results also indicate that compared to standard diagnostic protocols, BNP testing has considerable economic savings in populations with a high prevalence of CHF (i.e. the elderly). Considerable cost savings associated with reducing the number of hospitalization days alone was only observed for those patients aged 75 years or older and the magnitude of total costs saved for this single age cohort was greater than that of all younger age cohorts combined.

The economic utility of BNP testing therefore may prove more valuable in the future in light of the current demographic shift in the elderly population in Alberta. Since 1990/1991 the mean annual population growth of seniors in Alberta is 3% [41] and the projected proportion of persons aged 65 years and older will increase from 10.2% in 2004 to 19.5% in 2030 [42].

It is important to distinguish however that only when comparing BNP to standard diagnostic protocols are there significant cost savings associated with a higher prevalence of CHF. When directly comparing the total costs of BNP testing between age cohorts, the total cost of BNP testing for those patients aged 75 years or older was greater than that of all younger age cohorts combined (i.e. more costly). This occurred because a highly specific test such as BNP, utilized in a population with a high prevalence of CHF, does not result in fewer patients being sent inappropriately for ECHO. Therefore when comparing total costs of BNP testing between age cohorts, BNP testing provides greater economic benefit in a population with a lower prevalence of CHF (when compared to a high prevalence population). Nonetheless, given that BNP is assumed to be an add-on diagnostic test (i.e. does not replace

current diagnostic protocols), comparing costs against standard diagnostic protocols is considered the appropriate cost comparison.

Caveats

Interest for this report originated from the CLL and from their perspective as managers of regional laboratory services, regardless of the potential cost savings overall, there is an ubiquitous add-on cost associated with BNP testing. The total add-on cost for BNP testing in Alberta is estimated to be $101,644. This add-on cost refers only to patients without other comorbidities and assumes that only half of dyspneic patients are referred to ECHO for suspected CHF. Consequently, the add-on cost of BNP testing is underestimated given that the number of dyspneic patients who receive BNP testing in the ED will likely be much greater in actual practice. Results from the sensitivity analysis indicate that the add-on cost of BNP testing in urban settings alone could be as much as $120,000 (20% greater than base case results). Thus, from the perspective of the regional laboratories the add-on cost of BNP testing is likely much greater in reality.

The cost saving potential and economic utility of BNP moreover is highly dependent on its ability to effectively reduce the number of patients who receive other expensive diagnostic technologies such as ECHO. In urban settings, there was a significant reduction in total costs when both the number of ECHOs and hospitalization days were decreased but considerably less when reducing the number of hospitalization days alone. This raises the question of which BNP cost scenario is most likely to apply.

At this point in time it is uncertain how BNP testing will actually affect the use of ECHO in Alberta. While there is some evidence to suggest that BNP testing would reduce the number of ECHOs in other countries [21, 22], these studies are based on the assumption that ED physicians will actually use BNP testing to rule out CHF and the need for ECHO. Ultimately, whether BNP reduces the number of ECHOs will depend on physician behaviour once the test is implemented.

Critical to the implementation of BNP testing therefore is the development of clear diagnostic protocols regarding BNP blood concentration levels for varying populations. Strict protocols must be obeyed with clear diagnostic guidelines for physicians such that BNP is used properly. However, the effects of age, gender, comorbid conditions, medications and genetics remain to be studied more comprehensively before suitable diagnostic guidelines can be developed [14].

The European Society of Cardiology recommends the use of natriuretic peptides to rule out CHF [1] but whether diagnostic protocols developed in Alberta will reflect this algorithm or the models developed herein is uncertain.

Model Assumptions and Sensitivity Analysis

The analysis was based on the principle assumptions that BNP testing rules out CHF (does not confirm) and is not conducted on all patients presenting to the ED with symptoms of acute dyspnea but rather on those referred to ECHO for suspected CHF. This has particular significance in rural contexts where it is unlikely that patients presenting with acute dyspnea are referred to an urban centre for ECHO. The critical issue is the role of BNP for the 95% (assumed in the present analysis) of dyspneic patients where threatening cardiac pathology is not suspected but these patients may nevertheless benefit from BNP testing.

Accordingly, in rural EDs with limited resources and diagnostic tools, BNP testing may in fact be used to rule out CHF in all patients presenting with acute dyspnea despite the extremely limited cost saving potential (i.e. will not avert other expensive diagnostic technologies). From a clinical perspective, providing a BNP test to anyone presenting with acute dyspnea may be warranted because there are no other diagnostic alternatives readily available to rural ED physicians. In the present analysis there were approximately 3260 annual dyspneic patients who presented at a rural centre. The cost of conducting a BNP test ($40 per test) for these patients is $128,000. Therefore the total add-on cost (Scenario E) may be $128,000 rather than $1646.

Results from the sensitivity analysis indicate that in urban settings the cost estimation was sensitive to the proportion referred to ECHO, diagnostic accuracy, and costs (rural settings had similar results). Furthermore, model probabilities were based on available literature and it is unknown whether these values can be directly generalized to the Alberta population.

Accordingly, given that the epidemiology associated with BNP testing has been observed to vary across studies coupled with the uncertainty regarding how ED physicians will use BNP, there is significant variability in the potential cost impact of BNP testing. Across the three model scenarios in urban settings for instance, by either increasing the proportion referred to ECHO from 50% to 60% or by simply reducing the specificity of diagnostic tests by 20%, there is a greater than 25% increase in costs.

Therefore, in addition to careful consideration regarding how BNP testing will be used in actual practice, serious thought must be given to the uncertainty surrounding the diagnostic precision of the tests used to identify CHF and especially the precision of BNP. It is completely conceivable that ED physicians will provide BNP testing to a greater proportion of dyspneic patients and that BNP testing may have a lower specificity than originally assumed.

Patient Outcomes

Economic considerations are secondary to the health outcomes of dyspneic patients who receive BNP testing. While CMA assumes that outcomes are equivalent between comparators, whether BNP testing truly improves health outcomes for persons with acute dyspnea remains to be resolved. Health outcomes were not captured in the present analysis due to the unavailability of context-specific data and the explicit focus on diagnosis (not treatment management or monitoring), that did not allow for a broad long-term analysis.

The most important factor affecting health outcomes of dyspneic persons is misdiagnosis. Misdiagnosis of heart failure increases the time for initiation of the most appropriate treatment and the time to discharge resulting in undue morbidity [4, 5, 43] and mortality [4]. Treatment strategies for pulmonary conditions such as chronic obstructive pulmonary disease may be hazardous to patients with heart failure and vice versa [9]. Furthermore, misdiagnosed patients eventually return to the ED with exacerbated symptoms while adding unnecessary costs [44].

Wu and colleagues [45] recently conducted a study investigating the readmission rate for misdiagnosed patients before and after the implementation of BNP testing. Their results indicated that the use of BNP testing may contribute to a reduced number of readmissions for patients with CHF and other pulmonary conditions. The authors suggest that BNP testing may enable ED physicians to correctly diagnosis more dyspneic patients leading to improved health outcomes and substantial cost savings in unnecessary readmissions.

Still, results of their study were not conclusive and merely suggested that BNP testing may play a role in decreasing the number of readmissions due to misdiagnosis. Currently this is the sole published study that has addressed the long-term outcomes of BNP testing and the existing literature has yet to provide any additional insight regarding misdiagnosis, readmission, and associated quality of life.

CONCLUSION

In light of increasing budgetary and political constraint in the health care system the cost of BNP may be unattractive due to the initial added cost of the test [44]. Justification for BNP testing must be predicated on the basis of improved clinical care or efficiency of clinical services delivered which serve to improve health outcomes while reducing costs [45]. If the benefits lost are greater than the benefits gained (in terms of health outcomes and costs) than the decision is not optimal.

Overall, BNP testing has the potential for considerable cost savings. However, this potential is dependent on the assumptions integrated into the present analysis and whether or not they hold true in actual settings. In an attempt to circumvent this limitation, various BNP scenarios were modelled to better identify the economic impact of BNP testing including the additional cost of the test if it were proven to be completely ineffective.

An important consideration is how ED physicians use the test in actual practice and how dyspneic patients who receive the test progress through their disease and use available health care resources. Ultimately, the utility of BNP testing will be based on how it is used (or misused) in everyday settings. Yet, the potential application of BNP testing for other diagnostic and treatment modalities is great [46]. If made available, BNP testing will inevitably expand beyond diagnosis of the dyspneic patient and begin being used in prognosis, management and patient monitoring (personal communication, Dr D. Isaac).

In conclusion, the present analysis provides insight into the potential costs of BNP testing when used to differentiate CHF from other pulmonary conditions in the ED. However, this analysis is merely a first step to better identify the potential cost implications of the test. Further study is required to delineate a comprehensive cost framework taken from a societal perspective that not only includes treatment management and patient monitoring but also long-term health outcomes and quality of life for persons with multiple comorbidities.

One alternative worth exploring would be to conduct a pilot study with primary data collection. A pilot study would provide explicit insight into how BNP testing would actually be used in urban and rural settings and could be designed to capture short and long-term outcomes in terms of both cost and health. This would lead to more definitive conclusions about the impact of BNP testing based on concrete information generated from actual use.

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APPENDIX A: SEARCH METHOD

Search Strategy

Database	Platform or URL	Date Searched/ Edition	Search Terms
PubMed	www.pubmed.gov	June 3, 2004	(CHF OR congestive heart failure OR left ventrical dysfunction OR ventrical dysfunction, left OR left ventrical dysfunction* OR ventric* dysfunction* OR "shortness of breath" OR acute dyspnea OR dyspnoea) AND (natriuretic peptide, brain OR b-type natriuretic peptide OR b type natriuretic peptide OR natriuretic peptide, b type OR type b natriuretic peptide OR natriuretic peptide type b OR natriuretic peptide, type b OR BNP) AND (expenditure* OR health care expenditure* OR cost*)
MEDLINE	(Ovid- licensed resource)	June 1, 2004	(health care expenditures.mp. OR exp "health care cost"/ OR expenditure* OR cost*) AND (Natriuretic peptide, brain OR b-type natriuretic peptide OR b type natriuretic peptide OR natriuretic peptide type b OR natriuretic peptide, type b) BNP AND "b type") OR (BNP AND "type b) OR (BNP AND "B-type) OR (BNP AND "B Type")) AND (acute dyspnea OR dyspnoea).mp. OR (shortness adj breath) OR (CHF OR congestive heart failure OR left ventric* dysfunction*)
ECRI	http://www.ecri.org/ (licensed resource)	May 21, 2004	ECRI's International Health Technology Assessment Database Brain natriuretic peptide* OR BNP ECRI's Healthcare Standards Directory Brain natriuretic peptide* OR BNP ECRI's Medical Device Safety Alerts Database Brain Natriuretic Peptide* OR BNP

Database	Platform or URL	Date Searched/ Edition	Search Terms
EMBASE	(Ovid- licensed resource)	June 1, 2004	(health care expenditures.mp. OR exp "health care cost"/ OR expenditure* OR cost") AND (Natriuretic peptide, brain OR b-type natriuretic peptide OR b type natriuretic peptide OR natriuretic peptide type b OR natriuretic peptide, type b) BNP AND "b type") OR (BNP AND "type b) OR (BNP AND "B-type) OR (BNP AND "B Type")) AND (acute dyspnea OR dyspnoea).mp. OR (shortness adj breath) OR (CHF OR congestive heart failure OR left ventric* dysfunction*)
PsycINFO (Ovid-licensed resource)	(Ovid- licensed resource)	June 1, 2004	(health care expenditures.mp. OR exp "health care cost"/ OR expenditure* OR cost") AND (Natriuretic peptide, brain OR b-type natriuretic peptide OR b type natriuretic peptide OR natriuretic peptide type b OR natriuretic peptide, type b) BNP AND "b type") OR (BNP AND "type b) OR (BNP AND "B-type) OR (BNP AND "B Type")) AND (acute dyspnea OR dyspnoea).mp. OR (shortness adj breath) OR (CHF OR congestive heart failure OR left ventric* dysfunction*)
Web of Science	(ISI- licensed resource)	June 3, 2004	TS=(natriuretic brain peptide OR b type natriuretic brain peptide OR BNP) AND (TS = (acute dyspnea* OR dyspnoea* OR CHF OR congestiveheart failure* OR left ventric* dysfunction* OR shortness of breath) AND TS=(health care expenditure* OR expenditure OR cost* OR health care cost*)
Cochrane Library (licensed resource)	(Licensed resource)	May 21, 2004/ 2003 Issue 4	Brain natriuretic peptide* OR BNP

Database	Platform or URL	Date Searched/ Edition	Search Terms
CINAHL (Ovid-licensed resource)	(Ovid- licensed resource)	June 3, 2004	(expenditure* OR health care expenditure* OR cost*) AND (CHF OR congestive heart failure OR heart failure, congestive OR left ventrical dysfunction OR ventrical dysfunction, left OR left ventrical dysfunction* OR ventric* dysfunction* OR "shortness of breath" OR acute dyspnea OR dyspnoea) (expenditure* OR health care expenditure* OR cost*) AND (natriuretic peptide, brain OR b-type natriuretic peptide OR b type natriuretic peptide OR natriuretic peptide, b type OR type b natriuretic peptide OR natriuretic peptide type b OR natriuretic peptide, type b) OR (BNP AND "b type") OR (NP AND "type b") OR (BNP AND 'b-type') OR (BNP AND "B Type"))
CRD Databases (DARE, NHS EED, HTA)	http://www.york.ac.uk/inst/crd/crddatabases.htm	May 21, 2004	Brain natriuretic peptide* OR BNP
Evidence-Based Resources: EBM Reviews Bandolier Clinical Evidence TRIP Database	 Ovid (Licensed Resource) http://www.jr2.ox.ac.uk/bandolier/index.html Licensed Resource http://www.tripdatabase.com	June 3, 2004	Brain natriuretic peptide* OR BNP
Clinicaltrials.gov	www.clinicaltrials.gov	June 3, 2004	Brain natriuretic peptide* OR BNP

Database	Platform or URL	Date Searched/ Edition	Search Terms
Guidelines: Alberta Medical Association	http://www.topalbertadoctors.org/home/home.aspx	June 3, 2004	Brain natriuretic peptide* OR BNP
Canadian Association of Emergency Physicians	http://www.caep.ca/002.policies/002-01.guidelines.htm)		
CMAInfobase	http://mdm.ca/cpgsnew/cpgs/index.asp		
National Guidelines Clearinghouse	www.guideline.gov		
Websites:		June 3, 2004	Brain natriuretic peptide* OR BNP
CCOHTA	http://www.ccohta.ca		
AETMIS	http://www.aetmis.gouv.qc.ca/en/		
NICE	http://www.nice.nhs.uk		
UK National Register	http://www.update-software.com/national/		
FDA	http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm		
Blue Cross/ Blue Shield	http://www.bcbs.com/		

Notes: The * symbol is a truncation character that retrieves all possible suffix variations of the root word e.g. surg* retrieves surgery, surgical, surgeon, etc. †Searches were limited to English publications on humans between 1998 and 2004.

Inclusion Criteria

1. Studies address or identify the costs associated with BNP in diagnosing CHF from other pulmonary conditions in the ED or equivalent.
2. Studies are conducted in the context of diagnosis.
3. Studies compare the costs of BNP with some comparator or standard.

Exclusion Criteria

1. Studies that analyze the costs of BNP in a context other than the urgent care setting.
2. Studies that focused on the costs of BNP in the context of prognosis, treatment management or treatment monitoring only.

Search Results

Six citations were retrieved and, based on the inclusion/exclusion criteria, three articles were retrieved for review – two primary studies and one systematic review.

APPENDIX B: SUMMARY AND REVIEW OF ECONOMIC EVALUATION LITERATURE

Summary of Published Journal Articles

Study	Objectives & Population/Setting	Design/Method/Comparator	Results	Conclusion
Mueller et al. 2004 [21]	**Objective**: To conduct a RCT to determine whether a diagnostic strategy guided by BNP would improve the evaluation and care of patients with acute dyspnea who present to ED and thereby reduce the time to discharge and the total cost of treatment. **Setting**: Emergency Dept, Basel, Switz. **Total N**: Screened 665 adults sent to ED between May 2001 and April 2002. 452 were randomized without stratification into BNP group (225) and control group (227). **Age**: 70.3 yrs (BNP) & 70.8 yrs (control). **Gender**: 59% M (BNP) and 57% F (control) **Inclusion**: Acute dyspnea with no obvious traumatic cause of dyspnea. **Exclusion**: Patients with cardiogenic shock and those who requested transfer to another hospital.	**Type**: RCT without stratification. **Perspective**: Not stated but implicitly a societal perspective. **Timeline**: beginning of trial to 1 month. **Comparison**: BNP vs. Control. **Protocols**: All patients underwent a clinical assessment that included history, physical, ECG, pulse oximetry, blood test, and chest radiography. BNP group assessed with Biosite Triage Point of Care (diagnosis assessed in context of other info) only. Control group received clinical guideline procedures – ECHO. **Resources**: Did not specify resources for BNP or ECHO. **Costs**: Hospital charges used as estimates of true cost. BNP = $47/assay based on current reimbursement for BNP in Switzerland. Did not identify or state the source of resource valuation for control group. **Cost Strategy**: Compared the time to discharge and the associated total cost of treatment between study groups.	Baseline characteristics well matched between study groups. 75% of BNP group was hospitalized versus 85% in control. 15% of BNP group required intensive care versus 24% in control. Median of 8 days for discharge in BNP group versus 11 in control group. Mean total cost (includes variable and fixed) of treatment BNP group was $5410 versus $7264 in control.	Use of BNP test in conjunction with other clinical information reduced the time to the initiation of the most appropriate therapy, the need for hospitalization and intensive care, the time to discharge, and the total cost of treatment.

Study	Objectives & Population/Setting	Design/Method/Comparator	Results	Conclusion
Sim et al. 2003 [22]	**Objective**: To assess the value of BNP as a selective pre-screen for breathless patients referred for open access echocardiography. **Setting**: Open access echocardiography service in Emergency Dept. Newport, South Wales catchment area (556,622) **Total N**: 83 patients. **Age**: Not provided **Gender**: Not provided **Inclusion**: Patients with symptoms of breathlessness **Exclusion**: Patients with breathlessness and heart murmur.	**Type**: Within Group Comparative Cost Effectiveness Analysis. **Perspective**: Not stated but implicitly a provider perspective **Timeline**: 1 year. **Comparison**: ECHO versus BNP screen + ECHO. **Protocols**: patients with symptoms of breathlessness underwent ECHO and BNP measurements (radioimmunoassay kit). **Resources**: ECHO – machine, service contract, supplies and echocardiographer. BNP – consumables per test & labour. **Costs**: ECHO based on published articles (£54/investigation) and included cost of machine and amortization. BNP based on standard costing package provided by Data Tree International (£6.60/patient). **Cost Strategy**: All patients undergo ECHO and compare this with the cost where all patients receive BNP screening + ECHO at different levels of concentration thresholds.	At threshold of 19 pg/ml 26 patients diagnosed with LVSD using BNP screening and 26 diagnosed with LVSD by ECHO (no FN). Total cost for ECHO was £4482 and total cost for BNP pre-screen was £3517.80 (Diff = £964.20). At threshold of 20 pg/ml 26 patients diagnosed with LVSD using BNP screening and 25 diagnosed with LVSD by ECHO (1 FN). Total cost for ECHO was £4482 and total cost for BNP pre-screen £3193.80 (Diff = £1288.20).	Study demonstrates a NPV of 100% and a PPV of 6.9% using a BNP value of 19 pg/ml in detecting LVSD. The data suggests that it is cost effective to use BNP at the threshold of 19-20 pg/ml as a pre-screen for ECHO. Threshold above 20 pg/ml will compromise the sensitivity of BNP and increase the risk of missed diagnosis (FN). Strength of study is that it assessed effectiveness.

Notes: Summary does not include report conducted by Craig and colleagues [23] because cost effectiveness of BNP testing in the ED setting was an extremely small component of the entire report.

Critical Assessment of Economic Evaluation Literature

(adapted from Drummond and colleagues [20])

Mueller et al. [21]:Use of B-Type natriuretic peptide in the evaluation and management of acute dyspnea
1. Was a well-defined question posed in answerable form? ☑ 1.1 Did the study examine both costs and effects of the service(s) or program(s)? ☑ 1.2 Did the study involve a comparison of alternatives? ☑ 1.3 Was a viewpoint for the analysis stated and was the study placed in any particular decision-making context? ☒ • The objective was to determine whether a diagnostic strategy guided by the rapid measurement of B-type natriuretic peptide levels would improve the evaluation and care of patients with acute dyspnea who present to the ED and would thereby reduce the time to discharge and the total cost of treatment. • However, the viewpoint for the analysis was not explicitly stated.
2. Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where, and how often)? ☑ 2.1 Were any important alternatives omitted? ☒ 2.2 Was (Should) a do-nothing alternative (be) considered? ☒ • A comprehensive description of the competing alternatives was identified. The alternatives were BNP versus ECHO in the diagnosis of CHF for patients presented with symptoms of dyspnea at the emergency department.
3. Was the effectiveness of the program or services established? ☑ 3.1 Was this done through a randomized, controlled clinical trial? If so, did the trial protocol reflect what would happen in regular practice? ☑ 3.2 Was effectiveness established through an overview of clinical studies? ☒ 3.3 Were observational data or assumptions used to establish effectiveness? If so, what are the potential biases? ☑ • This study was a RCT without stratification. However there were assumptions that were used to determine effectiveness, namely the BNP threshold used to determine the diagnosis of CHF. NPV and PPV vary with different levels of BNP concentration.

Mueller et al. [21]:Use of B-Type natriuretic peptide in the evaluation and management of acute dyspnea
4. Were all the important and relevant costs and consequences for each alternative identified? ☒ 4.1 Was the range wide enough for the research question at hand? ☒ 4.2 Did it cover all relevant viewpoints? (Possible viewpoints include the community or social viewpoint, and those of patients and third-party payers. Other viewpoints may also be relevant depending upon the particular analysis). ☒ 4.3 Were capital costs, as well as operating costs, included? ☒ • Not all relevant costs and consequences were identified nor did it specify a viewpoint from which the study is based. In determining the total cost of treatment, the study did not consider the cost of 1) FN who later returns to the ED and 2) FP who did not require ECHO.
5. Were costs and consequences measured accurately in appropriate physical units (e.g. hours of nursing time, number of physician visits, lost work-days, gained life-years)? ☑ 5.1 Were any of the identified items omitted from measurement? If so, does this mean that they carried no weight in the subsequent analysis? ☒ 5.2 Were there any special circumstances (e.g. joint use of resources) that made measurement difficult? Were these circumstances handled appropriately? ☒ • Hospital charges (were standardized) were used as the most appropriate estimate of the true costs which is what has been recommended by previously published studies of cost effectiveness. Time to discharge was defined as the interval from presentation at the ED to discharge and the time to treatment was defined as the interval from presentation to the initiation of the appropriate therapy. Furthermore all end points were assessed in a blinded fashion by physicians who were not involved in patient care.

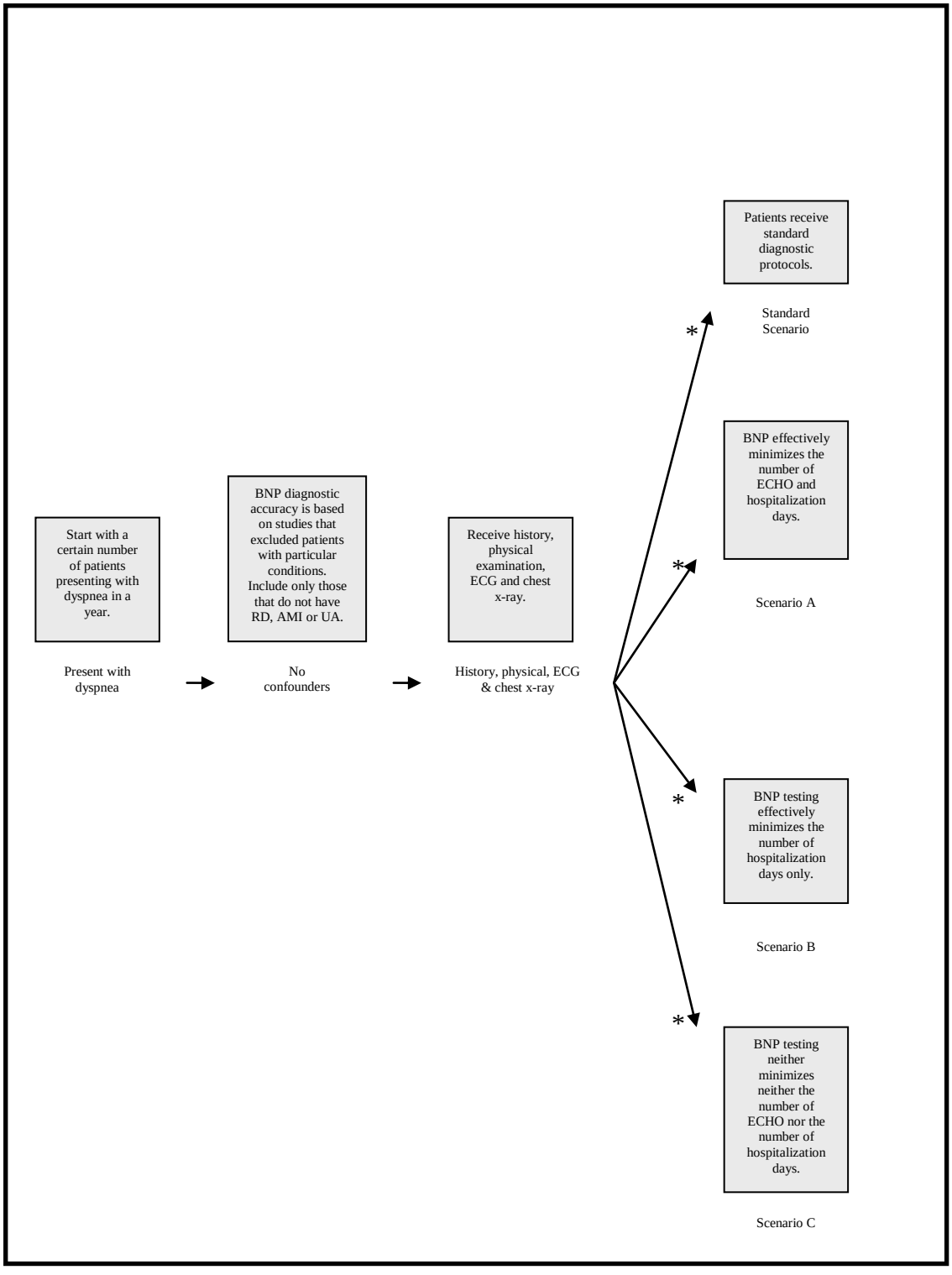
Mueller et al. [21]:Use of B-Type natriuretic peptide in the evaluation and management of acute dyspnea
6. Were costs and consequences valued credibly? ☑ 6.1 Were the sources of all values clearly identified? (Possible sources include market values, patient or client preferences and views, policy-makers' views and health professionals' judgments). ☑ 6.2 Were market values employed for changes involving resources gained or depleted? ☒ 6.3 Where market values were absent (e.g. volunteer labour), or market values did not reflect actual values (such as clinic space donated at a reduced rate), were adjustments made to approximate market values? ☑ 6.4 Was the valuation of consequences appropriate for the question posed (i.e. has the appropriate type or types of analysis – cost effectiveness, cost-benefit, cost-utility – been selected)? ☑ • Sources of valuation were identified and in the absence of market values, hospital charges were used as the most appropriate estimate of true costs which were also standardized to avoid an imbalance owing to differences in reimbursement or charges associated with different types or classes of insurance.
7. Were costs and consequences adjusted for differential timing? ☒ 7.1 Were costs and consequences which occur in the future 'discounted' to their present values? ☒ 7.2 Was any justification given for the discount rate used? • No discounting was used.
8. Was an incremental analysis of costs and consequences of alternatives performed? ☑ 8.1 Were the additional (incremental) costs generated by one alternative over another compared to the additional effects, benefits, or utilities generated? ☑ • An incremental cost was conducted between BNP and ECHO.
9. Was allowance made for uncertainty in the estimates of costs and consequences? ☒ 9.1 If data on costs or consequences were stochastic, were appropriate statistical analyses performed? ☑ 9.2. If a sensitivity analysis was employed, was justification provided for the ranges of values (for key study parameters)? ☒ 9.3. Were study results sensitive to changes in the values (within the assumed range for sensitivity analysis, or within the confidence interval around the ratio of costs to consequences)? • No sensitivity analysis was conducted.

Sim et al. [22]: The use of BNP as a screening test for LVSD-cost effectiveness in relation to open access echocardiography
1. Was a well-defined question posed in answerable form? ☑ 1.1 Did the study examine both costs and effects of the service(s) or program(s)? ☑ 1.2 Did the study involve a comparison of alternatives? ☑ 1.3 Was a viewpoint for the analysis stated and was the study placed in any particular decision-making context? ☒ • To assess the value of BNP measurement as a selective pre-screen for breathless patients referred for open access echocardiography. • However, the viewpoint for the analysis was not explicitly stated.
2. Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where, and how often)? ☑ 2.1 Were any important alternatives omitted? ☒ 2.2 Was (Should) a do-nothing alternative (be) considered? ☒ • A comprehensive description of the competing alternatives was identified. The alternatives were BNP versus ECHO in the diagnosis of CHF for patients presented with symptoms of dyspnea at the emergency department.
3. Was the effectiveness of the program or services established? ☑ 3.1 Was this done through a randomized, controlled clinical trial? If so, did the trial protocol reflect what would happen in regular practice? ☑ 3.2 Was effectiveness established through an overview of clinical studies? ☒ 3.3 Were observational data or assumptions used to establish effectiveness? If so, what are the potential biases? ☑ • This study was a within group comparative analysis. It should be noted however that the cost for echocardiography was based on a published article in the British Society of echocardiography Newsletter. Thus, it is unclear what is included in the cost of echocardiography.

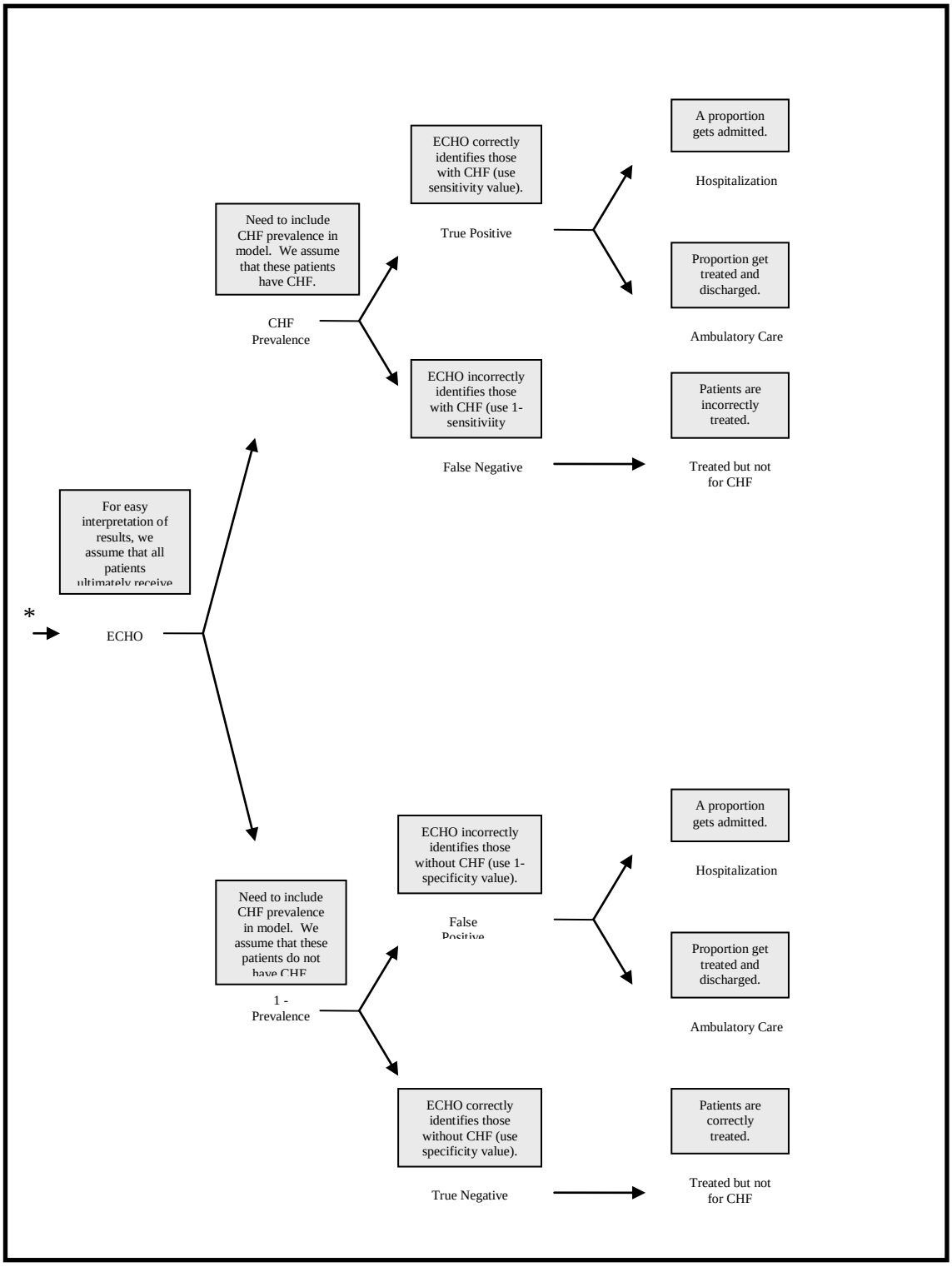
Sim et al. [22]: The use of BNP as a screening test for LVSD-cost effectiveness in relation to open access echocardiography
4. Were all the important and relevant costs and consequences for each alternative identified? 4.1 Was the range wide enough for the research question at hand? ☑ 4.2 Did it cover all relevant viewpoints? (Possible viewpoints include the community or social viewpoint, and those of patients and third-party payers. Other viewpoints may also be relevant depending upon the particular analysis). ☒ 4.3 Were capital costs, as well as operating costs, included? ☑ • Most of the relevant costs and consequences were identified (Tables 1-3) but the study did not specify a viewpoint from which the study is based. The study identified all relevant outcomes especially prevalence, sensitivity, specificity, PPV and NPV of the BNP test.
5. Were costs and consequences measured accurately in appropriate physical units (e.g. hours of nursing time, number of physician visits, lost work-days, gained life-years)? ☑ 5.1 Were any of the identified items omitted from measurement? If so, does this mean that they carried no weight in the subsequent analysis? ☒ 5.2 Were there any special circumstances (e.g. joint use of resources) that made measurement difficult? Were these circumstances handled appropriately? ☒ • Costs (tables 1-3) and consequences were measured accurately. The study provided the range of sensitivity, specificity, NPV, and PPV at varied levels of BNP concentration (figures 1 & 2).
6. Were costs and consequences valued credibly? ☑ 6.1 Were the sources of all values clearly identified? (Possible sources include market values, patient or client preferences and views, policy-makers' views and health professionals' judgments). ☑ 6.2 Were market values employed for changes involving resources gained or depleted? ☒ 6.3 Where market values were absent (e.g. volunteer labour), or market values did not reflect actual values (such as clinic space donated at a reduced rate), were adjustments made to approximate market values? ☒ 6.4 Was the valuation of consequences appropriate for the question posed (i.e. has the appropriate type or types of analysis – cost-effectiveness, cost-benefit, cost-utility – been selected)? ☑ • Sources of valuation were identified but it is unknown whether values reflect actual costs.

Sim et al. [22]: The use of BNP as a screening test for LVSD-cost effectiveness in relation to open access echocardiography
7. Were costs and consequences adjusted for differential timing? ☑ 7.1 Were costs and consequences which occur in the future 'discounted' to their present values? ☒ 7.2 Was any justification given for the discount rate used? • Yes. An annual cost over the life of the echocardiogram was provided.
8. Was an incremental analysis of costs and consequences of alternatives performed? ☑ 8.1 Were the additional (incremental) costs generated by one alternative over another compared to the additional effects, benefits, or utilities generated? ☑ • An incremental cost was conducted between BNP and ECHO.
9. Was allowance made for uncertainty in the estimates of costs and consequences? ☑ 9.1 If data on costs or consequences were stochastic, were appropriate statistical analyses performed? ☑ 9.2. If a sensitivity analysis was employed, was justification provided for the ranges of values (for key study parameters)? ☑ 9.3. Were study results sensitive to changes in the values (within the assumed range for sensitivity analysis, or within the confidence interval around the ratio of costs to consequences)? ☒ • A simple sensitivity analysis was conducted to determine the change in incremental costs at a lower cost per echocardiogram.

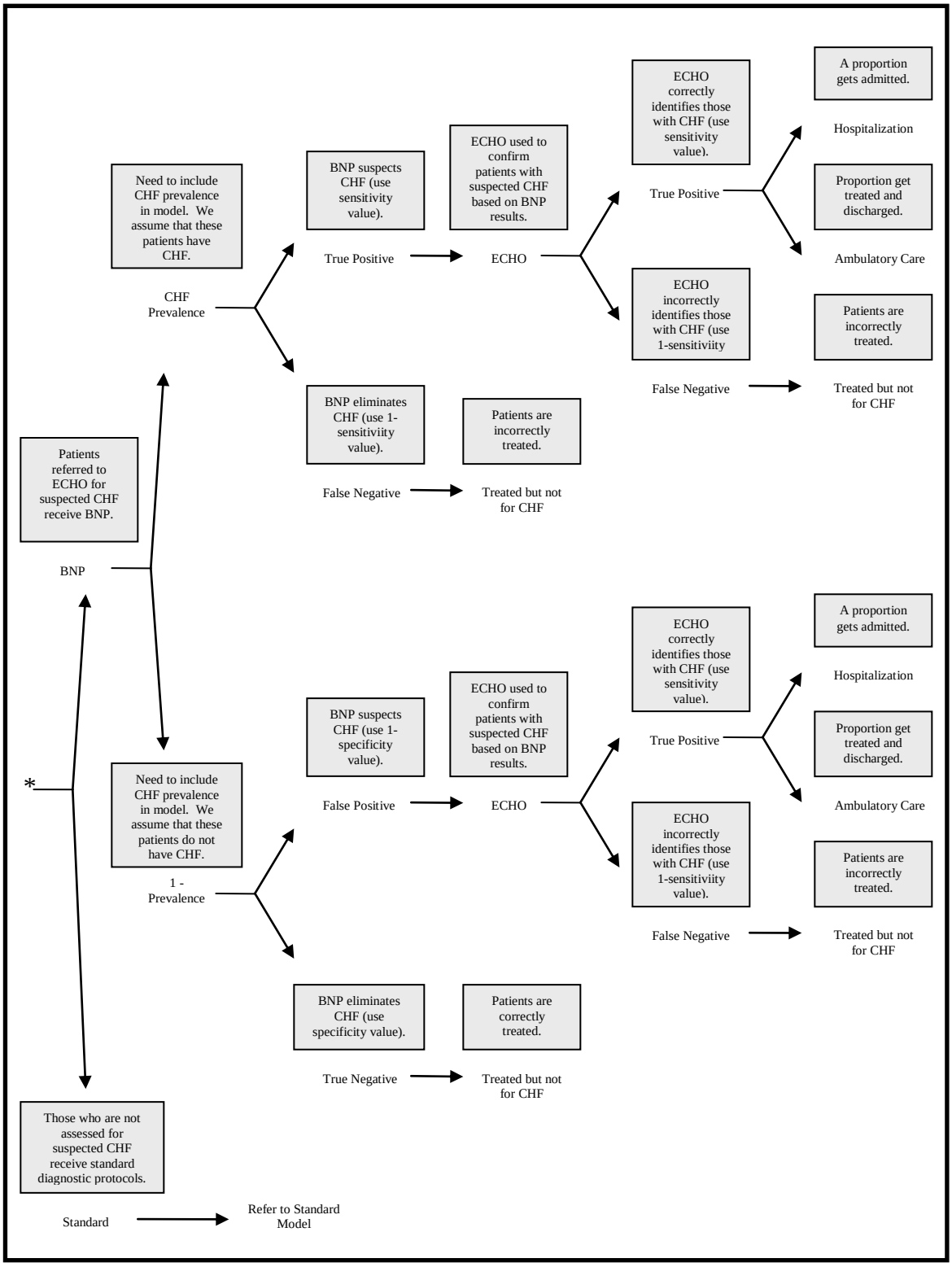
APPENDIX C: COST MODELS - URBAN CONTEXT



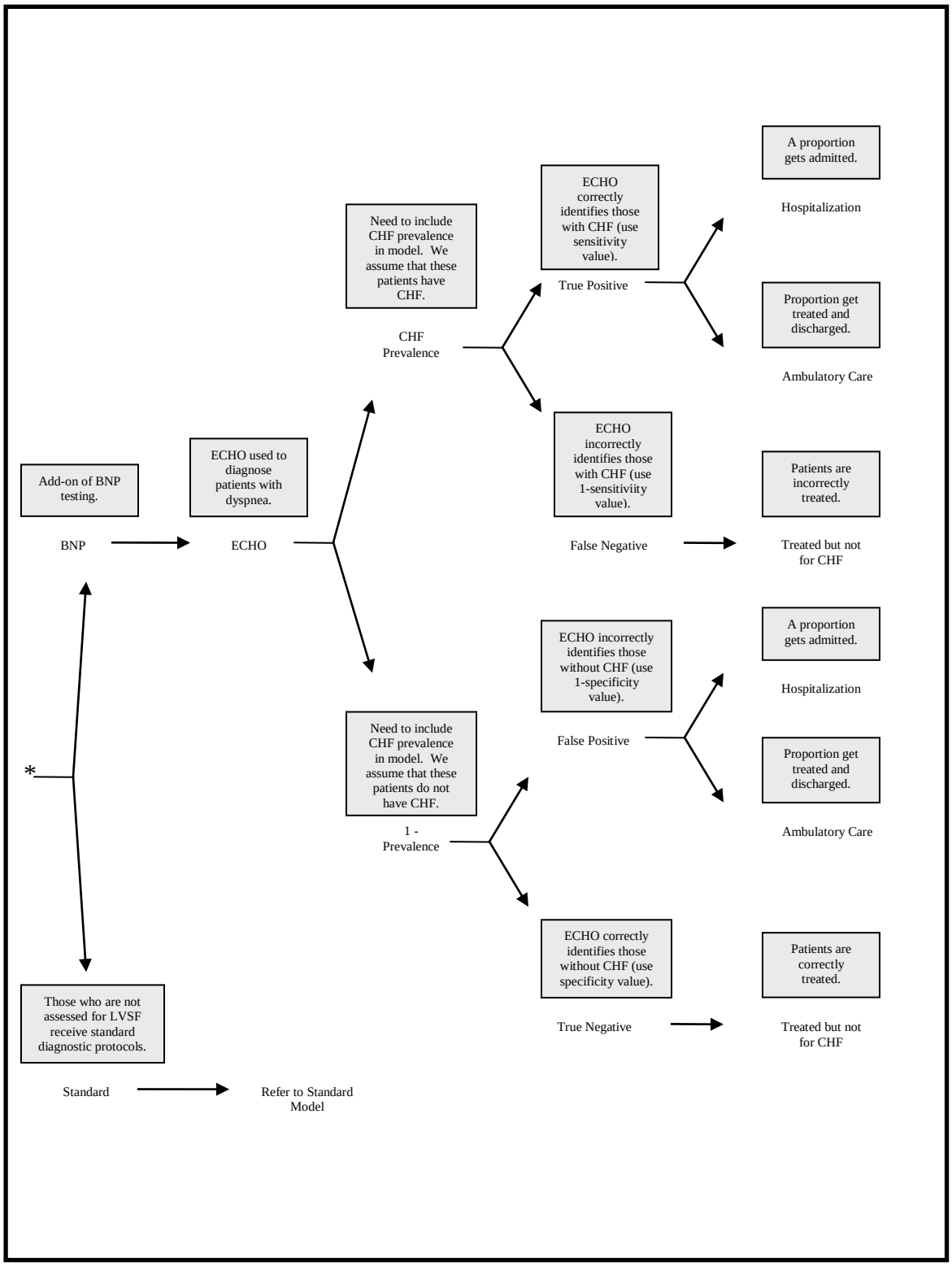
Model for Standard Scenario



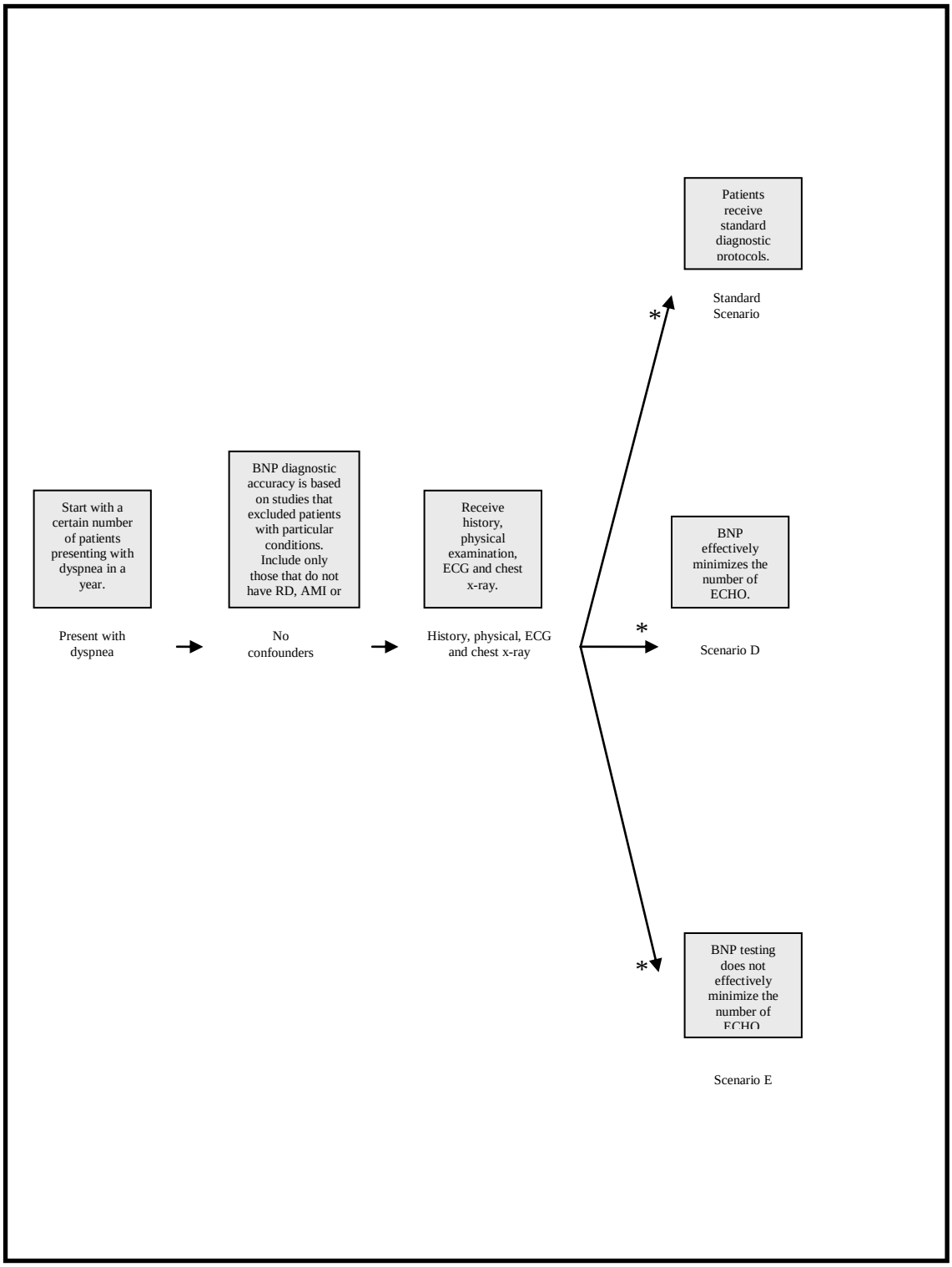
Model for Scenario A and B



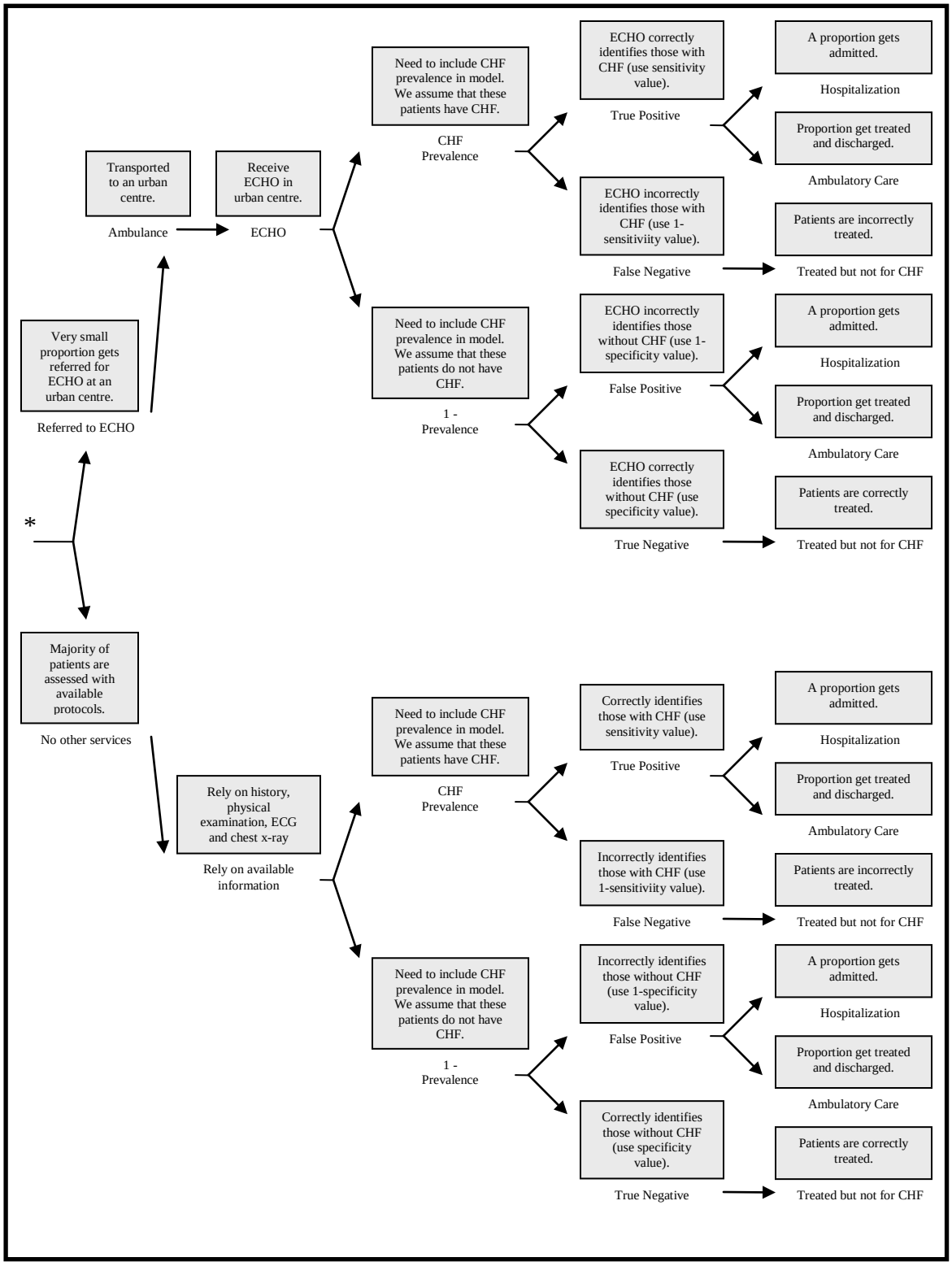
Model for Scenario C



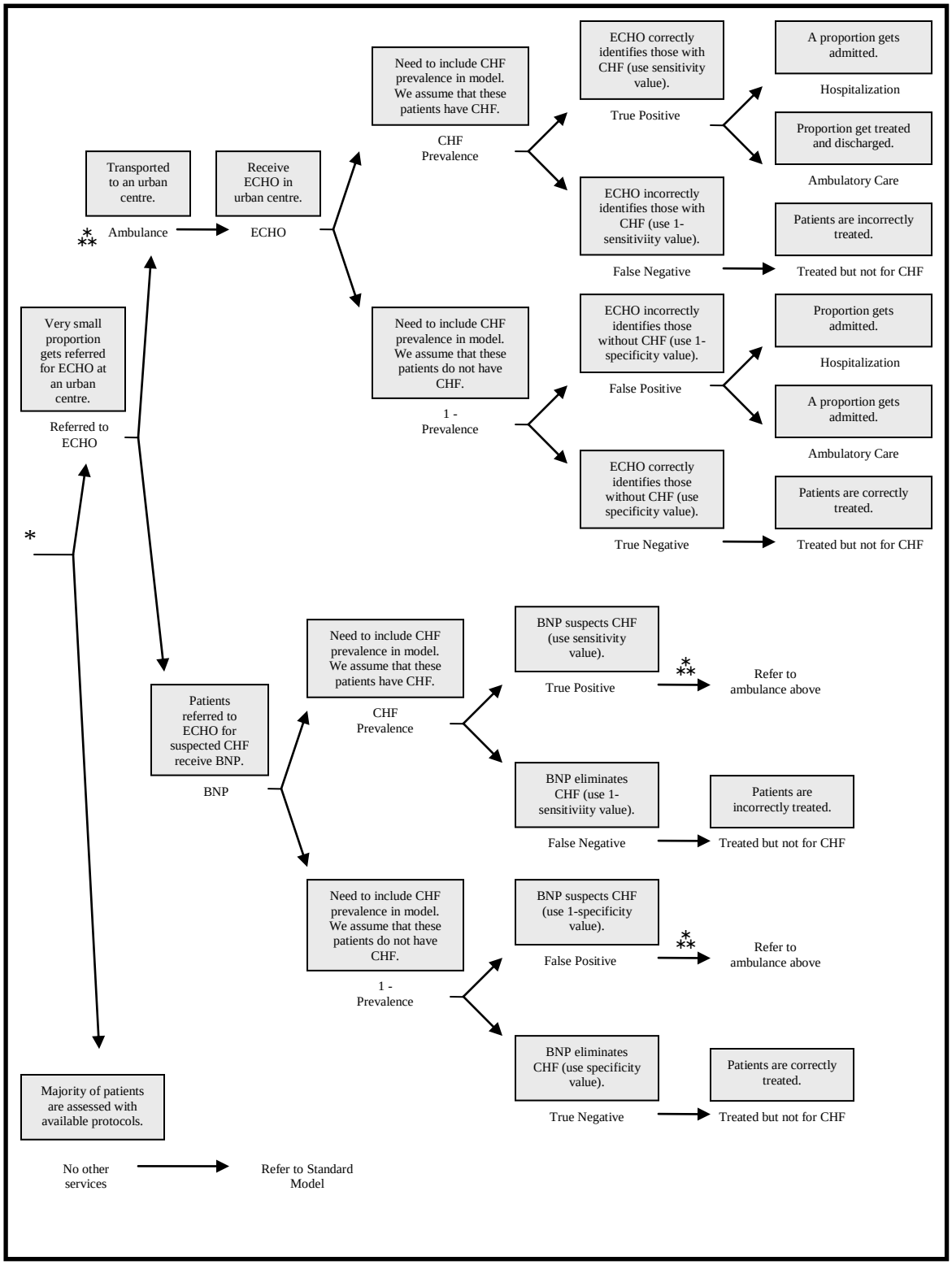
APPENDIX D: COST MODELS - RURAL CONTEXT



Model for Standard Scenario



Model for Scenario D



Model for Scenario E